Characteristics and outcomes of patients with de-novo kidney injury whilst admitted to intensive care

Mark Andonovic

MBChB, FRCA

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

Department of Anaesthesia, Critical Care and Perioperative Medicine
School of Medicine
College of Medicine, Veterinary and Life Sciences
University of Glasgow

May 2022

Word count: 70,251

Abstract

Kidney injury is a common occurrence amongst patients admitted to the intensive care unit (ICU). Whilst features and short-term outcomes of acute kidney injury (AKI) in ICU have been well documented over the past decade, less research is available regarding longer-term outcomes. A relatively new definition for protracted kidney injury referred to as acute kidney disease (AKD) has been proposed, but minimal data exist as to the characteristics of patients with this condition and their short- and long-term outcomes.

The studies including in this thesis aimed to identify the features of kidney injury suffered whilst admitted to ICU; the short- and long-term survival of patients with kidney injury and the subset of patients who progress to AKD; long-term development of major adverse kidney events and secondary cardiovascular events in these patients; and the features and outcomes of patients with oliguric kidney injury when compared to non-oliguric kidney injury.

This thesis performed retrospective observational cohort studies which identified patients aged 16 or older admitted to the Glasgow Royal Infirmary and Queen Elizabeth University Hospital ICUs in Scotland between 1st July 2015 and 30th June 2018. Patients with known pre-existing established kidney failure (EKF) were identified and classed as their own group. Baseline serum creatinine and subsequent values were used to identify patients with de-novo kidney injury (DNKI) and the remaining patients were classified as having no kidney injury. Patients with DNKI with recovery prior to day 7 were classified as AKI; recovery at day 7 or beyond was classified as AKD. Data extracted from the Scottish Intensive Care Society Audit Group (SICSAG) and Strathclyde Electronic Renal Patient Records (SERPR) databases included patient demographics, in-hospital and long-term mortality, proportion of major adverse kidney events (MAKEs), and cardiovascular events. Data on 24-hour urine output values were extracted from the Carevue™ database to identify and compare oliguric and non-oliguric kidney injury. Multivariable logistic regression was used to identify risk factors for AKD and reported in terms of odds ratios (ORs) and 95% confidence intervals (95% CIs). A Cox proportional hazards model was used to identify factors associated with long-term outcomes and reported as hazard ratios (HRs) and 95% CIs.

Two in every five patients admitted to ICU during the study period went on to suffer from a kidney injury during their admission (40.4%). Approximately one in four of patients who survived to day seven after their injury, progressed to AKD (24.9%). Kidney injury was more common in older, comorbid, male patients admitted from medical specialties with lower baseline estimated glomerular filtration rate (eGFR) admitted as a result of sepsis; progression to AKD was significantly associated with male sex, admission due to sepsis and a lower baseline eGFR. In-hospital mortality was significantly higher in the DNKI group compared to the no injury group (35.9% vs 11.4%); this was also the case for AKD patients compared with AKI patients who survived to day 7 following the initial injury (26.1% vs 11.6%).

In patients who survived to hospital discharge, mortality over the four- and half-year follow-up period showed a significant reduction in survival in the de-novo injury group when compared with the group without kidney injury with an independently associated 16% increased risk of dying. No significant long-term survival difference was associated with progression to AKD. Development of de-novo kidney injury and progression to AKD were both significantly associated with a faster decline in eGFR over time as well as development of MAKEs over the total follow up period (OR = 2.28 for DNKI and OR = 1.25 for AKD).

Presence of DNKI whilst in ICU was significantly associated with a biochemical myocardial injury (HR=1.46); however, progression to AKD did not show any significant association. Neither presence of AKI nor prolonged length of injury had any statistically significant effect on future coronary artery interventions. Whilst DNKI did not show a significant association for future cerebrovascular events, a sub-group analysis on DNKI patients showed progression to AKD was significantly associated with future cerebrovascular events (OR=2.34).

On analysis of DNKI patients with data available on 24-hourly urine output during their admission, 46.4% suffered from oliguric injury. Development of oliguric kidney injury was more commonly seen in older patients, patient admitted from medical specialties, patients with a lower baseline eGFR, and patients admitted due to sepsis. In-hospital mortality was significantly higher in patients with oliguric kidney injury compared to patients with non-oliguric injury (41.9% vs 31.5%). In patients to survive to hospital discharge, oliguric injury was

independently associated with increased mortality at 18 months compared with non-oliguric injury, but no significant between group difference was seen in future development of MAKEs. No differences in outcomes were observed between patients with point oliguria compared with persisting oliguria.

The work contained within this thesis thoroughly details the available literature on kidney injury within intensive care, summarises the features of kidney injury in a large cohort of patients admitted to ICU and demonstrates the significant increased risk it confers on in-hospital mortality, long-term survival, future adverse kidney events and future myocardial injury. It also characterises patients with AKD and describes the independently increased risk associated with it and in-hospital mortality and future MAKEs. This information can help clinicians to stratify patients at risk of future adverse outcomes. Future research could be expanded to include a much larger cohort of patients over a wider geographical region thus ensuring these increased risk profiles are not confined to patients solely from the West of Scotland. By helping to identify these high-risk patients, future work could aim to further detail AKD patients at routine ICU follow-up clinics by taking routine blood samples and urinalysis. The data obtained could be used to detect those patients with ongoing kidney dysfunction who may benefit from follow-up with expert nephrologists who could potentially implement therapy tailored to individual patients which may prevent progression to future adverse outcomes.

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- **Andonovic M**, Shemilt R, Sim M, Traynor JP, Shaw M, Mark PB, Puxty KA. Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis. *J Intensive Care Soc*. 2021 Feb; **22**(1): 67-77. DOI: 10.1177/1751143720901688

- **Andonovic M**, Traynor JP, Shaw M, Sim MAB, Mark PB, Puxty KA. Short- and long-term outcomes of intensive care patients with acute kidney disease. *EClinicalMedicine*. 2022 Feb 12; **44**: 101291. DOI: 10.1016/j.eclinm.2022.101291

Published Abstracts

- Singh S, **Andonovic M**, Traynor JP, Shaw M, Sim MAB, Mark PB, Puxty KA. Comparison of de-novo acute kidney injury in intensive care patients requiring and not requiring renal replacement therapy. *Intensive Care Medicine Experimental*. 2020; **9**(1): 000626

- Shemilt R, **Andonovic M**, Traynor JP, Shaw M, Sim MAB, Mark PB, Puxty KA. Incidence of de-novo renal injury in patients admitted to intensive care with sepsis and associated in-ICU and in-hospital mortality. *Intensive Care Medicine Experimental*. 2020; **9**(1): 000345

- Ross K, **Andonovic M**, Traynor JP, Shaw M, Sim MAB, Mark PB, Puxty KA. Acute kidney injury in patients with pre-existing diabetes admitted to intensive care. *Intensive Care Medicine Experimental*. 2020; **9**(1): 000355

- Watson T, **Andonovic M**, Traynor JP, Shaw M, Sim MAB, Mark PB, Puxty KA. Incidence and outcomes of acute kidney injury in patients admitted to intensive care with underlying cardiovascular disease. *Intensive Care Medicine Experimental*. 2020; **9**(1): 000412

Presentations

Presented at the Scottish Renal Association Annual Meeting, Dumfries, October 2019

- Systematic review and meta-analysis on optimal timing of initiation of kidney replacement therapy

Presented at Scottish Intensive Care Society Annual Meeting, St Andrews, January 2020

- Outcomes of patients requiring kidney replacement therapy for acute kidney injury in intensive care

- Outcomes of renal transplant patients admitted to intensive care

Presented at European Society for Intensive Care Medicine, Copenhagen (run virtually), October 2021

- Incidence and outcomes in patients suffering from acute kidney disease whilst admitted to intensive care

Preface

This work was initially conducted as part of a 2-year full time post as a clinical research fellow attached to the academic department of Anaesthesia, Critical Care and Perioperative Medicine in the University of Glasgow. I have subsequently continued this work as part of my role as a Clinical Lecturer in Anaesthesia and Critical Care.

Acknowledgement

I am sincerely grateful and indebted to my supervisory team of Dr Kathryn Puxty and Professor Patrick Mark for their unwavering support, encouragement, and advice during the entirety of this period of work. I am also extremely thankful to the additional support and advice provided by Professor Tara Quasim, Professor Malcolm Sim, and several other members of the University department of Anaesthesia, Critical Care and Perioperative Medicine throughout the period of my postgraduate studies.

I am grateful to the help provided by Dr Jamie Traynor in accessing and extracting the data, without which none of this work would be possible. Furthermore, I would like to extend my significant thanks to Dr Martin Shaw for his statistical advice throughout this work and my postgraduate studies.

I would like to acknowledge the work of Drs Sarjit Singh, Richard Shemilt and Jennifer Curle, who helped in certain aspects of data collection and interpretation which was vital to the completion of this thesis.

Finally, I wish to sincerely thank my wife and family for their unbelievable support throughout this time.

Author's Declaration

I declare that this thesis is entirely of my own composition, and that the work contained within is entirely my own unless stated otherwise. No part of this work has been submitted for any other degree or professional qualification.

The work within this thesis is not replicated elsewhere unless indicated. The appendix containing a systematic review and meta-analysis was published in the *Journal of the Intensive Care Society* in 2021 and an abridged version of the chapter describing the characteristics of the study population and the chapter detailing long-term outcomes was published in *The Lancet's EClinicalMedicine* journal in 2022.

Mark Andonovic

May 2022

List of Abbreviations

ABW	Actual body weight
ACP	Augmented Care Period
ADQI	Acute Dialysis Quality Initiative
AKD	Acute kidney disease
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology And Chronic Health Evaluation
CABG	Coronary artery bypass graft
CHI	Community Health Index
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CKRT	Continuous kidney replacement therapy
CPAP	Continuous positive airway pressure
CT	Computed tomography
CVP	Central venous pressure
CVS	Cardiovascular support
DNKI	De-novo kidney injury
eGFR	Estimated glomerular filtration rate

ECMO	Extracorporeal membrane oxygenation
EKF	Established kidney failure
GRI	Glasgow Royal Infirmary
HD	Haemodialysis
HDF	Haemodiafiltration
HDU	High dependency unit
HF	Haemofiltration
HFNO	High flow nasal oxygen
HR	Hazard ratio
ICU	Intensive care unit
IHD	Intermittent haemodialysis
IMV	Invasive mechanical ventilation
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
MAKE	Major adverse kidney event
MDRD	Modified Diet in Renal Disease
MI	Myocardial infarction
MOD	Multiple Organ Dysfunction

MODS	Multi-organ dysfunction syndrome
MPM	Mortality Prediction Model
MRI	Magnetic resonance imaging
NHS GG&C	National Health Service Greater Glasgow & Clyde
NIV	Non-invasive ventilation
OSF	Organ System Failure
OR	Odds ratio
PBW	Predicted body weight
PCI	Percutaneous coronary intervention
PH	Proportional hazards
PICS	Post Intensive Care Syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QEUH	Queen Elizabeth University Hospital
QoL	Quality of life
RCT	Randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss, End-stage
RR	Risk ratio
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score

SCI	Scottish Care Information
SERPR	Strathclyde Electronic Renal Patient Records
SICS	Scottish Intensive Care Society
SICSAG	Scottish Intensive Care Society Audit Group
SLED	Sustained low-efficiency dialysis
SMR	Standardised mortality ratio
SOFA	Sequential Organ Failure Assessment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
95% CI	95% confidence interval

Chapter 1 Introduction

1.1 Acute kidney injury

The kidneys are a vital organ for preserving homeostasis within the human body. They play a role in several essential functions which are integral to maintaining normal physiology such as the maintenance of appropriate fluid volume within blood, regulation of electrolytes found within the body, maintenance and correction of pH, excretion of waste or toxins and production of certain hormones which help regulate red blood cell production and salt and water balance. Whilst these functions can be used to alter the composition of blood and therefore affect blood flow both to other organs and to themselves, the kidneys are particularly susceptible to injury due to a variety of different pathological mechanisms.

To fully understand the potential implications of any injury to the kidneys, consideration must be given to exactly what the term “acute kidney injury” means and how it can be defined. This involves looking at the history of the term and where it first originated from.

1.1.1 Definition of acute kidney injury

Acute kidney injury (AKI) is an evolution of the term “acute renal failure” which was first documented in studies dating back to the 1950s (1, 2). Whilst this term was widely utilised until the turn of the millennium (3), it was primarily used to broadly describe a rapid-onset failure of the kidneys’ ability to concentrate and produce urine due to a variety of reasons. As a result, there was no definition which existed to identify any injury which occurred to the kidneys which did not result in “failure”, over 30 differing definitions, and no criteria by which to quantify the severity of this injury. This changed in 2004, when the Acute Dialysis Quality Initiative (ADQI) workgroup proposed the concept of acute kidney injury and a method to help determine the extent of the injury: the RIFLE criteria (4).

1.1.1.1 RIFLE Classification

The RIFLE classification system was designed to categorise the varying severity of damage to the kidneys following an acute insult (4). This brought into sharper focus the idea of an AKI: an abrupt insult or injury to the kidneys which results in a structural change or a reduction in function and is often multifactorial (5). The term RIFLE is an acronym used to describe either the extent or length of kidney injury: R for risk; I for Injury; F for Failure; L for Loss; and E for End-Stage. The latter two of these are used to classify prolonged reduction in kidney function. The loss category is defined as persistent acute kidney failure for greater than four weeks; end-stage refers to end-stage kidney disease, which is also defined as long-term requirement for kidney replacement therapy (KRT) such as haemodialysis or peritoneal dialysis (Table 1.1).

Stage of injury	Creatinine/eGFR criteria	Urine output criteria
Risk	Serum creatinine increased 1.5 times from baseline OR eGFR decrease by 25%	Urine output less than 0.5ml/kg/hr for 6 hours
Injury	Serum creatinine increased 2 times from baseline OR eGFR decrease by 50%	Urine output less than 0.5ml/kg/hr for 12 hours
Failure	Serum creatinine increased 3 times from baseline OR eGFR decrease by 75% OR serum creatinine greater than 353.6 micromoles/l	Urine output less than 0.3ml/kg/hr for 24 hours OR anuria for 12 hours
Loss	Persistent Failure or complete loss of function for 4 weeks	
End-stage	End-stage kidney disease for 3 months	

Table 1.1: Stages of AKI according to RIFLE criteria

The other categories of risk, injury and failure are used to classify the severity of acute kidney injury which has occurred. These categories also broadly form the basis for current up to date international guidance on the classification of severity of kidney injury. Classification is done using either of two criteria: urine output and changes in serum creatinine levels. Urine output can be measured accurately using a urinary catheter attached to a container which quantifies the volume of urine produced and excreted from the body. If this is

done accurately every hour, acute kidney injury can be diagnosed when the volume produced drops below a certain value.

Creatinine is a non-protein nitrogenous compound which is produced following the normal breakdown of creatine phosphate from both protein and muscle metabolism. It is filtered efficiently by the kidneys, minimally reabsorbed back into the body and excreted unchanged. Measurement of creatinine concentrations in both the urine and blood can be used to calculate creatinine clearance; as a result of the way it is handled by the kidneys, this is a very effective approximation of the rate at which the kidneys can filter blood, referred to as glomerular filtration rate. Using only measurements taken from blood samples, this value can be estimated using a single creatinine value which is referred to as estimated glomerular filtration rate (eGFR); whilst this is a useful marker of chronic kidney function, the value is only really of use in steady state conditions. These values are serum values: serum is the liquid portion of blood which remains after cells have been removed and the blood has clotted. Serum creatinine can be easily measured in micromoles per litre using standard laboratory analysis widely available in the UK.

Following the creation of the RIFLE criteria in 2004, multiple studies were performed in the following years to ascertain how it performed in both defining and determining the severity of AKI. These used the new criteria to assess incidence of AKI along with outcomes which may be associated with either the presence of kidney injury or more severe injury (6-9). Whilst these studies found that RIFLE criteria performed well in identifying and stratifying degree of kidney injury which correlated with poorer short- and long-term outcomes, within a few years an alternative classification system was created.

1.1.1.2 AKIN Classification

In 2007, the Acute Kidney Injury Network (AKIN) met to discuss the most recent evidence available for the identification and management of AKI (10). Their workgroup devised a new classification system referred to as the AKIN criteria. The system was again based upon the two variables of changes in serum creatinine values and measured urine output over a set time period. However, the values involved were slightly different from RIFLE criteria. In addition, the

equivalent classes of Risk, Injury and Failure were defined as stage 1, stage 2 and stage 3 injury respectively (Table 1.2).

Stage of injury	RIFLE Stage	Creatinine criteria	Urine output criteria
Stage 1	Risk	Serum creatinine increased 1.5 times from baseline OR serum creatinine increased by 26.5 micromoles/l	Urine output less than 0.5ml/kg/hr for 6 hours
Stage 2	Injury	Serum creatinine increased 2 times from baseline	Urine output less than 0.5ml/kg/hr for 12 hours
Stage 3	Failure	Serum creatinine increased 3 times from baseline OR serum creatinine greater than 353.6 micromoles/l	Urine output less than 0.3ml/kg/hr for 24 hours OR anuria for 12 hours

Table 1.2: AKIN criteria and equivalent RIFLE stage for AKI

The rationale behind the release of the AKIN criteria was stated as aiming to increase the sensitivity and specificity of the diagnosis of AKI (11). However, due to the relatively short time period between its release and the release of the RIFLE criteria, this created ambiguity as to the best criteria to use. In the years that followed, multiple studies were carried out to attempt to validate these new criteria and compare it with RIFLE criteria (11-15). Whilst the incidence of AKI identified were similar between the two classification systems, there remained a disparity in almost all studies that were conducted. As a result of this, the primary goal of creating a unifying definition for AKI remained uncertain. In addition, subsequent studies often defined AKI using one of these two systems, therefore comparison of the literature became more problematic due to studies defining AKI differently from each other. In an effort to combat the confusion, a workgroup met in 2012 with the goal of merging the RIFLE and AKIN systems and creating a unifying set of criteria which could be used as the standard from that point forward.

1.1.1.3 KDIGO Classification

The Kidney Disease Improving Global Outcomes (KDIGO) workgroup met in 2012 to address the problem of how to define AKI. They produced a wide-ranging AKI

guideline covering multiple facets of the phenomenon including diagnosis, staging of severity, prevention, treatment and dialysis interventions (16). The criteria produced with regards to diagnosis of AKI was designed to incorporate elements of both the RIFLE and AKIN criteria. As with both prior classification systems, diagnosis is dependent on changes in serum creatinine values or measurement of urine output. This guideline created the currently most accepted internationally recognised criteria to both diagnose and stratify the severity of AKI (Table 1.3).

Stage of injury (KDIGO and AKIN)	RIFLE Stage	Creatinine/KRT criteria	Urine output criteria
Stage 1	Risk	Serum creatinine 1.5-1.9 times baseline OR serum creatinine increased by 26.5 micromoles/l	Urine output less than 0.5ml/kg/hr for 6 or more hours
Stage 2	Injury	Serum creatinine 2.0-2.9 times baseline	Urine output less than 0.5ml/kg/hr for 12 or more hours
Stage 3	Failure	Serum creatinine 3.0 times baseline OR serum creatinine greater than 353.6 micromoles/l OR initiation of kidney replacement therapy	Urine output less than 0.3ml/kg/hr for 24 hours OR anuria for 12 hours

Table 1.3: KDIGO criteria for diagnosing and staging AKI along with AKIN and RIFLE equivalent

In the wake of the publication of the KDIGO AKI guideline, the majority of research in this field has utilised its diagnostic criteria. Several large international studies to determine the incidence of AKI and their subsequent outcomes found that KDIGO criteria performed well at recognising kidney injury and that increasing severity correlated with worse outcomes (17-19). These studies helped to validate this new method of diagnosing AKI and identified it as the most currently accepted methodology for present and future studies. However, it is important to consider that whilst these remain the most accepted guidelines currently in use, there remain certain aspects which limit their use in clinical practice.

1.1.1.4 Limitations of current AKI guidelines

The complex interactions in kidneys often make it difficult to identify the ideal marker from which to estimate GFR: the amount of molecule remaining in urine will depend on its molecular weight, ionic charge, degree of protein binding and how it is handled within the nephron after it has been filtered at the glomerulus. An ideal marker would be freely filtered at the glomerulus and exhibit no reabsorption, secretion or metabolism within the nephron (20). Historically, a polysaccharide molecule called inulin was considered the gold standard for this (21). However, measurement of inulin clearance to determine eGFR is exceptionally cumbersome, as it requires a continuous and prolonged infusion of inulin and two or more recurrent urine samples to accurately determine its clearance (22).

As creatinine is an endogenously produced molecule, it lends itself to random sampling for estimated GFR in routine clinical practice. However, it is not considered an ideal marker as it undergoes a degree of tubular secretion and therefore serum levels are slightly lower than they would otherwise be with filtration only (23). Certain medications such as the anti-histamine medication Cimetidine can block the transporter within the kidney tubular cells and prevent the secretion of creatinine thereby provide a more accurate reflection of GFR, but this is again cumbersome and not reflective of routine clinical practice (23).

In addition to tubular secretion making creatinine a less reliable measure of glomerular filtration, several other factors exist which can confound the implementation of the AKI guidelines and potentially reduce the diagnostic sensitivity. As previously discussed, creatinine is produced following the normal breakdown of creatine phosphate from both protein and muscle metabolism: this means that serum levels are directly influenced by either increases or decreases in muscle metabolism. In the context of critical illness, this is a significant factor, as muscle wasting is accelerated in prolonged critical illness and can lead to profound drops in serum creatinine levels (24). This drop may suggest that eGFR has improved towards baseline levels, when in fact it may have remained static or even worsened.

Using KDIGO guidelines also relies on an accurate definition of baseline creatinine. Several methods that attempt to define this have been suggested, but they rely on some measure of creatinine ideally at a point with no ongoing acute disease process. If this value is from too long ago, such as several years, it may reflect a point at which the kidneys had a higher eGFR than they were just prior to their acute admission. Conversely, if the value is taken to close to their admission, then it may represent kidneys which have already suffered an insult and therefore misrepresent a baseline eGFR which is too low. To that end, NHS England currently uses an automated system which primarily utilises a median serum creatinine value from the preceding 8-365 days to define the baseline value: this has been shown to have a high degree of sensitivity when it was validated using hospital discharge coding for AKI (25).

Whilst the urine output values for diagnosing AKI have remained constant across the three suggested definitions, these again suffer from some limitations in their use in clinical practice. Accurate hourly measurements require patients to have a urinary catheter in place: whilst this may be very common for patients admitted to ICU, it is not a standard of care and requires a clinical indication. Furthermore, hourly urine output values rely on meticulous technique replicated every hour to ensure all urine in the catheter tubing has drained into the collection chamber, and that it is measured exactly one hour after the previous value. In busy ICU environments, this is unlikely to be the case across every patient as they may have other overriding clinical priorities. Due to these potential inaccuracies, urine output is rarely used in studies which investigate the incidence of AKI. Despite these limitations, the KDIGO guidelines remain the most accurate and internationally accepted for diagnosing AKI. Within these guidelines to aid diagnosis of the presence of AKI, KDIGO guidelines also produced a consistent set of rules in order to differentiate the severity of injury.

1.1.2 Stages of AKI

As referenced above, different classification systems have used varying systems for defining severity of AKI. The RIFLE system (4) grouped injury as Risk, Injury and Failure as opposed to AKIN (10) and KDIGO (16), which both chose to define severity as stage 1 (correlating to RIFLE-Risk), stage 2 (correlating to RIFLE-Injury) and stage 3 (correlating to RIFLE-Failure). When looking specifically at

the KDIGO criteria as the currently accepted international standard, stage 1 injury is the least severe as opposed to stage 3 injury which is the most severe. Increasing severity of injury is determined according to how significant changes in serum creatinine levels are or by how much urine output has reduced over a specified time period.

Changes in serum creatinine levels can be measured in two different ways – absolute rise in the value from baseline or magnitude in change from baseline. Concentrating on serum creatinine only, stage 1 injury is defined as follows: absolute increase of at least 26.5 micromoles per litre or 1.5 to 1.9 times the baseline value. Stage 2 injury can only be diagnosed if serum creatinine has risen to 2.0 to 2.9 times the baseline value. Stage 3 injury is defined as a rise in serum creatinine to 3.0 times the baseline value or an increase to an absolute value of 353.6 micromoles per litre. In addition, stage 3 injury can also be diagnosed upon the initiation of kidney replacement therapy for an acute cause.

Urine output criteria can be applied over a period of 6 hours ranging to 24 hours depending on the volume produced; an accurate weight is also required to utilise these criteria. Stage 1 injury is defined as less than 0.5 millilitres per kilogram body weight per hour for a period of 6 to 12 hours. Stage 2 injury is diagnosed if the above criteria is met for greater than 12 hours. Stage 3 injury is classed as a patient who has had a urine output of less than 0.3 millilitres per kilogram body weight per hour for a period of 24 hours or more. Stage 3 injury can also be diagnosed if the patient has produced no urine for a period of 12 hours or longer. This classification system is designed to identify the most severe injury: therefore, if a patient meets the criteria for a stage 1 injury based on urine output but a stage 3 injury based on serum creatinine, they have suffered from a stage 3 AKI. Similarly, if a patient has a rise of 1.7 times their baseline creatinine but that value takes them over the 353.6 micromoles per litre threshold, they have suffered from a stage 3 injury (Table 1.3).

The importance of staging of injury has become apparent ever since the original RIFLE criteria was produced; multiple studies have demonstrated that no matter which classification system is used, the rates of short- and long-term mortality increase as the severity of AKI increased (26-30). In addition to this, multiple studies examined the association between a single episode of AKI and the effect

on long-term kidney function; all these studies supported the hypothesis that stage 3 injury (or RIFLE-Failure) were more likely to result in poorer kidney function on long-term follow up compared to less severe AKI (31-34). The effect of AKI as a syndrome with significant consequences for patients is well documented; it is also important to consider the various pathologies which can lead to AKI.

1.1.3 Causes of AKI

Whilst the cause of AKI is often multifactorial, especially in the context of critical illness, pathophysiology of the condition is often separated into three broad categories: pre-kidney, intra-kidney and post-kidney (35). Individual causes within these groups can also be classified according to aetiology such as hypoxia or nephrotoxicity, but these also have various potential underlying mechanisms (36). Pre-kidney AKI is caused by reduced perfusion of the kidneys: this can be due to loss of circulating blood volume (as seen in haemorrhage or reduced fluid intake), impaired cardiac function (seen in acute myocardial infarction or congestive heart failure) or reduced systemic vascular resistance (seen in sepsis or cirrhotic liver disease) (35).

Intra-kidney AKI can be further grouped based on the structures within the kidneys that are affected: kidney tubules, glomeruli, interstitium and intra-kidney blood vessels (37). Kidney tubules are the structures most commonly affected by ischaemia and nephrotoxic drugs; certain medications such as various antibiotics or non-steroidal anti-inflammatory drugs can also affect the kidney interstitium. Acute glomerulonephritis is the most common conditions affecting glomeruli, whereas small intra-kidney blood vessels can contribute to AKI when affected by vasculitis.

Using the above structure for classifying intra-kidney AKI can provide a framework for identifying the various pathophysiological processes which can contribute to AKI. The most common cause of tubular damage results from kidney ischaemia, and the structural associations between the outer medulla and the tubules renders them highly susceptible to injury (37). Multiple changes occur at a cellular level as a result of ischaemia, with both vascular and kidney tubular epithelial cells unable to maintain adequate intracellular levels of

adenosine triphosphate which are required for essential processes (36). This depletion leads to cell injury and cytoskeleton disruption followed by cell apoptosis or necrosis if hypoxia is severe enough. The cellular shedding, loss of tight junctions and cytokine release which results from this can instigate tubular obstruction and back-leak and ultimately trigger a reduction in eGFR and concentrating ability of the kidneys (36). The mechanism of injury due to hypoxia is often supplemented by a significant inflammatory response activated by the initial ischaemic insult; this leucocyte activation and subsequent cascade can lead to initially reduced microvascular flow which can then exacerbate hypoxia within the local environment.

Nephrotoxic agents are another common cause of intra-kidney AKI in ICU. Depending on the causative agent, multiple structures within the kidneys can be affected. Aminoglycoside antibiotics are commonly used in the context of treatment for sepsis: these have direct chemical nephrotoxicity against kidney tubular cells (38). However, certain agents can also induce an immune mediated response which can lead to inflammation in both the tubules and the interstitium. Vascular tone can be strongly affected by multiple medications commonly in use in the community such as angiotensin converting enzyme inhibitors, and these can precipitate reduced blood flow to the kidneys during critical illness which may further exacerbate the injury caused by the initial insult (38). Finally, drug metabolites may crystallise within the tubules themselves, leading to an obstructive nephropathy within the kidney rather than in the kidney outflow tract.

Post-kidney AKI is caused by obstruction of the kidney outflow tract at any point between the kidneys and the urethra; this causes a blockage in urinary flow which thereby leads to increased intra-tubular pressure and thus decreased glomerular filtration (37). In addition, acute obstruction can lead to impaired kidney blood flow and further contribute to kidney damage (39). Obstruction of the kidney outflow tract can either be due to blockage within the urinary collection system (such as nephrolithiasis or a ureteric tumour) or from pathology outside the urinary collection system (such as benign prostate hypertrophy or cervical cancer). AKI in the context of critical illness is usually caused by a combination of pre- intra- and post- kidney aetiologies, all of which

can have different underlying pathologies contributing to making a patient systemically unwell (40).

1.1.4 Prognostic implications of AKI

The importance of AKI as a significant event has been highlighted in a large body of work conducted internationally over the past decade; these studies agree that onset of AKI is associated with both a higher resource utilisation and risk of death than patients without AKI (6, 41). Multiple studies have examined in-hospital mortality comparing patients with AKI to patients without: a retrospective observational study including over 500,000 patients by Bedford et al. showed a significant increase to mortality risk based on both presence and severity of AKI (42). Analysis of long-term outcomes in the same study population showed an ongoing association with development of AKI and reduced long-term survival. Beyond the impact of AKI on both short- and long mortality, there is suggestion that it has potentially long-lasting systemic effects on both the immune system and cardiovascular system (43, 44).

Given the long-lasting consequences of such disease and how its course can result in vastly different outcomes, the AKI guideline produced by KDIGO suggested the principle of acute kidney disease (AKD) as a greater spectrum of disorders which encompasses AKI. Whilst this was first proposed in 2012, the concept was not formally defined until 2017 (16, 45).

1.1.5 Acute kidney disease

1.1.5.1 Definition of acute kidney disease

The ADQI workgroup met again in 2017 to discuss how AKI fits in to the wider disease process (45). As discussed above, definition of AKI and its severity were well recognised at this point. An additional, important concept that was well established was chronic kidney disease (CKD), also known as persistence of kidney disease (either structure or function) for a period of 90 days or longer with implications for health (46). Whilst there had been prior research conducted into how the length of injury affects outcomes (47-49), there was a growing recognition that AKI that recovered quickly should be considered as a separate entity to “prolonged or “persistent” AKI. Thus, the ADQI workgroup

proposed a continuous spectrum of the disease process, encompassing rapid-reversal AKI recovering within 48 hours through to CKD with sustained disease at 90 days or longer. This primary reason for this was a recognition that whilst AKI was a significant clinical event, there was a subset of patients for which this persistent injury may have far greater implications for health over the longer term (50).

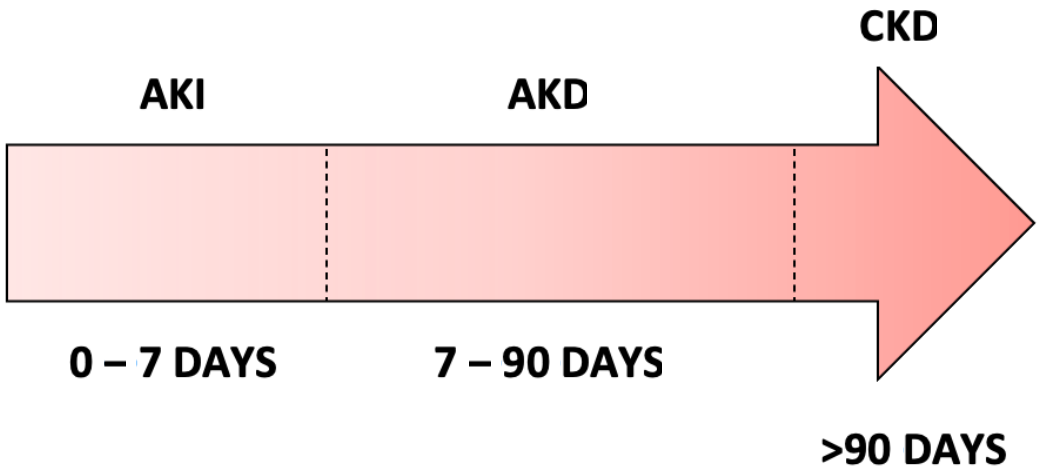


Figure 1.1: Summary of proposed continuum of kidney disease

The ADQI workgroup defines AKD as an acute kidney injury meeting established KDIGO AKI criteria lasting for 7 days or longer (45). This in turn differentiates it from AKI which is defined as an injury which lasts 6 days or shorter. The rationale behind this definition was to bridge the gap between AKI and CKD in what is felt to be the continuum of a singular disease process (Figure 1.1). To date, there is a paucity of available data on this subject: prior studies have looked at trajectories of kidney recovery depending on length of initial injury (51), but due to the definition of AKD being relatively novel, very little research has addressed the impact of AKD compared to short-term AKI. Part of this is due to the historical difficulty in defining "kidney recovery", with multiple wide-ranging definitions previously suggested involving both eGFR and serum creatinine levels and comparing absolute levels with changes from baseline.

1.1.5.2 Definition of kidney recovery

Part of the goals of the ADQI workgroup involved defining kidney recovery, as it was integrally linked with future research into AKD. Previous definitions

include: serum creatinine dropping to below baseline value + 44 micromoles/millilitre (52); serum creatine value returning to within baseline value + 25% (53); and eGFR at discharge of at least 90% of baseline (54). Due to the variation in definition, prior research on kidney recovery and length of kidney injury has been difficult to compare. One proposed definition during the 2017 workgroup was to categorise kidney recovery as being when patients no longer met the criteria for any stage of AKI (45). They suggested at this point that subacute AKI/AKD (stage 0) may still exist; for example, if serum creatinine has returned to normal levels but still have evidence of kidney damage or injury using alternative biomarkers. As many of these biomarkers are still undergoing research to determine their validity, ongoing subacute injury is difficult to quantify.

Whilst the definition of kidney recovery as "no longer fulfilling criteria for having an acute injury" would appear to be the most logical, it suffers from some limitations. The diagnosis of AKI based on serum creatinine changes from a pre-morbid state to the current timepoint is more likely to only be influenced by the disease process and its effect on the filtration ability of the kidneys. However, once AKI is identified in a hospital setting, a number of external factors can then influence a potentially artificial return of serum creatinine to normal. These include: loss of muscle mass which would reduce amount of creatinine produced rather than indicate an increase in filtration and excretion (55); increase in intravenous fluid input by clinicians managing other disease processes can cause increased blood volume and a subsequent decrease in creatinine concentration (56, 57); reduced production of creatinine as a result of other concurrent pathophysiological processes (58); and changes in kidney reserve as a result of the acute process (59). To fully understand exactly how these factors can be influenced by acute illness, consideration must be given to the concept of severe illness, and how this is most commonly managed within a specialised area of medicine: intensive care medicine.

1.2 Intensive Care Medicine

Intensive care medicine is an area of medicine which specialises in the care of critically unwell patients. As a result of this, patients admitted to the intensive care unit (ICU) are often found to suffer from damage to one or more organs

which may require treatment which is not available in other hospital wards. This means that rates of kidney injury within ICU are high, as are mortality rates. ICUs have specific systems for monitoring the physiological status of patients and therefore are well placed to track organ function and identify injury and recovery using a number of available variables. It is therefore important to appreciate the origin of intensive care medicine and what organ support ICUs can provide.

1.2.1 Definition of Intensive Care Medicine

ICUs are specialised areas of the hospital (sometimes referred to as critical care or intensive therapy units) which look after patients with conditions which are acutely life-threatening and usually accommodate the sickest patients within the hospital. These patients require constant 24-hour monitoring with increased staffing levels who are trained in the management of severely unwell patients. In addition, specialist treatment and monitoring can be instigated which are unavailable in any other area of the hospital.

The origins of intensive care medicine can be traced back to the polio epidemic in the 20th century. During an outbreak in Denmark in the 1952, several hundred patients were admitted to Blegdam hospital in Copenhagen over a period of several weeks (60, 61). Polio infection had resulted in these patients developing respiratory muscle paralysis and bulbar palsy which led to pooling of secretions and respiratory failure. At the time the predominant mechanism of artificially ventilating patients was using negative pressure ventilation; patients would be enclosed in a respirator which then generated a negative pressure outside their body to expand the lungs and cause inspiration of oxygen. An anaesthetist, Dr Bjorn Ibsen, instead suggested managing these patients by intubating the trachea with a cuffed rubber tube and instead applying intermittent positive pressure to ventilate patients. Over 1,000 medical and dental students were recruited to hand ventilate these patients; the mortality of the 316 patients who received this management was found to be approximately 40%, compared to the estimated 85-90% mortality throughout the polio population with respiratory failure (60). The following year, Dr Ibsen set up the world's first ICU which marked the foundation of intensive care medicine.

Whilst the adoption of ICUs was embraced globally over the following decades, consideration must be given to what intensive care medicine means in certain countries compared to others. Due to differences in healthcare systems and available budgets, the number of intensive care beds per capita can vary drastically; a recent study from 2020 found that USA has 34.7 critical care beds per 100,000 inhabitants compared to 6.6 per 100,000 in the UK (62). This inherently changes the patient population due to the difference in availability of beds, with longer hospital stays prior to admission, higher percentages of mechanically ventilated patients and greater severity of illness on ICU admission in the UK compared to the USA. Given how different the patient cohort can be as a result of this, it can be difficult to compare studies of the ICU population from different countries. Therefore, considering the focus of this study, it is important to understand what the ICU population comprises of in the UK.

1.2.2 Critical care and organ support

The UK Department of Health produced guidelines in 2000 to help quantify the level of care which is required by individual patients (63). These encompassed four levels of care across all hospital inpatients:

- Level 0 - Patients whose needs can be met through routine/basic care.

- Level 1 - Patients requiring higher levels of care or are at risk of their condition deteriorating, whose needs can be met with advice and support from the critical care team.

- Level 2 - Patients requiring higher levels of care and more detailed observation/intervention. They may have a single failing organ system or require post-operative care.

- Level 3 - Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes complex patients requiring support for multi-organ failure.

Within the UK, level 1 or level 2 care is usually managed in a high dependency unit (HDU), whereas level 2 or level 3 care is delivered in ICUs – 62% of patient episodes in ICU recorded throughout Scotland over 2019 were categorised as level 3, with the vast majority of other episodes recorded as level 2 (64). The delivery of care in ICU revolves around the treatment of critical illness – an illness which impairs the ability of vital organs to function properly. Due to the nature of the underlying diseases which can cause this, much of intensive care medicine is focussed on supporting these various organ systems whilst either giving time for the appropriate treatment to take effect, or time for the body to recover from the initial phase of the illness. To fully explore the scope of what intensive care medicine can offer, the various support mechanisms for individual organ systems must be explored.

1.2.2.1 Respiratory support

The respiratory system is primarily responsible for exchange of important gases between the air inspired into the lungs and the blood. This takes place across the thin alveolar membranes which form the endpoint of the airways which allow passage of air from the mouth into the lungs. The gas exchange which occurs is primarily the movement of oxygen from these alveoli into the bloodstream in order to provide oxygen to the various tissues of the body and diffusion of waste carbon dioxide from the bloodstream into the alveoli so it can be expired. In awake and spontaneously breathing patients, this process occurs by generating negative pressure to draw air into and inflate the lungs.

Simple support for respiratory failure can be delivered by means of supplemental oxygen using either a facemask or nasal cannula. These devices can either use a set flow of oxygen but an uncertain concentration, or they can be set up to deliver a known concentration of oxygen. In more severe cases of respiratory failure, specialised equipment can provide more support such as high-flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV). Additional treatment can be delivered using invasive mechanical ventilation (IMV) by way of intubating the trachea with an endotracheal tube followed by positive pressure ventilation using a ventilator. The delivery of most of these treatments is usually confined to either HDU or ICU, with IMV requiring admission to ICU.

1.2.2.2 Cardiovascular support

The cardiovascular system comprises of the heart and the blood vessels which carry blood around the body. Blood travels from the right side of the heart through the lungs to collect oxygen, back to the left side of the heart before being pumped round the body to deliver oxygen to the tissues. The cardiovascular system therefore works closely in tandem with the respiratory system to ensure adequate oxygen delivery throughout the body. It achieves this through a combination of the preservation of the correct volume and composition of blood, effective contraction of heart muscle to propel the blood forward, and maintenance of the appropriate diameter of blood vessels throughout the body.

Cardiovascular support (CVS) is wide-ranging and encompasses management of the various aspects of the cardiovascular system referred to above. Due to the nature of critical illness and the multiple underlying pathophysiological changes associated with the variety of precipitating diseases, maintenance of adequate blood volume, blood vessel tone and heart contractility may all be affected. Blood volume and composition can be supported through administration of intravenous fluids and, if required, blood products. Support of inadequate muscle tone within the blood vessels can be delivered using infusions of vasoactive agents which work to increase the resistance of these vessels and therefore increase blood pressure. Inotropic agents can be given to support a damaged heart which is unable to produce enough muscle tone to pump blood effectively. Beyond these measures, mechanical support can be provided in the form of an intra-aortic balloon pump or ventricular assist devices; these are usually only implemented in ICUs specialised in dealing with cardiac care. Continued, appropriate haemodynamic management is essential in intensive care to ensure preserved blood flow to the vital organs; prior literature in this area has shown that high-quality haemodynamic management is effective in reducing patient mortality (65, 66).

1.2.2.3 Kidney support

The kidney system comprises of the kidneys and the subsequent excretion of urine. The role of the kidneys has been covered extensively above, but they are

primarily responsible for the filtration of blood in order to help maintain fluid balance and remove waste products from the body. Due to its role in controlling fluid volume, the kidney system is intrinsically linked with the cardiovascular system as it can be a determining factor in the circulating volume of blood. Undesirable waste products produced in the body are filtered through the kidney and then travel to the bladder where they can be excreted in urine. Due to this, if the kidneys are damaged and unable to filter these toxins such as in AKI, build-up occurs within the body which can begin to cause problems with other major organs.

Monitoring of the kidney system in ICU is primarily done through two main mechanisms: continuous monitoring of urine output and intermittent blood tests to assess concentrations of common waste products within the bloodstream. Urine output is measured hourly using a catheter inserted into the bladder which drains urine into a canister which measures volume. Blood tests can be taken regularly to assess the concentration of creatinine, urea and electrolytes and the absolute values combined with their trends over time can then be used to infer the relative function of the kidneys.

Support of the kidney system is dependent on identifying the precipitating causes and directing treatment to manage this. Acute kidney injury is often caused by three broad factors: inadequate blood flow due to either low circulating blood volume or low blood pressure (known as pre-kidney), direct damage to the functional units of the kidneys (known as intra-kidney), or an obstruction preventing the flow of urine from either the kidney to the bladder or from the bladder to outside the body (known as post-kidney). Simple management of these causes can include administration of intravenous fluids to improve blood volume, cardiovascular support using vasoactive medications to improve blood pressure, or removal of a cause of obstruction preventing outflow of urine.

More advanced kidney support can be instigated in patients with severe injury: kidney replacement therapy (KRT). KRT involves removal of fluid and toxins from the body which would normally be carried out by the kidneys. This can either be done by passing the blood through an external machine which removes toxins and fluid or by filling the abdominal cavity with fluid which waste

products can filter into before the fluid is removed again. Whilst KRT is regularly carried out in kidney wards due to patients requiring it long-term for CKD, any patient with multi-organ failure or critical illness will most commonly have KRT initiated in ICU.

KRT performed in ICU is most often done by external removal of toxins from the blood. This can be performed in a variety of different ways: intermittent haemodialysis (IHD), sustained low efficiency dialysis (SLED) or continuous kidney replacement therapy (CKRT); haemodialysis (HD), haemofiltration (HF) or haemodiafiltration (HDF); and low-dose vs high-dose KRT. Multiple theoretical benefits have been postulated around which modality is superior, however prior studies have found no difference in mortality depending on continuous vs intermittent (67) or dialysis vs filtration (68). Consequently, modality of KRT will often differ depending on which ICU has initiated it, circumstances of the individual patients and staff familiarity of the various methods.

As well as differing KRT modalities in critical care, the indications for initiation of KRT can also differ; there has been recent debate as to whether KRT should be commenced “early” or “late” (69). Consequently, physicians differ on whether to start KRT at a certain time period after identification of AKI or when a patient reaches a certain stage of AKI. Physicians adopting a “late” approach to commencing KRT will often wait for the patient to reach a circumstance that necessitates the removal of fluid, electrolytes or toxins from the blood. These criteria are commonly quoted as: high concentrations of potassium in blood which have failed to respond to standard medical treatment; high blood concentrations of urea; blood acidosis due to a metabolic cause; or fluid overload resulting in respiratory compromise (70, 71).

1.2.3 Severity of illness and organ failure

Significant research in the area of intensive care medicine has been conducted on how unwell patients are and if this can be used to quantify their chances of survival. The intensive care population varies widely depending on locale and it can often be difficult to compare patient cohorts internationally. To combat this, specialists in intensive care medicine in the 1980s developed multiple methods to assess for severity of illness and attempt to predict the likelihood of

surviving to hospital discharge (72). The ideal scoring system would incorporate the following features (73): based on easily recorded variables; well calibrated; highly discriminatory; applicable to all ICU patient populations; can be used internationally; and able to predict quality of life after ICU discharge.

Outcomes following intensive care are usually dependent on three broad factors: the underlying health conditions, variables on initial presentation to ICU and required support during ICU stay. Several ICU scoring systems utilise data collected from the first 24 hours in ICU: Acute Physiology and Chronic Health Evaluation (APACHE) (74); Simplified Acute Physiology Score (SAPS) (75); and Mortality Prediction Model (MPM) (76). In addition to the above, other scores have been developed which periodically assess the degree of organ dysfunction daily either for the entire ICU admission or for the first 72 hours. These systems assess physiological parameters daily and include: Organ System Failure (OSF) (77); Sequential Organ Failure Assessment (SOFA) (78); and Multiple Organ Dysfunction score (MOD) (79). Within the record systems in place across Scottish ICUs, only APACHE II score is widely documented and therefore available for this study.

1.2.3.1 APACHE severity scoring

The original APACHE score developed in 1981 was the first example of a score attempting to quantify severity of critical illness (74). In the subsequent decades, it has been altered to improve the validity and accuracy of the predicted in-hospital mortality. The APACHE II score was first detailed in 1985 (80), and is currently the most commonly used score throughout UK ICUs. Whilst a further development of the APACHE scoring system (APACHE III) was released in 1991 (81), it has not been adopted throughout the UK to the same extent.

The APACHE II name derives from the components which are used to calculate the severity score, which is in turn used to estimate the likelihood of dying during the current hospital admission. The score is calculated using admission diagnosis and existing comorbidities (both from a rigorous, pre-defined list) and physiological parameters collected within the first 24 hours of ICU admission; the score itself ranges from 0 to 71 points and the predicted mortality estimates the in-hospital mortality for that particular patient compared to other patients

with the same severity of illness. Since they use variables from the 24 hours after admission, these scores cannot be used to aid decisions regarding suitability for ICU admission.

As a determinant of ICU survival, the APACHE II scoring system has been validated on numerous occasions. Initial data from 1993 assessed how the APACHE II predicted mortality compared to actual mortality in over 16,000 patients and found that the ratio of observed to predicted number of deaths varied from 0.67 to 1.21 across various ICUs (82). In the decades that followed, improvements in data collection have resulted in increased accuracy of the prediction model, with it comparing similarly to the alternative methods of assessing disease severity (83-86). Importantly, this scoring system is only validated in estimating in-hospital mortality, and as recent data has demonstrated there is no association with higher APACHE II scores and long-term outcomes (85).

1.3 Outcomes following ICU admission

1.3.1 Short-term outcome after ICU admission

Due to the fact that ICU frequently looks after the sickest patients in the hospital, and as a reflection of the serious nature of critical illness, the mortality rates in ICU are high. In 2019, the overall crude hospital mortality rates of patients admitted to all Scottish ICUs was 17% (64). The majority of these deaths occurred prior to ICU discharge (approx. 14% of all patients) with the remainder of patients dying at some point between discharge from ICU and ultimate hospital discharge.

There has been a gradual decreasing trend in mortality in ICU over the past decade. In 2010, 25% of ICU admissions died prior to discharge from hospital. This compares to a 17% mortality rate in 2019, which was slightly reduced from the 19% in 2017 and 18% in 2018. This is in spite of a gradual increase in ICU admissions over the past 10 years: approximately 12,000 patients were admitted to Scottish ICUs in 2019 compared to 9,800 in 2010. This is partly a consequence of providing ICU care to patients with lower severity of illness: care of these patients is sometimes delivered in combined ICU/HDU areas which report all

patients within the ICU cohort. These combined units have become more commonplace over this time period and the lower severity patients account for a larger proportion of the newer "ICU" cohort. Nevertheless, a more objective measure of mortality referred to as Standardised Mortality Ratio (SMR) is calculated by dividing observed mortality by the expected mortality using the APACHE II methodology described above; this has also showed a consistent downward trend over the past decade (64).

A multitude of factors have been linked with affecting rates of mortality within intensive care. Amongst these, increasing age strongly correlates with an increase in mortality (87-90) and an increase in just 1 year has been associated with up to a 4% increase in mortality. Other factors such as patient sex have been implicated in influencing mortality rates; female sex has been identified as protective (OR=0.57) for all-cause mortality in trauma patients admitted to ICU (91). Medical admitting specialties have been described as having approximately 1.5 times increase in all-cause mortality (53% vs 34%) (92).

Illnesses precipitating admission to ICU can also carry a significantly different risk profile for both short- and long-term mortality (93): Zimmerman et al. looked at almost 500,000 ICU admissions across 15 years and found that cardiac arrest and intracerebral haemorrhage had persistently higher raw mortality rates over the study period compared with other diagnoses (94). Pre-existing comorbidities such as cardiovascular disease and diabetes have also been strongly associated with increased mortality in patients admitted to ICU (95-97). Considering the exhaustive evidence produced demonstrating how these factors can alter mortality, it is essential that analysis of any outcomes of ICU patients account for these factors to determine if differences between pre-determined groups is significant.

1.3.2 Long-term outcomes after ICU survival

The effect of critical illness is both profound and long-lasting. Significant research has been conducted in this area to attempt to determine how an ICU admission can alter outcomes over several years. The work in this field has included analysis of long-term survival; the data generated suggests that an episode of critical illness carries an elevated mortality risk for up to five years

following hospital discharge (98, 99). Alongside this, ICU admission has been associated with higher rates of hospital readmission within the following year, as well as increased healthcare costs (99). This is a consequence of both the costs related to readmission and the increase in disease burden that results following an episode of critical illness. Indeed, the majority of recent literature on long-term outcomes following ICU has focussed on measures of quality of life (QoL).

QoL is defined by the World Health Organization as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (100). It is an increasing important measure in long-term outcomes following significant illnesses. This can be measured using several tools developed specifically for QoL, but regardless of the outcome measure used, the extensive data available on the subject agrees that QoL is significantly impacted following critical illness. Specifically, admission to ICU is associated with an increase in functional decline, inability to manage daily activities, reduction in mental health and reduced cognition (101-103). Recognitions of these adverse outcomes has given rise to the concept of Post-Intensive Care Syndrome (PICS): the detrimental changes in cognition, mental health, and physical function which individuals face following intensive care (104).

The possible underlying causes behind the development of all of these outcomes has been theorised in the literature; it has postulated that patients follow two different trajectories based on their health prior to admission. If a patient was "healthy", they are far less likely to die or develop a severe ability compared to a "morbid" patient (105). Using this hypothesis, the other main determinant of disease trajectory is considered to be severity of acute illness. This theory is support by a large cohort study in Canada, where characteristics of acute illness were most likely to account for short-term mortality, whilst comorbidities and age had the greatest effect on long-term outcomes (106). Considering this data, and similarly to analysis of short-term outcomes, it is vital to account for the potential influence of these variables when examining long-term outcomes following ICU.

1.3.3 Outcomes following acute kidney injury in ICU

1.3.3.1 Short- and long-term survival

As discussed above, AKI in all hospitalised patients has been linked to increased mortality both in-hospital and for a period of 2 years after discharge (42). Similarly, ICU patients have high rates of raw in-hospital mortality as well as an increased mortality risk for up to 5 years after discharge (64, 98). Considering this, it stands to reason that ICU patients with AKI will have a higher mortality risk than both these patient groups. Indeed, extensive work has been conducted into comparing ICU patients with and without AKI and the consequences on short-term mortality (17, 107, 108); the FINNAKI study found an approximately 70% increased mortality risk over 90 days for patients with AKI whilst admitted to ICU when compared to ICU patients without AKI (107). This also documented an increased mortality risk as severity of kidney injury increased.

However, a study which was inclusive of all hospitalised patients reported on the outcomes of over 19,000 participants: whilst the incidence of AKI was significantly lower than that seen in the ICU population, they reported that an episode of AKI was independently associated with an adjusted odds ratio of 4.43 for in-hospital mortality (109). Whilst this is a much larger difference than the increased risk between patients with and without AKI reported in the FINNAKI study, this is more likely to represent the higher mortality rate seen in ICU patients regardless of AKI when compared to all hospitalised patients. This significant disparity highlights why studies looking at AKI in the context of critical illness should be interpreted separately from those which look at vastly different patient cohorts. Whilst there is a strong evidence base to suggest that AKI (and higher stages of AKI) are associated with worsening mortality, it should be noted that all the available studies to date have reported on all types of AKI without separating groups into shorter-term AKI and longer-term AKD. As a result, the effect of progression to AKD on these outcomes is not yet known.

A similar evidence base exists with regards to effect of ICU induced AKI on long-term survival: the data documented in the literature suggest that AKI is associated with a long-term increased risk of mortality and poorer prognosis (26, 30, 110, 111). Given the breadth of evidence available on the subject, the

reported effect on long-term survival varied between these studies; reported hazard ratios ranged from 1.3 to 1.6. Whilst the difference between studying outcomes of AKI in the general hospital population and ICU population has been discussed above, a large observational study reported in 2014 reported that long-term survival was significantly poorer in patients discharged following an episode of AKI when compared with those discharged following a diagnosis of myocardial infarction (112). A meta-analysis conducted in 2019 which contained mixed study populations from 82 studies found that the pooled results showed an 80% (HR = 1.80) increased risk of dying over the longer-term when compared to patients without AKI (113). This highlights the significant and long-lasting effect of AKI, and whilst the pathophysiology behind this mechanism is likely multifactorial and is partly dependant on aetiology of the initial kidney injury, the link between this and mortality reflects the integral role that the kidneys play in maintaining normal homeostasis within the body. Furthermore, the risks associated with AKI in ICU are not confined to mortality, with well-documented links between critical care induced AKI and long-term reduced kidney function and chronic kidney disease.

1.3.3.2 Kidney outcomes

AKI in ICU often exists as part of the multi-organ dysfunction syndrome (MODS) and is associated with an increased severity of illness. The original RIFLE criteria described above classifies the need for ongoing kidney replacement therapy beyond 90 days from the original injury as end stage kidney failure (4); this term has largely been replaced by the concept of established kidney failure (EKF). Evidence has demonstrated that patients admitted to ICU with pre-existing EKF have better outcomes and this may reflect patients with a lower severity of illness for whom KRT requirement does not reflect multi-organ failure (114, 115). As a consequence of the original RIFLE definition, many studies of patients with AKI in the critical care setting have used ongoing KRT at 90 days as a definitive endpoint (116, 117).

Current literature on progression of AKI to CKD has often used study populations taken from all hospital inpatients. A systematic review and meta-analysis looking at rates of CKD following AKI found an adjusted hazard ratio of 8.8 compared with hospitalised patients without AKI (33). Chawla and colleagues

utilised a large cohort of hospitalised veterans in the United States and detailed long-term adverse outcomes: they found that patients had a greater than two-fold increased risk (HR = 2.07) of suffering from a major adverse kidney event following an episode of AKI whilst in hospital (112). Considering these patients were not just from the critical care population, it is difficult to interpret these results in the context of critical illness. There is a current paucity of data available for rates of CKD following admission to ICU. Furthermore, as previously discussed, data on long-term kidney outcomes following an episode of AKD is lacking due to the novelty of the definition, as all previous studies have reported on AKI of all lengths as one group.

Other data has looked at the opportunity for intervention to improve outcomes following ICU discharge. A study conducted in USA using a population of 4,000 patients who survived AKI that required KRT found that early follow up with a nephrologist within 90 days resulted in a 24% reduction in all-cause mortality at 2 years (118). The current AKI guidelines produced by KDIGO recommend that patients are reviewed by a nephrologist at 3 months following AKI resolution (16). However, a review of patient follow up after an episode of AKI demonstrated that on average, only 37.5% of patients were referred to a nephrologist within 90 days (119); an annual report published by the US kidney data system in 2015 detailed that only 19% of patients had a follow-up appointment with a nephrologist in the 12 months following a hospitalisation which included a diagnosis of AKI (120). Unfortunately, little work has been done to examine the impact that such follow up would have on nephrology services; data produced on this would be difficult to interpret, as the ability to deliver this follow-up care would be dependent on the availability of outpatient nephrology clinics and the healthcare system of the specific country. Given the incidence of AKI in both intensive care and hospital inpatients, it is unrealistic to suggest that nephrology services in the UK would be able to review every patient that recovered from an episode of AKI.

1.3.3.3 Cardiovascular outcomes

The link between existing kidney disease and cardiovascular disease such as hypertension, coronary artery disease, acute myocardial infarction and cerebrovascular events has been previously described in detail. There are

multiple mechanisms felt to be implicated in this process (121): high levels of sodium and cholesterol throughout the cardiovascular system; chronic low grade inflammation of the blood vessels; imbalance of hormones; calcification of the soft tissues throughout the body; and resistance to erythropoietin leading to anaemia. A combination of all these factors is thought to contribute to increased stimulation of inflammatory pathways and increased risk of developing cardiovascular disease. This is well documented in patients with CKD, but an increased risk profile has also been expressed following an episode of AKI; previous studies noted that acute myocardial infarction and heart failure are significantly more likely after AKI (122, 123). Whilst the study by Wu et al. looked at all hospitalised patients, they used a subset of patients who recovered from severe AKI; their results demonstrated that across these 4,869 patients, these patients were 67% more likely to develop subsequent coronary events compared to patients who did not suffer from AKI.

In addition to the increased risk of cardiovascular disease associated with an AKI, there has also been research conducted into the incidence of major cardiovascular events following critical illness; the study by Yende et al. found that survivors of severe sepsis admitted to ICU carried a 13-fold higher risk of cardiovascular events compared to a control group (124). A similar cohort of sepsis patients from all hospitalised patients were found to have a higher risk of suffering from myocardial infarction, ischaemic stroke, haemorrhagic stroke, heart failure and sudden cardiac death (125). Whilst both these studies used specifically survivors of sepsis in both ICU and hospitalised patient cohorts, this group makes up a major proportion of the patients admitted to ICU and can therefore be considered a reasonable representation of the critically unwell.

A large-scale retrospective cohort study was performed by Lee and colleagues on patients admitted over a ten-year period: the study population was comprised of patients who underwent cardiac surgery, but the authors found that the risk of long-term major cardiovascular events was almost double for patients who required dialysis for AKI postoperatively (126). A further study on 968 patients who underwent cardiac surgery also reported an association of both AKI and increasing AKI severity with an increased risk of long-term cardiovascular events (127). Whilst these studies have demonstrated a link between AKI and

cardiovascular events, and critical illness and subsequent cardiovascular disease, there is little detail looking at secondary cardiovascular events following AKI in ICU. Again, with such little research on AKD available, this is another area which could be explored further.

1.4 Conclusions

Admission to intensive care is a significant event and is strongly associated with development of acute kidney injury as well as poor outcomes. Defining injury to the kidneys has been challenging over the past decade due to differing terminologies and definitions which have been refined as knowledge within the field has grown. A novel concept of AKD as a persistent AKI has yet to be described in any great detail but has been identified as an area which requires exploration. This study will aim to identify the proportion of kidney injury within intensive care, and describe multiple short- and long-term outcomes, as well as determine how these data can be interpreted in the context of the new definition of AKD.

Chapter 2 Methods

In a review of the current literature surrounding the incidence of kidney injury during admission to intensive care units (ICUs), a recent workgroup suggested a novel categorisation regarding the concept of a "persistent" acute kidney injury (AKI); this was referred to as acute kidney disease (AKD) and the need for literature around this group of patients was identified. As patients requiring critical care have previously been recognised as having a high likelihood of suffering from AKI, they represent an ideal patient group to attempt to identify a cohort of patients suffering from both kidney injury of any length and, in particular, those who would fall within this new definition of AKD. In this retrospective, observational study, all patients admitted to either of two large ICUs within the NHS Greater Glasgow and Clyde health board within a three-year period were identified. The incidence of any form of kidney injury within this patient group was determined, then demographics of this group were compared with patients without kidney injury, followed by a further analysis of the differences for length and severity of injury. A long-term survival analysis and assessment of progression to chronic kidney disease (CKD) between these groups was carried out, followed by a comparison of the rates of secondary cardiovascular outcomes which can arise as a result of kidney injury.

2.1 Setting and time frame

NHS Greater Glasgow and Clyde (NHS GG&C) represents the largest health board in Scotland, providing services to a population of approximately 1,200,000 people. Within the region there are four general adult ICUs capable of admitting patients as well as three further specialised ICUs. The setting was chosen for two main reasons: as the largest health board, the numbers of admission to ICU are higher and therefore allow for more data to be compared and analysed; and the Strathclyde Electronic Renal Patient Records (SERPR) (*Vitalpulse*) database is only used amongst six NHS health boards in the West of Scotland and therefore data were required to be from this region.

The Scottish Intensive Care Society Audit Group (SIGSAG) Wardwatcher database (*Critical Care Audit Ltd*) is used in every ICU throughout Scotland. Whilst this would allow for collection of data from all ICUs from health boards which also

utilise SERPR, data collection was limited to NHS GG&C to ensure that missing or erroneous data could be identified from the Carevue (*Phillips Healthcare*) database. For the entirety of the study period, only Glasgow Royal Infirmary (GRI) and Queen Elizabeth University Hospital (QEUH) used the Carevue electronic patient records system; as a result of this, these two hospitals were selected as the setting for this study to allow for supplemental clinical information to be accessed. These two units comprised of 38 of the 47 funded general adult ICU beds available in NHS GG&C for the whole study period (128). Specialist ICUs were excluded as they represented a cohort of patients not generalisable to average critical care population.

Prior to July 2015, general adult ICU beds in city centre teaching hospitals across Glasgow were situated in 5 hospitals: Glasgow Royal Infirmary, Southern General Hospital, Stobhill Hospital, Western Infirmary and Victoria Infirmary. On July 3rd 2015, the acute receiving services in the latter four of these hospitals closed and their ICU capabilities were relocated to the newly opened QEUH. This also coincided with the use of an electronic patient record system, "Carevue" at the QEUH ICU. As a result of this, July 2015 until the most recent July prior to the beginning of the study (2018) was selected as the time frame for this study.

2.2 Data gathering

The data used throughout this study were extracted from two routinely used databases in ICU and kidney medicine: Scottish Intensive Care Society Audit Group (SICSAG) Wardwatcher and SERPR. These two databases are not routinely linked in any way, but both use unique patient identifiable information such as a Community Health Index (CHI) number. Every patient in Scotland has a unique 10-digit CHI number which is allocated to them on first registration with the health service. In addition, Wardwatcher assigns every patient a "Key" number, which represents a single admission and is unique for each patient within that specific ICU. Using these variables, all patients can be linked between the two systems by ensuring that the two numbers are consistent.

2.2.1 Sources of data

2.2.1.1 SICSAG Wardwatcher

The Wardwatcher system (*Critical Care Audit Ltd*) was established by SICSAG in 1995 and consists of a Scotland-wide database of all patients admitted to adult ICUs. It is used by every general adult ICU in Scotland. Every patient admitted is registered and multiple data fields are collected such as basic demographics, admission diagnosis, admitting specialty, previous comorbidities, severity of illness on admission, organ support delivered and outcome on discharge from both ICU and hospital.

Each patient will have a new record generated for each admission, regardless if they've been previously admitted to the same or any other ICU; this will generate the unique "Key" number for that individual ICU admission. The data are collected by multiple members of the health care team within each of the admitting units and will not allow a patient to be discharged from the system until certain mandatory data fields have been completed. The data for each individual ICU are stored locally within that site before central linkage within Public Health Scotland; as a result of this, within each Wardwatcher databases there may be the same "Key" number used to represent two different patients admitted to two different hospitals.

The initial admission screen allows for input of basic demographic information in addition to the referring specialty, the type of area they were admitted from and, if admitted directly from an operating theatre, whether the admission was an emergency or elective (planned). Information regarding patients' prior health is intrinsically linked to the Acute Physiology and Chronic Health II (APACHE II) scoring system (80). As a result of this, various data fields are restricted strictly to those options defined within the APACHE definitions; comorbidities are limited to 13 broad groups which are further clarified by very specific criteria on the database itself. Similarly, admission diagnoses are limited to pre-determined APACHE diagnoses which allow them to be incorporated into the APACHE II score. In addition to this, there is a Scottish Intensive Care Society (SICS) diagnosis field which allows for a much larger range of options in addition to the pre-defined APACHE choices.

A separate screen is used for determining severity of illness; this is again part of the APACHE II score which is generated and used to calculate a predicted mortality rate for that specific patient. This utilises data from the initial 24 hours of a patient's admission and can either be entered manually or transferred across from another system if electronic record keeping is used within that ICU. The Augmented Care Period (ACP) screen is updated on a daily basis. It contains set questions with reference to highest level of support that the patient has received on each specific day. This encompasses six main organ systems, including level of respiratory support, cardiovascular (vasoactive drugs) support, kidney replacement therapy, advanced neurological monitoring, nutritional support and requirement for advanced skin care such as complex dressings or extensive burns. The information gathered from this is used to automatically calculate the highest "level" of care that patient received on that specific day; it also allows data to be stored on which modalities of organ support were utilised during the stay, and for how many days they were utilised.

Before a patient can be discharged from the system, a final screen must be completed detailing if the patient is alive or dead at discharge, the discharge date and time and the discharge destination. In addition, on discharge from hospital a final entry is made to detail the date and time of discharge from hospital, if the patient is alive or dead, and their discharge destination.

As the majority of the data entered into Wardwatcher is done so manually, it utilises a number of measures to try and ensure that data entered is accurate. As an example, discharge date and time cannot be entered unless it is chronologically after the recorded admission date and time. It will also query the entry of data if it is out with normal expected ranges; this occurs on input of various physiological variables in the severity screen if they are much higher or lower than expected or if linked observations are considered to be unusual when compared with each other (arterial blood gas results with a higher carbon dioxide level than oxygen level). In addition to this, validations of individual cases are carried out periodically during site visits by Quality Assurance managers.

2.2.1.2 SERPR database

The SERPR (*Vitalpulse*) database was established in the West of Scotland in June 2010. It encompasses six health boards: NHS GG&C, NHS Lanarkshire, NHS Ayrshire and Arran, NHS Dumfries and Galloway, NHS Forth Valley and NHS National Waiting Times Centre. The system is used exclusively by kidney physicians and includes details on any patient whom they have been involved in the care of since the database was created. Patients are not automatically found on the database but are "installed" during their first point of contact; the patient's CHI number is used to search for and add the patient to the system. Following registration, SERPR automatically searches for and downloads information from the Scottish Care Information (SCI) store and populates various data fields within the patient's record.

SCI store is a data repository which retains patient information at a health board level: it integrates a significant amount of clinical information from a wide range of sources into a single patient record. Since it is maintained at a health board level, there are several SCI stores in use across the West of Scotland alone. To solve this, the SERPR database downloads information from all six of the SCI stores in use in the health boards it covers. This ensures that as much information is available for the wide geographical region that kidney medicine in the West of Scotland covers.

The data downloaded by SERPR includes patients' demographic information, previous hospital admissions, laboratory results, radiology results and date of death (if applicable). Within laboratory data, it provides each individual result for every biochemical and haematological test performed within any of the above health boards; this includes historical data for patients who are added to the system years after the test result was received. As SCI records are retained following patient death, deceased patients can be added to the system and the same historical information will be downloaded as for any other patient.

As all information is downloaded and transferred automatically, the system removes the possibility of transcription errors. Laboratory results are automatically uploaded to SCI store which is then automatically transferred to SERPR. SCI store also uses information from general practitioners, so

demographic information is kept as up to date as possible rather than being updated sporadically during interactions with secondary care.

2.2.1.3 Carevue database

The Critical Care Carevue database (*Phillips Healthcare*) is an electronic system used for keeping records on patients admitted to ICU. It is used in both the GRI and QEUH ICUs. The system is used by the entire multi-disciplinary team within critical care and encompasses several aspects involved in patient care. Patients are admitted onto the system at their point of admission to ICU using their CHI number to identify them – their demographic data is then transferred from existing medical records onto the database automatically.

Carevue stores all medical notes from both the critical care team and visiting specialties during a patient's ICU admission. This includes details on patients' past medical history and baseline demographics such as admission height and weight. Patient observations during their admission are routinely charted on an hourly basis and include variables such as heart rate, blood pressure, oxygen saturations, ventilation settings and urine output. All medications are also prescribed electronically using the system and include all details such as dose, route of administration and time given.

2.2.2 Dataset input

Prior to merging data from the two systems, patients must be common to both systems. To allow for this, an initial search was carried out on Wardwatcher to identify all patients admitted to the two ICUs during the study period. This data included details on patient baseline demographics, ICU admission date and physiological features, ICU discharge date and outcome and hospital discharge date and outcome. Once a list was generated, every patient was added to or updated on SERPR. This was done manually one patient at a time. The data fields involved documentation of ICU admission date, ICU discharge date, Wardwatcher Key number and start/end date of kidney replacement therapy if applicable. Due to the high volume of patients, data input was done over a prolonged period of time. This was not only due to the number of patients but also because the server which data on SERPR is stored on could not manage the

increased processor requirement needed for the addition of more than 50 patients per day. Any discrepancies in CHI numbers meant that patients could not be added: these electronic records were searched for manually and mistakes were corrected. If multiple admissions occurred within the study period, both admission dates and Key numbers were documented.

2.2.3 Dataset extraction and merge

Following completion of data input, data were extracted from the SERPR database containing all lifetime creatinine results, troponin results post discharge, radiology results post discharge and angiography results post discharge. Data on daily urine output and daily doses of diuretic medications were extracted from the Carevue database. To ensure accuracy, the statistical software R (version 3.5.1, The R foundation) was used to merge these datasets with the data initially extracted from Wardwatcher: this was performed in R Studio and utilised the packages "readxl", "dplyr", "stringr", "tidyr", "readr" and "lubridate". Duplicate records with CHI numbers matching a previous admission were removed. Following this, the software matched patient records only if both the CHI number and the Key number matched exactly. For remaining records where this was found to not be the case, a manual check was carried out and data corrected if necessary. Following this, all patient identifiable information used to allow merging was stripped from the final dataset to render it de-identified.

2.2.4 Approval for use of data

The data used throughout this study is routinely gathered using two databases used in the day-to-day management of patients admitted to intensive care and patients under the care of kidney physicians: the SICSAG Wardwatcher system and SERPR.

Permission to use Wardwatcher data was authorised by two of the lead consultants from the ICUs involved in the study. The use of data generated from SERPR was authorised by Dr Jamie Traynor, clinical lead in charge of the SERPR database, who also authorised the addition of ICU patients not involved with the kidney physicians to the database.

Whilst data used was routinely gathered, ethical approval was sought to allow for the gathering, merging and analysis of the data through the Integrated Research Application system. Ethical approval was granted via proportionate review with subsequent NHS research and development (R+D) department approval: research and ethics committee reference 18/LO/2060 (Appendix A).

To allow for potential use of additional data from the database responsible for electronic patient records in ICU (Carevue), a non-substantial amendment was subsequently submitted and approved by the NHS R+D which can be found in Appendix A.

2.3 Categorisation of kidney injury

In order to define the presence of an acute kidney injury based on serum creatinine levels, a baseline for each individual patient must be established. Various methods have been previously described for measuring the baseline of patients, however automated detection of AKI is currently in use in some health boards in NHS England. This uses 3 criteria to define baseline plasma creatinine:

- Criterion 1 – Median of all creatinine levels from previous 8 – 365 days
- Criterion 2 – Lowest creatinine in previous 7 days
- Criterion 3 – Lowest creatinine in previous 48 hours

The accuracy of this method for defining the baseline creatinine to detect AKI was validated by Sawhney et al. (25), who found that using these specific rules to define baseline recognised 91.2% of patients who had been documented as having an AKI upon hospital discharge.

2.3.1 Initial kidney injury

2.3.1.1 Presence of kidney injury

The most recent classification system in use for defining both the presence and severity of AKI is the guidelines produced by the Kidney Disease Improving Global Outcomes (KDIGO) workgroup in 2012 (16). These guidelines detail two broad

ways in recognising and staging the severity of AKI: serum creatinine levels or urine output. An AKI is defined if any of the following are true:

- Rule 1 - Increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Rule 2 - Increase in serum creatinine by ≥26.5μmol/l within 48 hours
- Rule 3 - Urine volume <0.5 ml/kg/h for 6 hours.

As per the automated NHS England algorithm used to define baseline creatine levels above (25), these rules are applied to the specific criterion which was used to calculate baseline; rule 1 is applied to baseline creatinine calculated using criterion 1 or 2 and rule 2 is applied to baseline creatinine calculated using criterion 3. If there were two separate values available for criterion 1 or 2 then the lowest value was used. Whilst urine output can be used to both define and stage kidney injury, it was felt that the hourly clinical data available during ICU stay was not accurate enough to be used for this study. Therefore, only serum creatinine levels were used for all categorisation purposes. All serum creatinine results from 365 days prior to admission until the final point of data extraction (31st March 2020) were retrieved for every patient admitted during the study period.

Patients admitted to ICU may have a pre-existing diagnosis of established kidney failure (EKF), with an ongoing requirement for kidney replacement therapy (KRT): either long-term dialysis or previous kidney transplant. These patients cannot be categorised using the system above and so were grouped separately; they were identified using SERPR which has a record of all patients who require either of the above forms of KRT. All other patients had the rules applied to the criterion as specified above and were grouped as having either a de-novo kidney injury during ICU admission, or no kidney injury. Any patient whose baseline creatinine could not be identified (due to the absence of all three of the criteria above) were excluded from the study. The R code used for identifying kidney injury is available in Appendix C.

2.3.1.2 Baseline estimated glomerular filtration rate

Using the baseline serum creatinine (SCr) as defined in section 1.3 above, the lowest value from criteria 1 and 2 were used to define each patient's baseline value. Once this was calculated, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) formula created in 2009 used this value to calculate each patient's baseline eGFR (129). The formula is defined as follows:

$$eGFR = 141 * min(SCr/k,1)^{a} * max(SCr/k, 1)^{-1.209} * 0.993^{Age} * 1.018\{if\ female\}$$

In the above formula, where SCr in micromoles/litre (which all values within this dataset were), *k* is 61.9 in females and 79.6 in males and *a* is -0.329 in females and -0.411 in males. This formula was originally developed using one more variable to correct for patient race, but recently suggestions have been made that this offers very little benefits in terms of precision and is being removed from use in certain biochemistry laboratories (130). Since race was not readily available within the dataset, it was not used in the calculation of baseline eGFR using the CKD-EPI formula. Furthermore, since data analysis concluded, the CKD-EPI formula has been updated in 2021 and has removed race as a variable: the updated formula slightly changes the value of *k* and *a* for both females and males but these alter the calculated eGFR values very slightly when compared with the formula stated above. The R code used to define baseline eGFR is available in Appendix C.

2.3.1.3 Severity and length of kidney injury

The severity classification system published by KDIGO separates AKI into three stages:

- Stage 1 - serum creatinine 1.5-1.9 times baseline OR ≥26.5μmol/l increase
- Stage 2 - serum creatinine 2.0-2.9 times baseline
- Stage 3 - serum creatinine 3.0 times baseline OR increase in Serum Creatinine to 353.6 μmol/l OR initiation of KRT

The severity of disease was applied to all patients who suffered from a de-novo injury during admission. In order to classify length of injury, kidney recovery was defined as the first point at which creatinine levels no longer met any criteria for even stage 1 disease. To help avoid KRT from lowering serum creatinine and artificially representing kidney recovery, all creatinine values taken from any day between first day and 24 hours after discontinuation of KRT were excluded. The length of injury was then calculated as the period of time the patient met AKI criteria before reaching kidney recovery criteria. Any injury lasting for 7 days or longer was classed as AKD. This created two distinct groups that patients with de-novo injury could ultimately be classified: AKI and AKD. The R code used to define severity of injury can be found in Appendix C.

2.3.1.4 Oliguric vs non-oliguric kidney injury

KDIGO define oliguria as <0.3ml/kg/hr for 24 hours or more (16). This corresponds to <7.2ml/kg over a 24-hour period. Values used in previous studies looking at oliguria in KRT patients have varied from using total 24 hour volumes of 400ml (131) and 428ml (132) although these two previous studies were carried out prior to the publishing of KDIGO criteria. Using an average 70kg adult as an example, this would correspond to a 24-hour urine output of 504ml which is slightly higher than previous studies but factors in differences in patient weight. Admission weight is routinely recorded on Carevue and can be used to calculate more accurate expected urine output. Oliguric kidney injury was therefore defined as urine output <7.2ml/kg/day and non-oliguric kidney injury was defined as 7.2ml/kg/day and above. For the purposes of this study, if a patient was missing data on either urine output or admission weight then they were excluded from these analyses as alternative means of estimating weight using height or sex may produce values which significantly differ from the measured admission weight.

2.3.2 Prolonged decline in kidney function

2.3.2.1 Chronic kidney disease

KDIGO have also produced a framework for categorisation on chronic kidney disease (CKD). They define CKD as abnormalities of kidney structure or function, present for >3 months, with implications for health (46). Their staging system

incorporates cause, estimated glomerular filtration rate (eGFR) category and albuminuria category. eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) equation; this uses serum creatinine level and accounts for differences in race, gender and age. Utilising the eGFR category, patients can be defined as the following stages:

- Stage G1: >= 90 ml/min/1.73m^2
- Stage G2: 60-89 ml/min/1.73m^2
- Stage G3a: 45-59 ml/min/1.73m^2
- Stage G3b: 30-44 ml/min/1.73m^2
- Stage G4: 15-29 ml/min/1.73m^2
- Stage G5: <15 ml/min/1.73m^2

As stage G1 incorporates all eGFR >= 90ml/min, this definition can only be met with additional information regarding cause, albuminuria and implications to health. Due to data available, this could not be identified from the dataset. However, eGFR values <90ml/min were used to determine presence and severity of CKD at various time points. eGFR estimates the filtration of the kidneys using creatinine as a surrogate marker. Whilst this is reasonably accurate, it does not always account for differences in race, sex, or age; this is more pronounced at higher GFR values. As a result, a formula was created which includes the above variables to more accurately estimate GFR at a specific time point based off of serum creatinine levels: the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) (129). SERPR automatically calculates CKD-EPI therefore these values are routinely available and were used to categorise CKD as described above.

2.3.2.2 Major adverse kidney events

A major adverse kidney event (MAKE) has been previously described in the literature as a composite endpoint which encompasses several different

measures to define a significant kidney event. These measures have been previously described as: a decrease in eGFR from a baseline value; development or increase in the quantity of albumin in urine; progression to established kidney failure; or death due to kidney disease (133). A drop of 40% or more in estimated baseline glomerular filtration rate from baseline is reported to be a sensitive marker of a MAKE in the literature; however, it has been recognised that a drop of 30% or more may be used as a valid surrogate endpoint (133). Due to the lack of data on patients' urinalysis for possible albuminuria, this endpoint was excluded from this study. Whilst death due to kidney disease is considered a valuable MAKE, the absolute numbers of this are very small and lack of data on cause of death prevented it from being used for the purposes of this study. Four well defined endpoints of drop in eGFR of 30% or more, 40% or more, doubling of serum creatinine or initiation of long-term KRT were used in the analysis for the purposes of identifying a MAKE (134). Each patient was screened for each of these before the time to first adverse event following hospital discharge was calculated.

2.4 Categorisation of other variables

Due to data fields available, certain variables were either organised into too many different groups to allow for adequate between group analysis or required manual searching as the results were only available in free text. To overcome this, these variables were re-categorised prior to data analysis. Other variables were defined based on information available at point of final data extraction.

2.4.1 Admitting specialty

Wardwatcher admission screen contains a data field which requires entry of the hospital specialty which the patient was admitted from. This must be completed from a pre-defined list of 31 options. Broadly speaking, these specialties could be classified as either surgical or medical. For the purposes of analysis, 14 of the specialties were defined as surgical admissions and the other 17 were classed as medical admissions. A list of these specialties and which group they were organised into can be found in Appendix B.

2.4.2 Emergency/elective admissions

Wardwatcher admission screen contains a data field defining the "Nature of surgery". This option is only available if a previous question "Admitted from (type)" is completed with the response "Operating theatre/recovery". As such, any patient admitted from surgical specialties who is either yet to undergo surgery; several days post-operation (and therefore in a ward or high dependency unit); or has been deemed not suitable for surgical intervention will not have this field completed. Patients that fell into these categories were not included in analyses involving differences between elective and emergency admissions. Of the surgical patients that were admitted directly from theatre or recovery, their admission was classed as either "elective/scheduled" or "emergency/urgent" based upon the nature of their surgery.

2.4.3 ICU admission diagnosis

Four data fields are available within Wardwatcher for defining primary diagnosis for each individual patient episode. The first two are strictly defined by APACHE rules (APACHE III diagnosis and corresponding APACHE II diagnosis): they are used in the calculation of the APACHE II score and utilise historical data to broadly group patients based on diagnoses which are similar in both pathology and have a comparable probability of mortality. They are limited to 212 diagnoses which are constrained by if the patient is admitted directly from theatre or recovery (surgical diagnosis), or if the patient was admitted from another location (medical diagnosis). As a result of this, patients with surgical diagnoses not admitted from theatre or post-operative patients admitted with a primary medical diagnosis can be labelled with a "best fit" wrong diagnosis. These criteria must be adhered to for calculation of APACHE scores as they are directly derived from APACHE methodology, but they can therefore cause misrepresentation of the precipitating cause leading to the need for critical care.

The alternative two data fields were created by SICS and these allow for a much broader range of options regardless of the location the patient was admitted from. They are separated into primary diagnosis on admission to hospital and primary diagnosis on admission to ICU: there are approximately 400 different

options available. For the purposes of this study, the SICS data field pertaining to primary diagnosis on admission to ICU was used for determining the precipitating cause requiring admission to intensive care. This was to prevent any restrictions being placed on record of admission diagnosis to allow for a more accurate interpretation of principal reason for admission. To permit for analyses between groups allowing for the vast array of options available, these 400+ diagnoses were re-classified into 26 diagnostic groups; a table detailing how each diagnosis was grouped is available in Appendix B.

2.4.4 Pre-existing comorbidities

Medical history known prior to admission to ICU is documented for every patient on the Carevue system. This is stored in the "Past Medical History" field and is input at the point of admission for every patient; the system does not allow a patient to be admitted unless this field contains data. This field was searched for reference to various pre-defined comorbidities: cardiovascular disease, respiratory disease, liver disease, diabetes and malignancy. To identify these, search terms were used along with potential misspelling or commonly used acronyms. Pre-existing cardiovascular comorbidities were defined using the following terms: "hypertension"; "ischaemic heart disease"; "angina"; "myocardial infarction"; "coronary artery disease"; "coronary artery bypass graft"; "percutaneous coronary intervention"; "cerebrovascular accident"; "transient ischaemic attack"; "stroke"; "peripheral vascular disease"; "deep vein thrombosis"; and "pulmonary embolism".

Pre-existing respiratory disease were identified with the following search terms: "chronic obstructive pulmonary disease"; "asthma"; "obstructive airway disease"; "pulmonary fibrosis"; "interstitial lung disease"; and "bronchiectasis". Pre-existing liver disease was found using these terms: "cirrhosis"; "alcoholic liver disease"; "Child's"; "non alcoholic fatty liver disease"; "hepatitis"; "portal hypertension"; and "haemochromatosis". Diabetes was identified by searching for: "diabetes mellitus"; "type 1 diabetes"; "type 2 diabetes"; "insulin dependent diabetes; and "non-insulin dependent diabetes". Pre-existing malignancy was identified by searching for the following terms: "cancer"; "malignancy"; "chemotherapy"; "radiotherapy"; and "tumour". These five

comorbidity groups were then each tagged as either true or false for each patient in the study population.

2.4.5 Organ support

The ACP screen on Wardwatcher is completed on a daily basis and details maximum level of organ support for individual organ systems received throughout that 24-hour period. Data fields are then generated with a series of "yes" or "no" for each day of admission based upon receipt of that particular organ support. In addition, Wardwatcher will also automatically calculate number of days for specific modalities such as invasive mechanical ventilation or KRT. For the purposes of this study, organ support was defined as delivery of invasive mechanical ventilation via an endotracheal tube or tracheostomy, cardiovascular support (single or multiple intravenous vasoactive drugs) or kidney replacement therapy during their admission. Additional data was available for neurological, nutritional and dermatological support; however these were not used in this study as the former is only available in specialist neurological ICUs and the latter two can be routinely delivered at ward level care.

2.4.6 Survival status

Survival outcomes were documented in three forms throughout the dataset: outcome on discharge from ICU in Wardwatcher details if the patient was alive or dead at ICU discharge; outcome on discharge from hospital in Wardwatcher does similarly for when the patient was discharged from hospital; and the SERPR database automatically downloads date of death directly from the relevant SCI store. SCI store is updated at a primary care level so maintains an accurate record if the patient has died both in, and outside, the hospital setting. The former two fields were used for determining in-ICU and in-hospital mortality respectively whereas, the date of death from SERPR was used to determine survival time. For the purposes of survival analysis for patients who are considered "ICU survivors", only patients alive 30 days post hospital discharge were analysed in order to eliminate any patients discharged for palliative care. If the date of death was empty at the point of final data extraction (31st March 2020), the patient was assumed to be alive at this point.

2.4.7 Secondary cardiovascular events

As all laboratory and radiology results are stored in SCI store, the SERPR dataset can also be searched for any results which may be linked to secondary cardiovascular events which may be associated with kidney disease. Troponin I is a cardiac enzyme which is found elevated in the blood following damage to myocardial cells. For the purposes of this study, all high-sensitivity troponin I results following discharge from ICU were extracted. If a test was found to be elevated above the normal range as defined by the NHS GG&C laboratories, then the patient was documented as having a troponin positive event.

If a patient underwent either a computed tomography (CT) or magnetic resonance imaging scan of their head post discharge, the request details and imaging report were downloaded. The text from these reports were manually reviewed by Dr Jennifer Curle, specialty doctor in radiology. These reports were classified as intra-cranial haemorrhage or infarct, based on whether these pathologies were present on the scan report without any mention of trauma as the precipitating cause. These patients were documented as having a positive cerebrovascular event.

The reports of any patients who underwent coronary angiography post discharge were downloaded and manually searched. These patients were documented to require coronary angiography; in addition, if the reporting physician recommended progression to either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), these were also detailed for each individual patient.

2.5 Missing data

2.5.1 Baseline kidney function

Data on baseline kidney function was calculated using one of three criteria; this baseline serum creatinine value was required to determine presence of kidney injury regardless of either length or severity. As such, missing baseline data rendered it impossible to detect de-novo kidney injury during the patient's ICU admission. There were only 22 patients without a baseline serum creatinine and these patients were therefore removed from the study population.

2.5.2 APACHE data

APACHE II scoring and predicted mortality data relies on all data fields required for calculation to be completed. Certain data fields are mandatory to allow the patient to be discharged from the Wardwatcher system, such as comorbidities, however, occasionally patients are discharged with missing APACHE diagnoses which prevent them from having a calculated predicted mortality rate. In addition, certain patient groups will not have an APACHE II severity score completed: patients admitted for less than 8 hours; and patients who are re-admitted to ICU during the same hospital admission. The admitting ICU could also opt out of severity scoring for individual patients at their own discretion. Any analysis involving comparison of APACHE II scores or predicted mortality were conducted having removed any patients for which either the APACHE II score or APACHE II diagnosis was missing.

2.5.3 Follow-up results

Certain patients were detected as either originating from outside the six NHS health boards from which SERPR draws its data or moving outside this catchment area in the period following hospital discharge and follow up. Survival data, prolonged reduction in kidney function and secondary cardiovascular events were therefore unable to be identified in these patients and they were removed from the analyses involving follow up post hospital discharge.

2.6 Data storage

The initial data gathered from the original sources during the project contained patient identifiable information. These unique identifiers were initially necessary to merge the two datasets. Raw data extracted from Wardwatcher and SERPR were stored on encrypted, password protected NHS GG&C computers accessible only from the author's account. Any transfer of information with patient identifiers required between individuals (such as raw data extracted from SERPR and transferred to the author) was done using encrypted, password protected emails or was exclusively saved to an encrypted USB drive. As the raw data could be extracted again from the source databases, backups were only created for de-identified data.

To ensure strict patient confidentiality, following the merging of datasets, all patient identifiers were then completely stripped from the new dataset to allow for a de-identified dataset to be used in analysis. Any additional information required from the original database following preliminary analysis were re-extracted on encrypted NHS computers and subsequently de-identified prior to further analyses. Due to the requirement to include age, date of admission and date of discharge in the dataset, data was not referred to as fully anonymised as a motivated individual could use these markers to theoretically reidentify an individual.

All data used during this study were uploaded to the University of Glasgow's secure, encrypted data repository Enlighten following completion of all data analyses where it will be stored for a minimum period of 10 years.

2.7 Data analysis

2.7.1 Descriptive analyses

All data analysis was conducted using the statistical software R (version 3.5.1, The R foundation). All analyses were conducted in R Studio, and the packages packages "dplyr", "stringr", "tidyr", "readr", "lubridate", "ggplot2", "lmtest", "tibble", "survminer", "survival", "ggfortify", "glmmTMB", "ggeffects", "broom" and "broom.mixed" were installed to facilitate manipulation of the data, analyses and subsequent visualisation.

Initial data were recorded using cumulative counts of numbers followed by a percentage of total numbers within the specified group. Any continuous variables were not normally distributed and were therefore presented in terms of median and interquartile ranges; as results were also non-paired, Wilcoxon rank sum test (Mann Whitney U test) was used to test for differences between groups. Wilcoxon rank sum test was developed to test for the probability that two independent samples were selected from populations which have the same distributions (135): the null hypothesis for this test states that the distribution of both of these populations are equal. If there is a significant difference between these two values, then the null hypothesis is rejected and the distributions of

the two populations are assumed to not be equal: a two-sided *p*-value of <0.05 was considered significant.

Proportions of groups were presented using exact 95% confidence intervals, and proportions between groups were compared using Pearson's chi-squared test. This test was developed to evaluate the likelihood that any observed differences between two sets of observations may have occurred by chance (136). The test calculates a chi-squared value by comparing the sum of squared deviations between the observed frequency and the theoretical frequency. The value of this statistic and the calculated degrees of freedom is compared to a chi-squared distribution to produce a *p*-value. Again, a two-sided *p*-value of <0.05 was considered significant.

Multivariable analyses were conducted using multiple logistic regression. Multiple logistic regression is used when there is one nominal (dependent) variable and two or more measurement (independent variables). It is useful for estimating the probability of one measurement variable contributing to the specified dependent variable when all other measurement variables are held at a set value (137). A generalised linear model was created using baseline variables against the chance of the event occurring. Variables included in the multivariable model were decided based on initial univariable analysis of each variable – any variable with a *p*-value of <0.2 was included in the multivariable analyses unless there was a risk of co-linearity. A cut-off value of <0.2 was used to ensure that no potentially significant variables were missed. In addition, if any variable was considered to be clinically relevant, it was included in the multivariable model regardless of the initial univariable *p*-value. Differences between groups were presented in terms of odds ratios (OR) of the variable contributing to the event; exact 95% confidence intervals for OR and *p*-values were also reported. Odds ratio is defined as the odds of an event occurring in one group compared to the odds of it occurring relative to a control group. The results were interpreted using a robust estimator for standard error.

2.7.2 Long-term and survival analyses

To compare chances of survival between groups, survival was described in terms of ICU, hospital and time-period. In-ICU and in-hospital mortality was described

as part of the descriptive analyses, whereas time period survival was assessed only in ICU survivors. ICU survivors were defined as patients that had survived to 30-days following hospital discharge after an ICU admission. The chances of survival over time were plotted using Kaplan Meier graphs for the pre-defined subgroups. The Kaplan Meier estimate is a measure of the fraction of an event occurring in each group for a certain amount of time after discharge (138). It also helps to account for censored data: this includes all the patients who are still alive at final point of data extraction. Each time an event is observed, the total number of deaths up to that points is compared with the expected number if there were no differences between the groups. Survival in each of the groups were then compared using a log-rank test. This is a test for which the null hypothesis states that no difference between the survival curves of the two populations exists by calculating a *p*-value. This is most likely to detect a difference between groups when the survival of one group is consistently higher over the total time period rather than the survival curves crossing on one or more occasion – to try account for this, all survival curves were plotted to ensure accuracy of interpretation. Since this method is not only limited to survival, but the chance of an event occurring over time, it was also used to describe rates of prolonged reduction in kidney function and secondary cardiovascular events occurring post-discharge.

As opposed to the methods detailed for descriptive analyses, a multivariable analysis of all factors which could influence the probability of survival was conducted using a Cox proportional hazards model (139). This model reports in terms of hazard ratios (HRs) of the event occurring based on that particular variable when all others have been standardised. The difference between this and ORs described above is that ORs are cumulative over an entire study using a defined endpoint whereas HRs describe the instantaneous risk of the event occurring over the study time period or a subset of it. This survival model can be viewed as a combination of the underlying baseline hazard function, describing how the risk of event per time unit changes over time at baseline levels of the multiple covariates; and the effect parameters, describing how the hazard varies in response to the independent variables.

In order to utilise the Cox proportional hazards model, the proportional hazards (PH) assumption must be met (140). This states that the covariates are multiplicatively related to the hazard and even if the magnitude of the hazard varies over time, the ratio remains constant. The Schoenfeld residuals for this model are automatically calculated by R, and these calculate the differences between observed and expected rates for each covariate; these differences should remain constant over time. If the differences vary over time, it is a suggestion that the PH assumption has not been met: a *p*-value is automatically calculated by R to represent the likelihood that this is the case. If the *p*-value of the residuals calculated on any variable was found to be <0.2, it was removed from the multivariable model as it was presumed to not obey the proportionality assumption. If any model failed these assumptions despite removal of multiple variables, ORs and 95% confidence intervals were reported instead as described above.

Chapter 3 Characterisation of kidney injury and associated factors following admission to the intensive care unit

3.1 Introduction

The development of kidney injury is a common occurrence amongst patients with critical illness admitted to the intensive care unit (ICU). It occurs as part of the multi organ dysfunction syndrome (MODS) and the aetiology is often multifactorial (3). As a result of this, there may be certain features which predispose patients to developing injury which takes longer to recover or is classified as more severe. If these factors could be recognised, it would give clinicians in ICU an opportunity to monitor these patients, work to improve modifiable risk factors, and attempt to minimise morbidity and mortality. This study aims to describe the factors associated with varying degrees of kidney injury amongst patients admitted to ICU with critical illness.

3.2 Study aims

3.2.1 What proportion of patients admitted to ICU experience de-novo kidney injury compared to no kidney injury?

The overall population of ICU patients will be described according to the degree of kidney injury they suffered after ICU admission and how this varies between patients when accounting for patient age, sex, hospital admitting specialty, precipitating illness and baseline kidney function. The varying degrees of organ support that each patient group received according to each modality used will also be detailed. In addition, features associated with development of kidney injury will be assessed and the relative risk of each detailed.

3.2.2 What are the differences between ICU patients with varying severity of kidney injury?

Comparing the above groups will document differences between patients without kidney injury and those of varying severity of injury; it may be expected that differences are seen comparative to degree of injury suffered. The proportion of patients who suffer from KDIGO stage 1-3 de-novo injury will be

described, as well as how each of these groups varies by patient age, sex, hospital admitting specialty, aetiology and varying organ support received.

3.2.3 What are the differences between patients with de-novo kidney injury who have rapid-reversal AKI compared to patients who progress to AKD?

The proportion of patients who suffer from acute kidney injury (AKI), and acute kidney disease (AKD) will be described, as well as how each of these groups varies by patient age, sex, hospital admitting specialty, comorbidities, aetiology and varying organ support received.

3.2.4 How do patients who receive kidney replacement therapy (KRT) compare to patients with de novo AKI/AKD not treated with KRT?

Kidney replacement therapy is considered a significant intervention in the management of severe kidney injury. It may be expected that the patients who receive this intervention differ from patients who have a kidney injury without KRT support. Patients with de novo kidney injury in ICU will be described and further evaluated based on whether they did or did not receive KRT during their ICU stay.

3.2.5 Which features are associated with development of de-novo kidney injury and progression to AKD?

Various features will influence both the initial development of de-novo injury and the potential progression from short-term AKI to longer-term AKD. An analysis will be conducted to determine if any of these features influence length of kidney injury and quantify to what degree each is important.

3.2.6 Does development of de-novo kidney injury, worse severity of disease and progression to AKD have any influence on ICU and hospital mortality?

It is possible that progression to AKD and severity of kidney injury may be associated with increasing mortality both in ICU and in hospital. The mortality rates for each group of patients in addition to the subgroups according to severity as well as recipients of KRT will be compared.

3.3 Methods

Total number of patients in each group were counted cumulatively and then expressed as a percentage of total number of admissions during the study period. The ICU population were organised into three categories of no kidney injury, de-novo kidney injury and pre-existing established kidney failure (EKF). De-novo kidney injury was termed as such to include all patients with a new onset injury regardless of underlying chronic kidney disease (with the exception of ERF patients) and was used to prevent confusion when referring to AKI and AKD patients within this group. These groups were then described in terms of total numbers and percentages for patient sex, hospital admitting specialty (described hereafter as either surgical or medical; specialties within each group are further detailed in Appendix B), baseline estimated glomerular filtration rate measured in millilitres per minute per 1.73 metres squared (eGFR), severity of illness score on admission (APACHE II), comorbidities and primary diagnosis responsible for admission. Within surgical admission, patients admitted directly from surgery could be further classed as following elective or emergency intervention. Precipitating illness requiring ICU admission was identified based on diagnosis on admission to ICU which has subsequently been grouped as indicated in Appendix B. Patient age and APACHE II score for each group was described in terms of median and interquartile ranges.

Subgroups according to severity, length and recipients of KRT within the de-novo kidney injury group were then described in a similar fashion. Degree of organ support provided was grouped into three categories: invasive mechanical ventilation (IMV), cardiovascular support (CVS) and kidney replacement therapy (KRT). Mortality within each group was initially described as total number of deaths within each group whilst in ICU and in hospital and were then presented as a percentage number of totals for each group with 95% confidence intervals (95% CIs) and representative *p*-values. Univariable analysis was conducted using Pearson's chi-squared test for proportions and Wilcoxon rank sum test for median values with *p*-values reported for each; variables with *p*-values <0.2 on univariable analyses were included in the multivariable model. Multivariable analysis was reported as odds ratios (ORs) with 95% CIs and representative *p*-values. A two-sided *p*-value of <0.05 was used to determine significance.

3.4 Results

Over a three-year period in between 1st July 2015 and 30th June 2018, 5,334 patients aged 16 years or older with critical illness were admitted to the GRI and QEUH ICUs.

3.4.1 Proportion of ICU patients with kidney injury

Out of the 5,334 patients identified, 22 patients (0.004%) were removed from all analyses as no data was available for calculation of baseline kidney function to allow calculation of degree of kidney injury. Of the remaining 5,312 patients (Table 3.1), 2,147 (40.4%) suffered a new kidney injury during their ICU admission, 103 (1.9%) had pre-existing EKF prior to admission to ICU, whilst 3,062 (57.7%) suffered no kidney injury during their ICU admission. A flow diagram detailing the categorisation of patients within the study population can be found in Figure 3.1.

Kidney injury	Total number – n (%)
No kidney injury	3,062 (57.7%)
De novo kidney injury	2,147 (40.4%)
Pre-existing established kidney failure	103 (1.9%)
Total patients	5,312 (100.0%)

Table 3.1: Proportion of ICU patients according to kidney injury

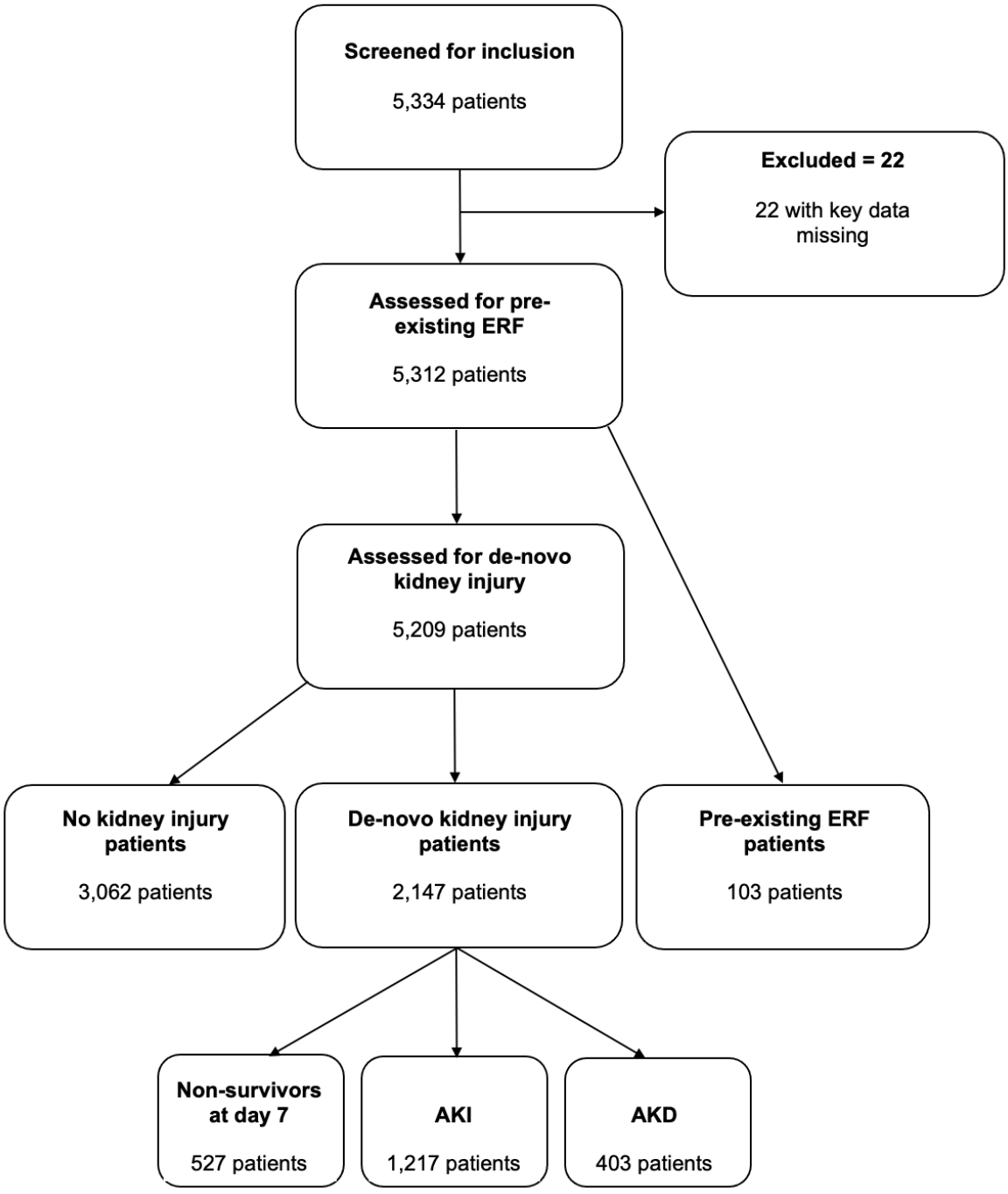


Figure 3.1: Flow diagram detailing categorisation of patients within the study population

3.4.2 Patient characteristics based on presence of kidney injury

3.4.2.1 Key baseline demographics

Of the 5,312 total patients, 2,953 were male (55.6%). Of the patients who were identified as having a de novo kidney injury (DNKI) of any length, 1,293 patients were male (60.2%), a comparatively higher proportion than the 1,599 (52.2%) male patients in the no kidney injury group (*p*-value <0.001). The proportion of male patients was also significantly higher in the pre-existing EKF group as

represented in Table 3.2 (61 male patients, 59.2%; *p*-value <0.001 vs no kidney injury group). For the total study population, the median age was calculated as 59.0 (IQR = 45.0 – 70.0). The de-novo injury group was represented by a median age of 61.0 (IQR = 49.0 – 72.0) compared to a median age of 56.0 in the no kidney injury group (IQR = 43.0 – 69.0). When compared with the median age of patients who did not experience a kidney injury during their ICU admission, the median ages of the de-novo kidney injury group (*p*-value <0.001) and the pre-existing EKF group (*p*-value = 0.044) were statistically significantly different. Median baseline eGFR was found to be lower in the de-novo injury group compared to the group who suffered from no kidney injury (82.5 vs 94.3; *p*-value <0.001). The median baseline eGFR in the pre-existing EKF group was substantially lower than the equivalent values in the other two groups due to the definition of the people within this group (*p*-value <0.001).

Of the total study population, the majority of admissions during the study period were from surgical specialties, with 3,043 patients admitted (57.3%). 36.4% of patients admitted from surgical specialties were found to have a de-novo kidney injury at any point during their ICU admission. In contrast, a higher proportion (45.8%) of the 2,269 patients admitted from medical specialties suffered from a de-novo injury. The 2,136 patients admitted directly from surgery were further classified as elective or emergency operative intervention. Within this group, 1,269 patients (59.4%) were classified as an emergency or urgent surgery; 535 (42.16%) of these patients went on to develop a de-novo kidney injury. In contrast, 142 of the 867 patients (16.4%) grouped as an elective or scheduled surgery developed a de-novo injury. The data generated from this demonstrated that the majority of patients who developed a de-novo kidney injury post-operatively did so after an emergency intervention (79.0%).

Calculated APACHE II scores were not available for 288 patients, therefore only the remaining 5,024 were used for this analysis. The median APACHE II score for all patients was calculated as 17.0 (IQR = 11.0 – 23.0). The median APACHE II score was lower in the no kidney injury group when compared to the de-novo kidney injury group (13.0 vs 22.0; *p*-value <0.001). This was also the case when comparing patients who did not experience a kidney injury with the pre-existing EKF group (13.0 vs 25.0; *p*-value <0.001).

Characteristic	Total patients (n = 5312)	No kidney injury (n = 3062)	De-novo injury (n = 2147)	Pre-existing established kidney failure (n = 103)
Age – median (IQR)	59.0 (45.0 – 70.0)	56.0 (43.0 – 69.0)	61.0 (49.0 – 72.0)	59.0 (50.5 – 68.0)
Male - n (%)	2953 (55.6%)	1599 (52.2%)	1293 (60.2%)	61 (59.2%)
Admitted from surgical specialty – n (%)	3043 (57.3%)	1893 (61.8%)	1107 (51.6%)	43 (41.8%)
Baseline eGFR – median (IQR)	89.8 (68.7 – 105.1)	94.3 (79.1 – 108.5)	82.5 (59.1 – 99.2)	9.5 (6.8 – 18.9)
APACHE II score – median[1] (IQR)	17.0 (11.0 – 23.0)	13.0 (9.0 – 18.0)	22.0 (17.0 – 29.0)	25.0 (21.0 – 32.0)
Comorbidities – n (%)				
Cardiovascular disease	2067 (38.9%)	1042 (34.0%)	960 (44.7%)	65 (63.1%)
Respiratory disease	1054 (19.8%)	611 (20.0%)	437 (20.4%)	6 (5.8%)
Liver disease	485 (9.1%)	243 (7.9%)	235 (11.0%)	7 (6.8%)
Diabetes	782 (14.7%)	344 (11.2%)	402 (18.7%)	36 (35.0%)
Malignancy	378 (7.1%)	228 (7.4%)	145 (6.8%)	5 (4.9%)

Table 3.2: Demographics of patients based on presence of kidney injury

Data regarding comorbidities was available in five main groups as detailed in Table 3.2. The total study population was found to have a high proportion of pre-existing cardiovascular disease in comparison to any other comorbidity (38.9%); 46.4% of this patient group went on to suffer from a de-novo injury

[1] Data unavailable for 288 patients – only 5024 patients used in these calculations (no kidney injury = 2896; de-novo injury = 2035; pre-existing ERF = 93)

during their ICU stay. A statistically significant difference was seen when comparing relative rates of cardiovascular comorbidity in the patients with no kidney injury and the de-novo injury group (34.0% vs 44.7%; *p*-value <0.001). When comparing patients admitted with pre-existing respiratory disease and pre-existing malignancy, similar proportions of patients were found in the de-novo injury group when compared to the no kidney injury group (*p*-value = 0.750 and *p*-value = 0.368 respectively). Rates of pre-existing liver disease were significantly higher in the de-novo injury group when compared with patients who experienced no kidney injury during their ICU admission (11.0% vs 7.9% respectively; *p*-value <0.001).

In patients with pre-existing diabetes admitted to the ICU, the majority of patients suffered from a de-novo kidney injury during their ICU admission (51.41%); a significantly higher proportion of the de-novo injury group had pre-existing diabetes compared to patients in the no kidney injury group (18.7% vs. 11.2%; *p*-value <0.001). When considering the patients admitted with pre-existing EKF, high rates of concurrent cardiovascular disease and diabetes were also identified in these patients (63.1% and 35.0% respectively); these were both significantly higher than the proportions seen in the no kidney injury patient groups (both *p*-values <0.001).

3.4.2.2 Precipitating illness requiring ICU admission

Precipitating illness	Total patients (n = 5312)	No kidney injury (n = 3062)	De-novo kidney injury (n = 2147)	Pre-existing established kidney failure (n = 103)
Sepsis/Infection	1132 (21.3%)	466 (15.2%)	636 (29.6%)	30 (29.1%)
Malignancy	538 (10.1%)	429 (14.0%)	105 (4.9%)	4 (3.9%)
Trauma	406 (7.6%)	285 (9.3%)	121 (5.6%)	-
Gastrointestinal (Other)	391 (7.4%)	260 (8.5%)	126 (5.9%)	5 (4.9%)
Respiratory/Airway	329 (6.2%)	211 (6.9%)	115 (5.4%)	3 (2.9%)
Drug Related	319 (6.0%)	269 (8.8%)	50 (2.3%)	-
Cardiac Arrest	300 (5.7%)	111 (3.6%)	180 (8.4%)	9 (8.8%)
Neurological	284 (5.4%)	195 (6.4%)	85 (4.0%)	4 (3.9%)
Gastrointestinal Perforation	225 (4.2%)	130 (4.3%)	92 (4.3%)	3 (2.9%)
Seizures	193 (3.6%)	119 (3.9%)	73 (3.4%)	1 (1.0%)
Haemorrhage	184 (3.5%)	101 (3.3%)	83 (3.9%)	-
Kidney	151 (2.8%)	20 (0.7%)	108 (5.0%)	23 (22.3%)

Hepatobiliary	148 (2.8%)	75 (2.5%)	71 (3.3%)	2 (1.9%)
Vascular	108 (2.0%)	25 (0.8%)	81 (3.8%)	2 (1.9%)
Post-operative Complications	89 (1.7%)	61 (2.0%)	24 (1.1%)	4 (3.9%)
Cardiac (Other)	82 (1.5%)	54 (1.8%)	24 (1.1%)	4 (3.9%)
Endocrine/Metabolic	75 (1.4%)	26 (0.9%)	46 (2.1%)	3 (2.9%)
Cardiac Failure	62 (1.2%)	19 (0.6%)	41 (1.9%)	2 (1.9%)
Miscellaneous	61 (1.2%)	48 (1.6%)	12 (0.6%)	1 (1.0%)
Burns Related	52 (1.0%)	36 (1.2%)	16 (0.8%)	-
Obstetrics/Gynaecology	51 (1.0%)	44 (1.4%)	7 (0.3%)	-
Musculoskeletal	39 (0.7%)	32 (1.1%)	6 (0.3%)	1 (1.0%)
Hypersensitivity/Immunocompromise	34 (0.6%)	22 (0.7%)	10 (0.5%)	2 (1.9%)
Liver Disease	29 (0.6%)	8 (0.3%)	21 (1.0%)	-
Ischaemic Heart Disease	21 (0.4%)	13 (0.4%)	8 (0.4%)	-
Haematology/Coagulation	9 (0.2%)	3 (0.1%)	6 (0.3%)	-

Table 3.3: Precipitating illness responsible for admission to ICU and proportion in each kidney injury group

The primary illness responsible for each patient group's admission to ICU is demonstrated in Table 3.3. The most common diagnosis associated with admission to ICU was sepsis: this was the case for 21.3% of the entire study population. Sepsis was also the most common reason for admission within each individual group. The second most common reason for admission was malignancy in the total study population and in the no kidney injury group. However, in the de-novo injury and pre-existing EKF groups, cardiac arrest and kidney disorders were the second most common reasons for admission to ICU.

Within the 1,132 patients admitted with sepsis, the majority suffered from a de-novo kidney injury (56.2%). This was in contrast to the second and third most common reason for admission: malignancy and trauma. Within these two groups, the vast majority of patients did not suffer from any form of kidney injury for the duration of their stay (79.7% and 70.2% respectively). Other admitting diagnoses associated with a high rate of DNKI were cardiac arrest (60.0%), kidney diagnosis (71.5%), and vascular diagnosis (75.0%).

3.4.2.3 Interventions during ICU stay

Organ support was provided to 3,757 patients during the study period accounting for 70.7% of the total population (Table 3.4). Multi-organ support was provided to 2,089 (39.3%) and of this group, 1,306 (62.5%) experienced a de-novo kidney injury. The most common type of organ support utilised amongst the total study population was IMV (58.3%). The majority of the 3,095 patients who received IMV were found to have suffered a de-novo kidney injury at some point during their ICU admission (51.3%). This was also the case for the 2,533 patients who received CVS: 1,451 patients (57.3%) of these patients suffered from a de-novo injury during their ICU stay.

The no kidney injury group were found to have a much lower proportion of patients receiving any organ support (57.5%) compared to the other two groups; only 23.4% of patients in this group required multi-organ support. Conversely, 88.9% of patients within the de-novo injury group received at least single organ support; 60.8% of all patients within this group received multiple modalities of organ support. Whilst the pre-existing EKF group had low numbers, a high proportion of these patients received KRT (72.8%); a similarly high proportion of pre-existing EKF patients received multi-organ support (64.1%). The majority of patients within this group also received IMV (52.4%) and CVS (58.3%). The proportion of patients who received KRT in this group was much higher when compared to the de-novo injury group (72.8% vs 23.3%).

Intervention	Total patients (n = 5312)	No kidney injury (n = 3062)	De-novo kidney injury (n = 2147)	Pre-existing established kidney failure (n = 103)
Modalities – n (%)				
Invasive mechanical ventilation	3095 (58.3%)	1454 (47.5%)	1587 (73.9%)	54 (52.4%)
Cardiovascular support	2533 (47.7%)	1022 (33.4%)	1451 (67.6%)	60 (58.3%)
Kidney replacement therapy	573 (10.8%)	-	498 (23.2%)	75 (72.8%)
Degree of organ support - n (%)				
None	1555 (29.3%)	1303 (42.6%)	238 (11.1%)	14 (13.6%)
Single	1668 (31.4%)	1042 (34.0%)	603 (28.1%)	23 (22.3%)
Multi	2089 (39.3%)	717 (23.4%)	1306 (60.8%)	66 (64.1%)

Table 3.4: Organ support received based on presence of kidney injury

3.4.3 Differences based on severity of kidney injury

3.4.3.1 Demographics on admission to ICU

Classification of severity of kidney injury was performed on all 2,147 patients suffering from a de-novo injury. These patients were classified according to stage of injury: the highest severity at any point during their ICU stay. The proportion of patients suffering from each stage of injury can be found in Table 3.5.

Across the three severity groups there was a similar proportion of males/females as well as median age. Rates of admission from surgical specialties were similar between the groups with stage 1 and stage 2 injury; a smaller proportion of patients were admitted from surgery who went on to suffer a stage 3 injury (47.3% vs. 53.8%; *p*-value <0.001 when compared to stage 1 injury). 677 of the 1,105 surgical patients were admitted directly from theatre and further classified as emergency or elective procedures. There were 213 patients with stage 3 injury who were admitted directly from theatre. Of these, 189 (88.7%) patients were classed as emergency procedures. Stage 3 injury occurred in 16.9% of patients admitted following an elective procedure as opposed to 35.3% of emergency procedures (*p*-value <0.001).

Median baseline eGFR was significantly lower in patients with stage 3 injury compared to those with stage 1 injury (79.5 vs 82.2 respectively; *p*-value = 0.011). Median calculated APACHE II scores increased as severity of disease increased from 19.0 in patients with stage 1 injury compared with 25.0 in patients with stage 3 injury (*p*-value <0.001). On comparing the rates of comorbidities between the stage 1 group and the stage 3 group, the latter had significantly higher proportions of pre-existing liver disease (*p*-value = 0.004) and pre-existing diabetes (*p*-value = <0.001). All other comorbidities were similar between these two groups.

Characteristic	De-novo injury (n = 2147)	Stage 1 (n = 801)	Stage 2 (n = 412)	Stage 3 (n = 934)
Age – median (IQR)	61.0 (49.0 – 72.0)	60.0 (47.0 – 73.0)	65.0 (51.0 – 74.0)	61.0 (49.0 – 70.0)
Male - n (%)	1293 (60.2%)	477 (59.6%)	255 (61.9%)	561 (60.1%)
Admitted from surgical specialty – n (%)	1107 (51.6%)	431 (53.8%)	234 (56.8%)	442 (47.3%)
Baseline eGFR – median (IQR)	82.5 (59.1 – 99.2)	82.2 (60.9 – 98.5)	87.0 (68.8 – 101.7)	79.5 (51.3 – 98.4)
APACHE II score – median[2] (IQR)	22.0 (17.0 – 29.0)	19.0 (14.0 – 24.0)	21.0 (16.0 – 28.0)	25.0 (20.0 – 31.0)
Comorbidities – n (%)				
Cardiovascular disease	960 (44.7%)	340 (42.5%)	185 (44.9%)	435 (46.6%)
Respiratory disease	437 (20.4%)	156 (19.5%)	102 (24.8%)	179 (19.2%)
Liver disease	235 (11.0%)	65 (8.1%)	53 (12.9%)	117 (12.5%)
Diabetes	402 (18.7%)	125 (15.6%)	61 (14.8%)	216 (23.1%)
Malignancy	145 (6.8%)	62 (7.7%)	28 (6.8%)	55 (5.9%)

Table 3.5: Demographics of patients based on severity of kidney injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

[2] Data unavailable for 112 patients – only 2035 patients used in these calculations (Stage 1 = 749; Stage 2 = 390; Stage 3 = 896)

3.4.3.2 Illness primarily responsible for admission to ICU

Precipitating illness	De-novo kidney injury (n = 2147)	Stage 1 (n = 801)	Stage 2 (n = 412)	Stage 3 (n = 934)
Sepsis/Infection	636 (29.6%)	180 (22.5%)	138 (33.5%)	318 (34.1%)
Cardiac Arrest	180 (8.4%)	73 (9.1%)	43 (10.4%)	64 (6.9%)
Gastrointestinal (Other)	126 (5.9%)	43 (5.4%)	36 (8.7%)	47 (5.0%)
Trauma	121 (5.6%)	77 (9.6%)	20 (4.9%)	24 (2.6%)
Respiratory/Airway	115 (5.4%)	57 (7.1%)	11 (2.7%)	47 (5.0%)
Kidney	108 (5.0%)	10 (1.3%)	3 (0.7%)	95 (10.2%)
Malignancy	105 (4.9%)	64 (8.0%)	21 (5.1%)	20 (2.1%)
Gastrointestinal Perforation	92 (4.3%)	28 (3.5%)	25 (6.1%)	39 (4.2%)
Neurological	85 (4.0%)	40 (5.0%)	14 (3.4%)	31 (3.3%)
Haemorrhage	83 (3.9%)	25 (3.1%)	18 (4.4%)	40 (4.3%)
Vascular	81 (3.8%)	26 (3.3%)	16 (3.9%)	39 (4.2%)
Seizures	73 (3.4%)	46 (5.7%)	7 (1.7%)	20 (2.1%)

Hepatobiliary	71 (3.3%)	24 (3.0%)	11 (2.7%)	36 (3.9%)
Drug Related	50 (2.3%)	32 (4.0%)	7 (1.7%)	11 (1.2%)
Endocrine/Metabolic	46 (2.1%)	7 (0.9%)	8 (1.9%)	31 (3.3%)
Cardiac Failure	41 (1.9%)	13 (1.6%)	8 (1.9%)	20 (2.1%)
Cardiac (Other)	24 (1.1%)	7 (0.9%)	6 (1.5%)	11 (1.2%)
Post-operative Complications	24 (1.1%)	13 (1.6%)	5 (1.2%)	6 (0.6%)
Liver Disease	21 (1.0%)	3 (0.4%)	2 (0.5%)	16 (1.7%)
Burns Related	16 (0.8%)	10 (1.3%)	1 (0.2%)	5 (0.5%)
Miscellaneous	12 (0.6%)	5 (0.6%)	4 (1.0%)	3 (0.3%)
Hypersensitivity/Immunocompromise	10 (0.5%)	6 (0.8%)	-	4 (0.4%)
Ischaemic Heart Disease	8 (0.4%)	4 (0.5%)	3 (0.7%)	1 (0.1%)
Obstetrics/Gynaecology	7 (0.3%)	4 (0.5%)	3 (0.7%)	-
Musculoskeletal	6 (0.3%)	4 (0.5%)	1 (0.2%)	1 (0.1%)
Haematology/Coagulation	6 (0.3%)	-	1 (0.2%)	5 (0.5%)

Table 3.6: Primary illness necessitating ICU admission based on severity of kidney injury

The most common reason precipitating ICU admission was sepsis/infection for all three stages of severity as demonstrated in Table 3.6. As the severity of disease increased, the relative proportion of patients who were admitted with sepsis also increased: 22.5%, 33.5% and 34.1%. Amongst the 636 patients admitted with sepsis, 318 went on to develop a stage 3 injury (50.0%). Other diagnoses which included a high rate of progression to stage 3 injury included: Kidney disorders (88.0%); Endocrine/Metabolic disorders (67.4%); Liver disease (76.2%); and Haematology/Coagulation disorders (83.3%). Admitting diagnoses which commonly did not progress beyond stage 1 injury included: Trauma (63.6%); Malignancy (61.0%); Seizures (63.0%); Drug related disease (64.0%); Burns related disease (62.5%); Hypersensitivity/Immunocompromise (60.0%); and Musculoskeletal disorders (66.7%). It was however noted that numbers in some of these diagnostic groups were very small.

3.4.3.3 Organ support based on severity of injury

Amongst all 2,147 patients with de-novo injury, the most common organ support was IMV (73.9%). There was an increasing trend in the proportion of patients requiring either IMV or CVS as the severity of kidney injury increased. 45.0% of patients requiring IMV progressed to a stage 3 injury; this was also the case in 47.4% of patients requiring CVS. Only stage 3 patients received KRT, as initiation of KRT is a criterion for stage 3 injury; 498 of these 934 patients required KRT (53.3%).

With regards to degree of organ support, there was an increasing trend in requirement for multi-organ support as the severity of kidney injury increased: 47.6% of patients in the stage 1 group compared to 75.3% in the stage 3 group (*p*-value <0.001). There was a corresponding decreasing trend in the proportion of patients that required no organ support as severity of disease increased: 15.7% in the stage 1 group compared to 6.32% in the stage 3 (*p*-value <0.001).

Intervention	De-novo kidney injury (n = 2147)	Stage 1 (n = 801)	Stage 2 (n = 412)	Stage 3 (n = 934)
Modalities – n (%)				
Invasive mechanical ventilation	1587 (73.9%)	574 (71.7%)	299 (72.6%)	714 (76.5%)
Cardiovascular support	1451 (67.6%)	482 (60.2%)	282 (68.5%)	687 (73.6%)
Kidney replacement therapy	498 (23.2%)	-	-	498 (53.3%)
Degree of organ support - n (%)				
None	238 (11.1%)	126 (15.7%)	53 (12.8%)	59 (6.3%)
Single	603 (28.1%)	294 (36.7%)	137 (33.3%)	172 (18.4%)
Multi	1306 (60.8%)	381 (47.6%)	222 (53.9%)	703 (75.3%)

Table 3.7: Rates of organ support based on severity of kidney injury

3.4.3.4 Rates of kidney recovery

The time taken until kidney recovery is represented in Table 3.8 and Figure 3.2. In order to prevent mortality from influencing interpretation of time until kidney recovery, the analysis was only performed on people who survived to ICU discharge. The median length of time for kidney recovery was 2.0 days for all patients suffering from de-novo injury. The median length of time until kidney recovery was 1.0 and 2.0 days for stages 1 and 2 respectively; stage 3 disease was associated with an increased median length of kidney injury of 7.0 days (*p*-values both <0.001 when compared with stage 1 and stage 2 injury). Furthermore, 278 of the 545 patients (51.0%) with stage 3 injury took seven or more days before kidney recovery and had thus progressed to AKD. In contrast, 669 out of the 697 patients (96.0%) to suffer from a stage 1 injury resolved

within 7 days and were classified as AKI. 86.8% of stage 2 disease resolved within 7 days and were also categorised as AKI.

Event	De-novo injury (n = 1500)	Stage 1 (n = 697)	Stage 2 (n = 258)	Stage 3 (n = 545)
Time to kidney recovery - days				
Median	2.0	1.0	2.0	7.0
Interquartile Range	1.0 - 5.0	1.0 - 2.0	1.0 - 4.0	2.5 - 19.0

Table 3.8: Length of kidney injury according to severity of disease in ICU survivors

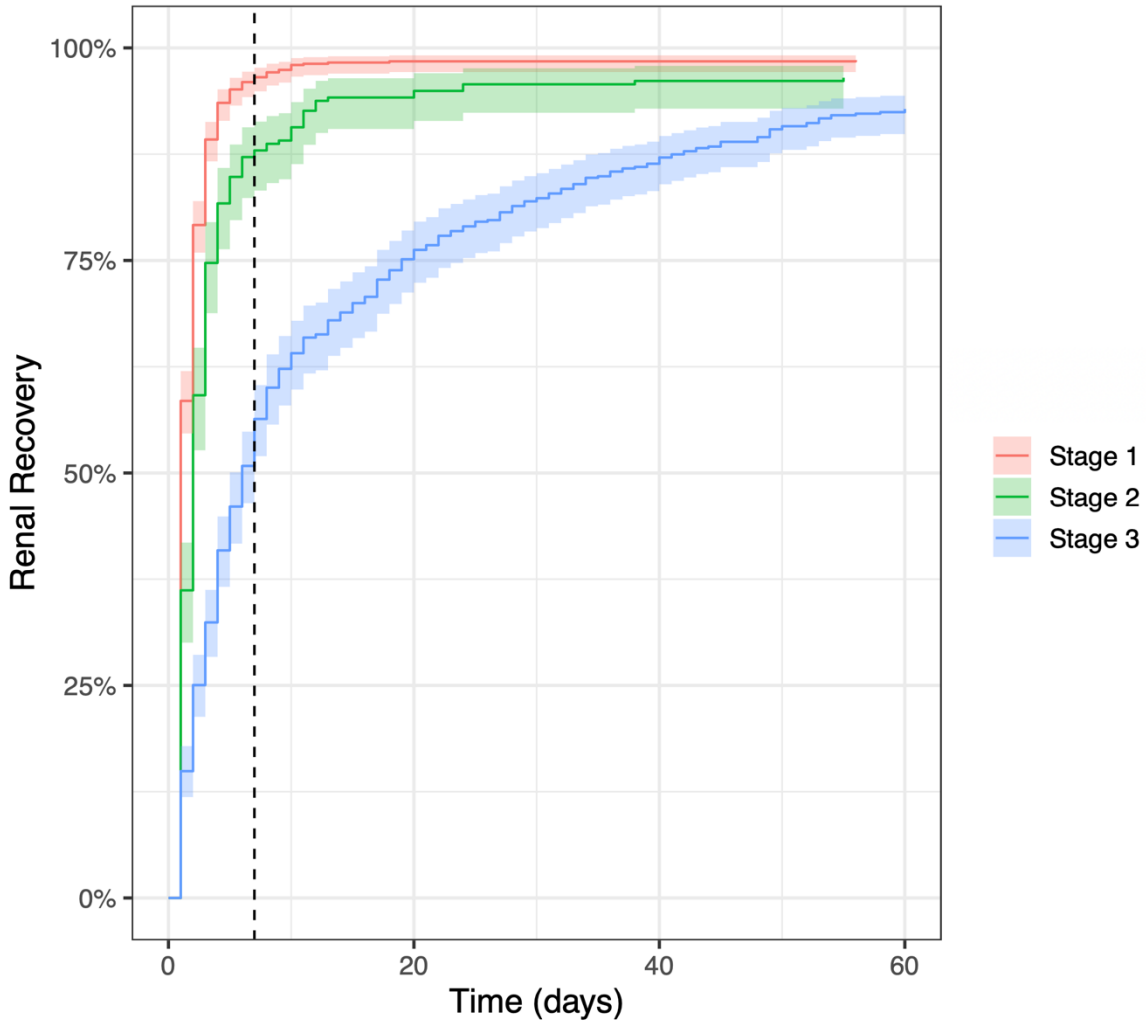


Figure 3.2: Time to kidney recovery based on severity over first 60 days in ICU survivors. The vertical line represents day 7 and progression to AKD. Reproduced from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

3.4.4 Progression to AKD

3.4.4.1 Baseline demographics

Characteristic	De-novo injury (n = 2147)	DNKI non-survivors at day 7 (n = 527)	Acute kidney injury (n = 1217)	Acute kidney disease (n = 403)
Age – median (IQR)	61.0 (49.0 – 72.0)	65.0 (52.0 – 73.0)	60.0 (48.0 – 72.0)	61.0 (48.5 – 71.0)
Male - n (%)	1293 (60.2%)	309 (58.6%)	723 (59.4%)	261 (64.8%)
Admitted from surgical specialty – n (%)	1107 (51.6%)	189 (35.9%)	713 (58.6%)	205 (50.9%)
Baseline eGFR – median (IQR)	82.5 (59.1 – 99.2)	80.5 (55.8 – 100.1)	84.9 (64.3 – 101.1)	72.8 (48.4 – 94.4)
APACHE II score – median[3] (IQR)	22.0 (17.0 – 29.0)	30.0 (25.0 – 36.0)	19.0 (14.0 – 24.0)	24.0 (20.0 – 29.0)
Comorbidities – n (%)				
Cardiovascular disease	960 (44.7%)	259 (49.2%)	514 (42.2%)	187 (46.4%)
Respiratory disease	437 (20.4%)	114 (21.6%)	251 (20.6%)	72 (17.9%)
Liver disease	235 (11.0%)	69 (13.1%)	129 (10.6%)	37 (9.2%)
Diabetes	402 (18.7%)	96 (18.2%)	208 (17.1%)	98 (24.3%)
Malignancy	145 (6.8%)	32 (6.1%)	88 (7.2%)	25 (6.2%)

Table 3.9: Demographics of patients in each kidney injury group at baseline. DNKI non-survivors group was defined as patients who died within the first 6 days from point of first kidney injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

[3] Data unavailable for 112 patients – only 2035 patients used in these calculations (Mortality within 6 days = 452; AKI = 1190; AKD = 393)

There were 2,147 patients with new kidney injury following ICU admission; 527 of these patients died within 6 days of their initial injury. Of the patients who survived to day 7 post injury, 1,217 (75.1%) had an injury length of 6 days or less and were classified as AKI, whilst 403 patients (24.9%) progressed to AKD.

1,293 of all de-novo injury patients were identified as male (60.2%). Whilst a higher proportion of all patients admitted were male, there was a slight increase in proportion of males when comparing AKI and AKD groups; 59.4% of patients with acute kidney injury were male, whereas 64.8% of all patients suffering from acute kidney disease were male (*p*-value = 0.064) (Table 3.9). The median age of all patients suffering a de-novo injury during the study period was 61.0 (IQR = 49.0 – 72.0) and this was similar between the AKI and AKD groups. Median baseline eGFR was found to be significantly lower in the AKD group when compared to the AKI group (72.8 vs 84.9 ml/min/1.73m^2; *p*-value <0.001).

The majority of patients with de-novo kidney injury during their ICU stay were admitted from a surgical specialty (51.6%) (Table 3.9). A comparatively lower proportion of patients to die within 6 days of initial injury were admitted from a surgical specialty (35.9%). A lower proportion of patients within the AKD group were admitted from surgical specialties compared with the AKI group (50.9% vs 58.6% respectively; *p*-value = 0.008). Of the 1,107 patients admitted from surgical specialties, 677 were admitted directly from the operating theatre and were therefore further classified as either an admission following an emergency/urgent operative intervention or following an elective/scheduled intervention. 535 of these were admissions following emergency interventions (79.0%): 343 of 460 patients in the AKI group (74.6%) and 98 of 113 patients in AKD group (86.7%).

Only the 2,035 patients with available APACHE II scores were used for severity of illness analysis. The median APACHE II score for all de-novo injury patients was calculated as 22.0 (IQR = 17.0 – 29.0). AKD patients had a statistically significantly higher score when compared to AKI patients (24.0 vs 19.0 respectively; *p*-value <0.001).

The data collected on comorbidities showed that a high proportion of all patients with de-novo injury suffered from pre-existing cardiovascular disease (44.7%). When comparing specifically the AKI and AKD groups, the proportions of patients within these groups were similar for several comorbidities including pre-existing cardiovascular comorbidities (*p*-value = 0.160) respiratory disease (*p*-value = 0.249), pre-existing liver disease (*p*-value = 0.416) and pre-existing malignancy (*p*-value = 0.556). In contrast, a significantly higher proportion of people with pre-existing diabetes were found in the AKD group when compared to patients in the AKI group (24.3% vs 17.1% respectively; *p*-value = 0.002).

3.4.4.2 Primary reason for admission to ICU

Precipitating illness	De-novo kidney injury (n = 2147)	DNKI non-survivors at day 7 (n = 527)	Acute kidney injury (n = 1217)	Acute kidney disease (n = 403)
Sepsis/Infection	636 (29.6%)	161 (30.6%)	327 (26.9%)	148 (36.7%)
Cardiac Arrest	180 (8.4%)	117 (22.2%)	42 (3.5%)	21 (5.2%)
Gastrointestinal (Other)	126 (5.9%)	25 (4.7%)	88 (7.2%)	13 (3.2%)
Trauma	121 (5.6%)	19 (3.6%)	92 (7.6%)	10 (2.5%)
Respiratory/Airway	115 (5.4%)	22 (4.2%)	73 (6.0%)	20 (5.0%)
Kidney	108 (5.0%)	14 (2.7%)	44 (3.6%)	50 (12.4%)
Malignancy	105 (4.9%)	11 (2.1%)	85 (7.0%)	9 (2.2%)
Gastrointestinal Perforation	92 (4.3%)	12 (2.3%)	64 (5.3%)	16 (4.0%)
Neurological	85 (4.0%)	29 (5.5%)	48 (3.9%)	8 (2.0%)
Haemorrhage	83 (3.9%)	16 (3.0%)	51 (4.2%)	16 (4.0%)
Vascular	81 (3.8%)	23 (4.4%)	32 (2.6%)	26 (6.5%)
Seizures	73 (3.4%)	3 (0.6%)	63 (5.2%)	7 (1.7%)

Hepatobiliary	71 (3.3%)	15 (2.9%)	39 (3.2%)	17 (4.2%)
Drug Related	50 (2.3%)	2 (0.4%)	38 (3.1%)	10 (2.5%)
Endocrine/Metabolic	46 (2.1%)	6 (1.1%)	32 (2.6%)	8 (2.0%)
Cardiac Failure	41 (1.9%)	16 (3.0%)	21 (1.7%)	4 (1.0%)
Cardiac (Other)	24 (1.1%)	6 (1.1%)	16 (1.3%)	2 (0.5%)
Post-operative Complications	24 (1.1%)	1 (0.2%)	20 (1.6%)	3 (0.7%)
Liver Disease	21 (1.0%)	15 (2.9%)	1 (0.1%)	5 (1.2%)
Burns Related	16 (0.8%)	4 (0.8%)	10 (0.8%)	2 (0.5%)
Miscellaneous	12 (0.6%)	4 (0.8%)	7 (0.6%)	1 (03%)
Hypersensitivity/Immunocompromise	10 (0.5%)	1 (0.2%)	7 (0.6%)	2 (0.5%)
Ischaemic Heart Disease	8 (0.4%)	2 (0.4%)	6 (0.5%)	-
Obstetrics/Gynaecology	7 (0.3%)	-	7 (0.6%)	-
Musculoskeletal	6 (0.3%)	2 (0.4%)	4 (0.3%)	-
Haematology/Coagulation	6 (0.3%)	1 (0.2%)	-	5 (1.2%)

Table 3.10: Primary admission diagnosis for de-novo kidney injury based on length of injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

The primary illness associated with admission to intensive care demonstrated that the most common reason for admission for all 2,147 de-novo injury patients was sepsis or infection (29.6%). When separated into early mortality, AKI and AKD groups, all three also had sepsis/infection as the most common reason for admission (Table 3.10). In the AKI group, 26.9% of patients had sepsis recorded as their primary reason for admission to critical care; the corresponding proportion in the AKD group was 36.7% (*p*-value <0.001).

The AKD group also had a higher proportion of patients admitted with a primarily kidney disorder when compared to the AKI group (12.4% vs 3.6%; *p*-value <0.001). Of all the diagnoses, higher rates of progression to AKD were demonstrated in patients admitted with kidney disorders (53.2%), vascular disorders (44.8%) and, whilst the relative numbers are very small (n = 6), haematology/coagulation disorders (100.0%). In contrast, none of the patients admitted with ischaemic heart disease, an obstetric/gynaecological disorder or a musculoskeletal disorder progressed to AKD; again, numbers in these patient groups were very small (8, 7 and 6 patients respectively).

3.4.4.3 Recipients of organ support

Out of the 2,147 patients who suffered from a de-novo injury at any point during admission to ICU, 1,909 (88.9%) required some form of organ support during their stay (Table 3.11). When comparing specific modalities of organ support, the rates of IMV and CVS were significantly higher in the AKD group compared to the AKI group (*p*-values <0.001 for both IMV and CVS). However, the most marked difference was seen with regards to KRT: 58.6% of patients in the AKD group received KRT compared to 8.8% of patients in the AKI group (*p*-value <0.001). Of the 498 patients that received KRT, 343 (68.9%) survived to day-7 post injury; among the KRT survivors, 236 (68.8%) progressed to AKD.

The majority of all patients with de-novo injury received multi-organ support (60.8%). Within the AKD subgroup, a higher proportion of patients received multi-organ support when compared to patients in the AKI group (74.9% vs 52.1%; *p*-value <0.001). In keeping with this, comparatively lower proportions of patients in the AKD group received no organ support than patients who suffered from AKI (5.5% vs 15.9%; *p*-value <0.001). Of the 936 patients who survived to

day-7 post injury and required multi-organ support, 302 progressed to AKD (32.3%). This compared to only 79 of 468 (16.9%) who required single organ support and 22 of 216 patients who required no organ support (10.2%).

Intervention	De-novo kidney injury (n = 2147)	DNKI non-survivors at day 7 (n = 527)	Acute kidney injury (n = 1217)	Acute kidney disease (n = 403)
Modalities – n (%)				
Invasive mechanical ventilation	1587 (73.9%)	469 (89.0%)	812 (66.7%)	306 (75.9%)
Cardiovascular support	1451 (67.6%)	339 (64.3%)	807 (66.3%)	305 (75.7%)
Kidney replacement therapy	498 (23.2%)	155 (29.4%)	107 (8.8%)	236 (58.6%)
Degree of organ support - n (%)				
None	238 (11.1%)	22 (4.2%)	194 (15.9%)	22 (5.5%)
Single	603 (28.1%)	135 (25.6%)	389 (32.0%)	79 (19.6%)
Multi	1306 (60.8%)	370 (70.2%)	634 (52.1%)	302 (74.9%)

Table 3.11: Recipients of varying modalities of organ support by length of kidney injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

3.4.5 KRT requirement in patients with de novo kidney injury

Characteristic	De-novo injury (n = 2147)	Did not receive KRT (n = 1649)	Received KRT (n = 498)
Age – median (IQR)	61.0 (49.0 – 72.0)	61.0 (48.0 – 73.0)	61.0 (49.0 – 70.0)
Male - n (%)	1293 (60.2%)	996 (60.4%)	297 (59.6%)
Admitted from surgical specialty – n (%)	1107 (51.6%)	881 (53.4%)	226 (45.4%)
Baseline eGFR – median (IQR)	82.5 (59.1 – 99.2)	84.5 (63.8 – 100.7)	70.0 (42.3 – 95.9)
APACHE II score – median[4] (IQR)	22.0 (17.0 – 29.0)	21.0 (15.0 – 27.0)	27.0 (22.0 – 32.0)
Comorbidities – n (%)			
Cardiovascular disease	960 (44.7%)	755 (45.8%)	205 (41.2%)
Respiratory disease	437 (20.4%)	347 (21.0%)	90 (18.1%)
Liver disease	235 (11.0%)	183 (11.1%)	52 (10.4%)
Diabetes	402 (18.7%)	279 (16.9%)	123 (24.7%)
Malignancy	145 (6.8%)	118 (7.2%)	27 (5.4%)
Most common precipitating illnesses necessitating ICU admission	1. Sepsis 2. Cardiac Arrest 3. Gastro (Other)	1. Sepsis 2. Cardiac Arrest 3. Gastro (Other)	1. Sepsis 2. Kidney 3. Vascular

Table 3.12: Demographics of de-novo injury patients at baseline stratified by receipt of KRT

[4] Data unavailable for 112 patients – only 2035 patients used in these calculations (Did not receive KRT = 1558; Received KRT = 477)

Of the 2,147 patients with new kidney injury following ICU admission, 498 patients (23.2%) received KRT. The baseline demographics comparing patients with de-novo kidney injury who did and did not receive KRT are described in Table 3.12. Similar proportions of male patients were found in both groups and the median age was the same. A smaller proportion of patients that received KRT were admitted from surgical specialties (45.4%) when compared to patients who did not receive KRT during their admission (53.4%; *p*-value <0.001). Median baseline eGFR was found to be significantly lower in the group which received KRT compared to the group which did not (70.0 vs 84.5; *p*-value <0.001).

As with the entire study population, a number of patients within this subgroup did not have an available APACHE score for analysis. As such, with regards to the analysis of APACHE II score, these 112 patients (5.2%) were excluded. The remaining 2,035 patients were stratified according to receipt of KRT. When comparing the non-KRT group to patients who received KRT, the median APACHE II score was higher in the KRT group: 21.0 vs 27.0 respectively (*p*-value <0.001).

On analysis of primary diagnosis on admission, the most common reason for admission in both groups was sepsis/infection; this constituted 455 patients (27.7%) in the non-KRT group and 180 patients (36.1%) in the KRT group (*p*-value <0.001). However, the KRT group's second and third most common admission reasons were kidney and vascular disorders; this is the same as the reasons for admission within the AKD subgroup (Table 3.10). The data also demonstrated that rates of all of the pre-defined comorbidities were similar between the two groups with the exception of diabetes; there was a significantly higher incidence of pre-existing diabetes within the patients who received KRT compared to those who did not (24.7% vs 16.9% respectively; *p*-value <0.001).

3.4.6 Features associated with developing kidney injury or progression to AKD

3.4.6.1 Factors associated with development of de-novo injury

The different clinical and demographic features of those who do and do not develop de-novo kidney injury in ICU are described in Table 3.2. The results of initial univariable analyses using these variables are then demonstrated in Table 3.13: statistical significance was found in all domains except for the presence of pre-existing respiratory disease and malignancy prior to ICU admission. Despite there being a statistically significant difference in APACHE II scores between the groups, it was not included in these analyses due to the risk of co-linearity: APACHE II utilises age, comorbidities and a marker of kidney function within its calculation. Patients that were older, male, admitted from medical specialties and had a lower baseline eGFR, were more likely to develop DNKI. In addition, patients with an admission diagnosis of sepsis or pre-existing cardiovascular comorbidities, liver disease or diabetes, had a higher chance of developing DNKI.

The subsequent multivariable analysis was performed using all the represented variables which were found to have a *p*-value <0.2 on their univariable analyses (Table 3.13). This multivariable analysis revealed that age was a strong contributing factor to development of de-novo kidney injury, with ORs of 1.35 and 1.64 for patients aged 45-65 and >65 years respectively when compared to the reference group of <45 years. Male sex also showed a strong correlation with the development of de-novo kidney injury (OR = 1.49). Admission from surgical specialties was associated with a decreased risk of developing of de-novo injury (OR = 0.70).

Admission due to sepsis demonstrated a significant association with development of DNKI (OR = 2.13). Similarly, decreasing baseline eGFR was strongly associated with development of DNKI during ICU admission: the ORs were 2.03 and 6.12 for patients with a baseline eGFR of 30-60 ml/min/1.73m^2 and <30 ml/min/1.73m^2 respectively when compared to the reference group of >60 ml/min/1.73m^2. When analysing comorbidities, pre-existing cardiovascular disease (OR = 1.22), liver disease (OR = 1.42) and diabetes (OR = 1.40) were all associated with the development of de-novo injury. Pre-existing respiratory comorbidities and pre-

existing malignancy did not reach significance on initial univariable analysis and therefore were not included in the multivariable analysis.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.51 (1.30 – 1.74)	<0.001	1.35 (1.16 – 1.58)	<0.001
>65 years	1.97 (1.70 - 2.28)	<0.001	1.64 (1.38 – 1.95)	<0.001
Sex				
Female	Ref	-	Ref	-
Male	1.39 (1.24 - 1.55)	<0.001	1.49 (1.33 – 1.68)	<0.001
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.66 (0.59 – 0.73)	<0.001	0.70 (0.62 – 0.79)	<0.001
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	2.38 (2.02 – 2.80)	<0.001	2.03 (1.70 – 2.41)	<0.001
<30 ml/min/1.73m^2	7.20 (5.02 – 9.89)	<0.001	6.12 (4.22 – 9.11)	<0.001
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	2.34 (2.05 – 2.69)	<0.001	2.13 (1.84 – 2.45)	<0.001
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.57 (1.40 – 1.76)	<0.001	1.22 (1.07 – 1.39)	0.003
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.43 (1.18 – 1.72)	<0.001	1.42 (1.16 – 1.73)	<0.001
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.82 (1.56 – 2.13)	<0.001	1.40 (1.18 – 1.65)	<0.001
Respiratory comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.03 (0.89 – 1.18)	0.750		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.90 (0.72 – 1.12)	0.368		

Table 3.13: Multivariable analysis of factors associated with de-novo kidney injury

3.4.6.2 Risk factors associated with progression from AKI to AKD

The clinical and demographic features of AKI patients compared to AKD patients are described in Table 3.9. For each of the described variables, initial univariable analyses are demonstrated in Table 3.14: these found that male sex, decreasing baseline eGFR, admission from surgical specialties, admission due to sepsis, pre-existing cardiovascular comorbidities and pre-existing diabetes had a *p*-value <0.2 and were therefore included in the multivariable model. However, age was considered too important a variable to exclude and was therefore included in the multivariable model despite having a *p*-values of 0.420 and 0.451. Initially, progression to stage 3 kidney injury was included in the predictive model; this was very strongly associated with protracted injury (OR = 8.57, $p < 0.001$). Since this association was so strong and it was felt to mask the effect of other variables, it was removed from the multivariable model; when an analysis of factors associated with progression to stage 3 injury was conducted, significant variables were similar to the results shown in Table 3.14.

The results of the multivariable analysis can be found in Table 3.14. In this analysis, male sex (OR = 1.25) and admission due to sepsis (OR = 1.35) demonstrated a significant association with progression from AKI to AKD. Furthermore, decreasing baseline eGFR was strongly associated with progression to AKD: the ORs were 1.44 and 1.95 for patients with a baseline eGFR of 30-60 ml/min/1.73m^2 and <30 ml/min/1.73m^2 respectively when compared to the reference group of >60 ml/min/1.73m^2. Initial univariable analysis suggested progression to AKD was decreased in patients admitted from surgical specialties and increased in patients with pre-existing diabetes, but neither of these variables displayed statistical significance when factored into the multivariable model (*p*-value = 0.099 and 0.072 respectively).

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.13 (0.84 – 1.55)	0.420	1.04 (0.79 – 1.38)	0.783
>65 years	1.12 (0.83 – 1.54)	0.451	1.00 (0.74 – 1.35)	0.998
Sex				
Female	Ref	-	Ref	-
Male	1.25 (0.99 – 1.59)	0.064	1.25 (1.02 – 1.54)	0.037
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.73 (0.46 – 0.92)	0.008	0.84 (0.69 – 1.03)	0.099
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.66 (1.25 – 2.20)	<0.001	1.44 (1.12 – 1.83)	0.004
<30 ml/min/1.73m^2	2.94 (1.95 – 4.42)	<0.001	1.95 (1.41 – 2.65)	<0.001
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	1.58 (1.24 – 2.00)	<0.001	1.35 (1.10 – 1.66)	0.004
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.18 (0.94 – 1.48)	0.160	1.04 (0.84 – 1.30)	0.698
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.56 (1.18 – 2.04)	0.002	1.24 (0.98 – 1.57)	0.072
Respiratory disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.83 (0.62 – 1.11)	0.249		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.85 (0.57 – 1.24)	0.416		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.85 (0.53 – 1.32)	0.556		
Stage of injury				
Limited to 1 or 2	Ref	-	-	-
Progression to 3	12.23 (9.23 – 16.42)	<0.001		

Table 3.14: Multivariable analysis of factors associated with prolonged kidney injury. Reproduced from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

3.4.7 In-patient mortality

3.4.7.1 In-ICU and in-hospital mortality for entire study population

The total number of deaths in-ICU during the study period was 919 with a corresponding ICU mortality rate of 17.3%. These mortality rates varied based on kidney injury group as shown in Table 3.15 and Figure 3.3. The raw ICU mortality figures amongst groups demonstrated that the de-novo injury group had a significantly higher mortality rate compared to the patient group who suffered no kidney injury (30.1% vs 8.2% respectively; *p*-value < 0.001). The total number of in-hospital deaths for patients admitted to ICU during the study period was 1,146 (in-hospital mortality rate of 21.6%). The raw mortality figures amongst the groups demonstrated a similar pattern to in-ICU mortality rates: the in-hospital mortality rate for the de-novo injury group was significantly higher when compared to patients who suffered from no kidney injury whilst admitted to ICU: (35.9% vs 11.4% respectively; *p*-value < 0.001).

Event	Total patients (n = 5312)	No kidney injury (n = 3062)	De-novo kidney injury (n = 2147)	Pre-existing established kidney failure (n = 103)
Death during ICU admission				
Number of deaths – n (%)	919 (17.3%)	251 (8.2%)	646 (30.1%)	22 (21.4%)
95% Confidence Intervals	16.3% - 18.3%	7.2% - 9.2%	28.1% - 32.0%	14.2% - 29.9%
Death during hospital admission				
Number of deaths – n (%)	1146 (21.6%)	349 (11.4%)	770 (35.9%)	27 (26.2%)
95% Confidence Intervals	20.5% - 22.8%	10.3% - 12.6%	34.0% - 38.1%	18.4% - 35.2%

Table 3.15: In-patient mortality rates based on presence of kidney injury

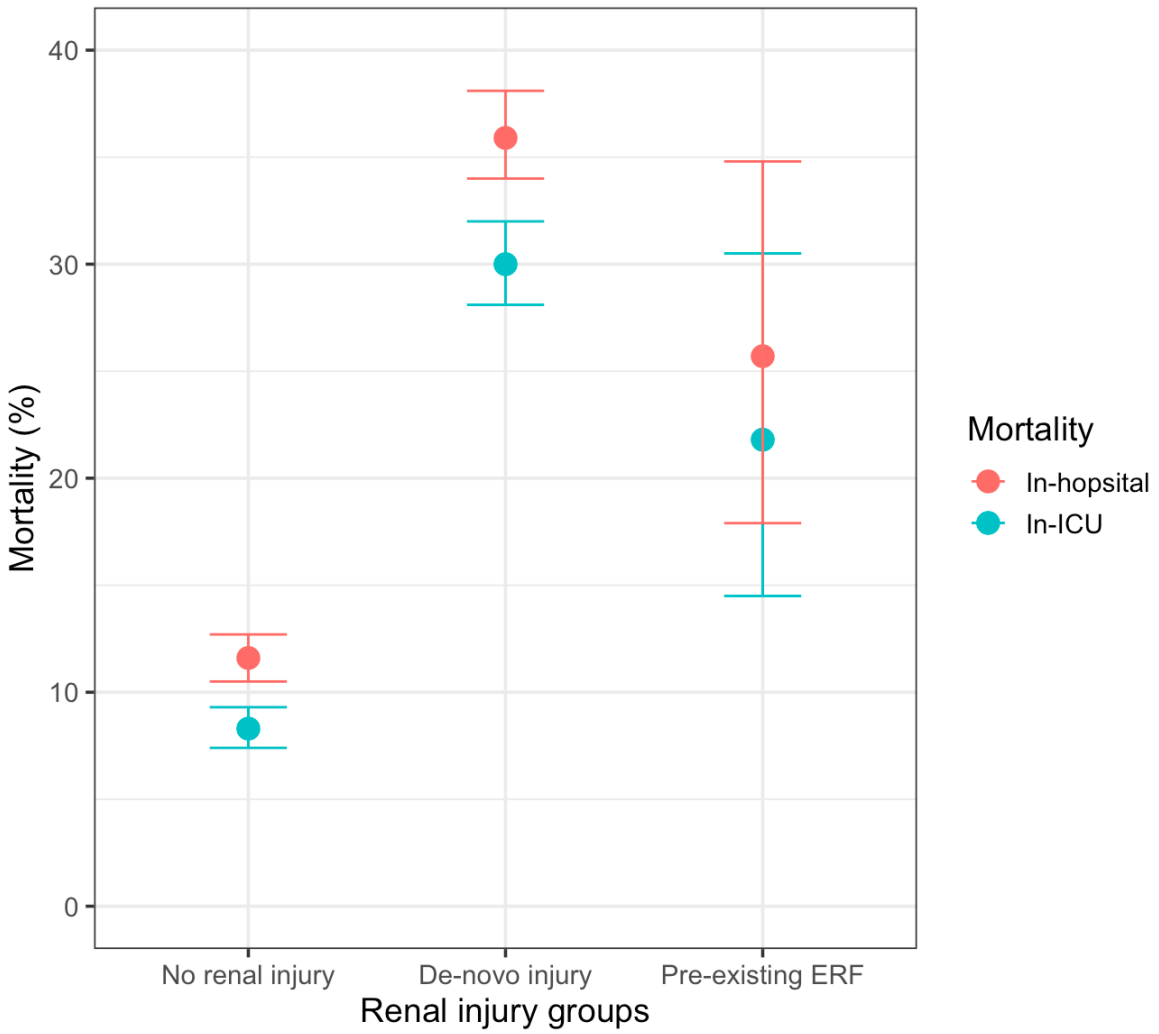


Figure 3.3: In-ICU and in-hospital raw mortality with 95% confidence intervals

3.4.7.2 In-patient mortality based on severity of injury

Event	De-novo kidney injury (n = 2147)	Stage 1 (n = 801)	Stage 2 (n = 412)	Stage 3 (n = 934)
Death during ICU admission				
Number of deaths – n (%)	646 (30.1%)	167 (20.9%)	134 (32.5%)	345 (36.9%)
95% Confidence Intervals	28.1% - 32.0%	18.2% - 23.5%	28.1% - 37.3%	33.9% - 40.2%
Death during hospital admission				
Number of deaths – n (%)	770 (35.9%)	209 (26.1%)	158 (38.4%)	403 (43.2%)
95% Confidence Intervals	34.0% - 38.1%	23.8% - 29.6%	33.6% - 43.1%	40.6% - 46.1%

Table 3.16 In-patient mortality based on severity of kidney injury. Reproduced from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

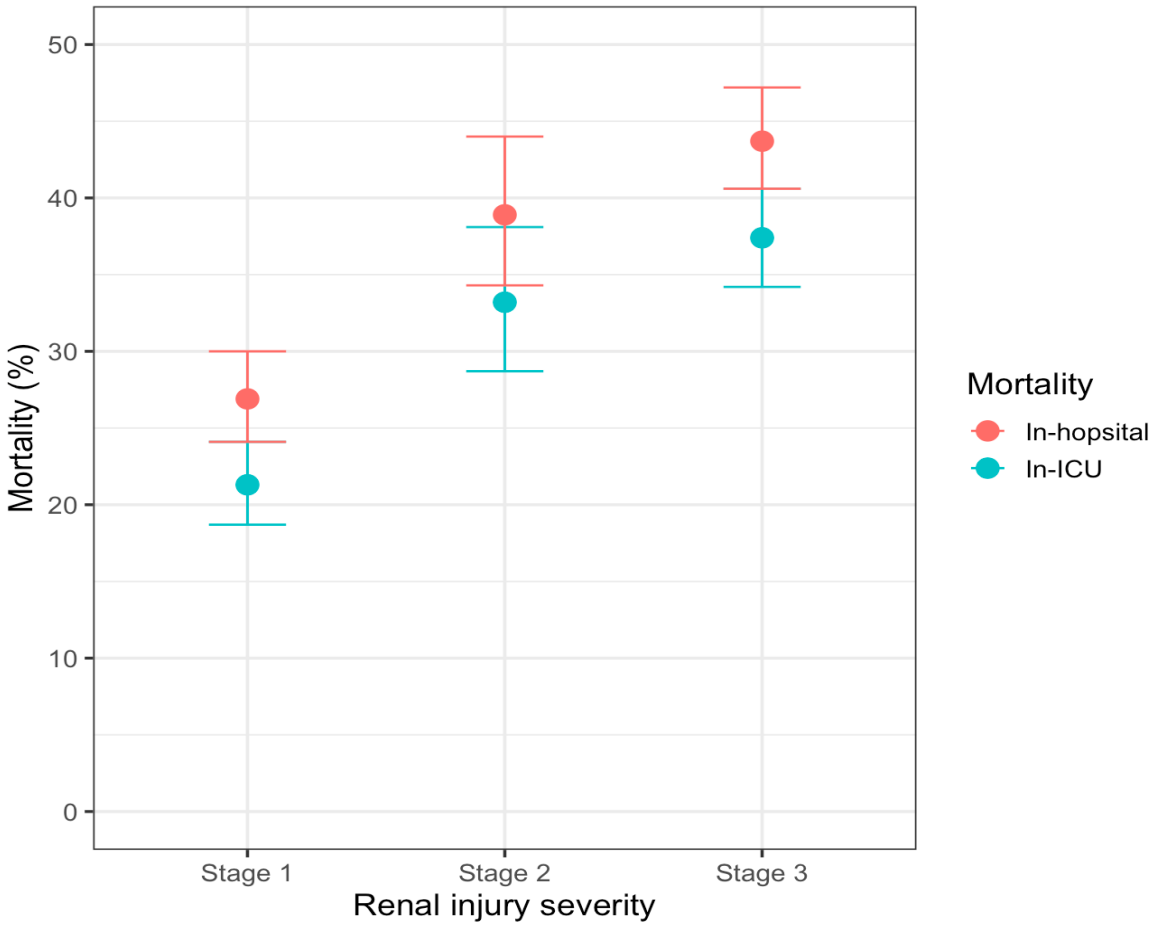


Figure 3.4: In-ICU and in-hospital mortality based on severity of injury

The ICU and hospital mortality rates categorised by degree of injury are reported in Table 3.16 and Figure 3.4. The data showed that increasing severity of DNKI was associated with an increase in both ICU and hospital mortality. Crude rates showed a marked increase between ICU mortality rates in patients who suffered from stage 1 disease compared to stage 2 (20.9% vs 32.5% respectively; $p < 0.001$). There was a similar increase seen when comparing in-hospital mortality for the same two groups. When comparing stage 2 injury to stage 3, there was another, less marked increase in ICU mortality (32.5% vs 36.9%; $p = 0.192$) which was again comparable to the increase seen in hospital mortality between these two groups.

3.4.7.3 Mortality based on progression to AKD

Within the 1,620 patients to survive at least 7 days following their initial injury, 141 deaths occurred. Raw in-ICU mortality was found to be higher in the AKD group compared to the AKI group at 16.1% and 6.2% respectively ($p < 0.001$). For in-hospital mortality rates, the patients within the AKD group again had the highest mortality rate at 26.0% (22.1% - 30.7%) compared to 11.6% in the AKI group ($p < 0.001$).

Event	Survival to day 7 (n = 1620)	Acute kidney injury (n = 1217)	Acute kidney disease (n = 403)
Death during ICU admission			
Number of deaths – n (%)	141 (8.7%)	76 (6.2%)	65 (16.1%)
95% Confidence Intervals	7.4% - 10.2%	5.0% - 7.7%	12.8% - 19.9%
Death during hospital admission			
Number of deaths – n (%)	246 (15.2%)	141 (11.6%)	105 (26.1%)
95% Confidence Intervals	13.6% - 17.1%	9.9% - 13.5%	22.1% - 30.7%

Table 3.17: In-patient mortality rates based on progression to AKD. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

3.4.7.4 Mortality based on receipt of KRT

Event	De-novo kidney injury (n = 2147)	Did not receive KRT (n = 1649)	Received KRT (n = 498)
Death during ICU admission			
Number of deaths – n (%)	646 (30.1%)	433 (26.3%)	211 (42.4%)
95% Confidence Intervals	28.1% - 32.0%	24.2% - 28.5%	38.1% - 46.7%
Death during hospital admission			
Number of deaths – n (%)	770 (35.9%)	535 (32.4%)	235 (47.2%)
95% Confidence Intervals	34.0% - 38.1%	30.3% - 34.9%	43.0% - 51.8%

Table 3.18: In-patient mortality rates based on receipt of KRT. Reproduced from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission.

The analysis of patients who suffered from a de-novo kidney injury categorised based on receipt of KRT is displayed in Table 3.18. The in-ICU mortality rate for the KRT group was higher compared to patients who suffered from a de-novo injury but did not receive KRT: 42.4% vs 26.3% ($p < 0.001$). The raw in-hospital mortality rate was also similarly higher in the KRT group compared to the non-KRT group: 47.2% vs 32.4% ($p < 0.001$).

3.5 Discussion

The results of this study demonstrated that approximately 2 in every 5 patients admitted to the selected ICUs during the study period (40.4%) suffered from a new onset kidney injury. Due to previous differences in both the definition of acute kidney injury and the criteria required for diagnosis, prior data regarding incidence of all de-novo kidney injury within the intensive care setting has produced results varying from 20-57% (7, 17, 141, 142). The most recent of these studies in 2015 by Hoste et al. was performed using updated consensus criteria from the KDIGO group (16) and reported the highest incidence of 57.3%.

The underlying reasons behind the disparity between this incidence found in this study and the AKI-EPI study (17) is potentially due to a discrepancy between the way in which baseline kidney function was calculated: this study utilised individualised baseline eGFR based on serum creatinine values from the preceding year whereas Hoste and colleagues calculated baseline eGFR using the Modification of Diet in Renal Disease (MDRD) equation if a serum creatinine value from the preceding three months was not available.

Data collected during this study suggested that injury was more prevalent amongst males, with a higher median age compared to patients with pre-existing established kidney failure or those who suffered from no kidney injury during admission. This was in keeping with previous studies that described prevalence of AKI (17, 141). Whilst epidemiology of AKI has been studied extensively in the past, very little work has been done looking into the novel definition of acute kidney disease (45). This study has demonstrated that patients with AKD had significantly higher in-ICU and in-hospital mortality rates than patients with a shorter-term AKI.

3.5.1 Features associated with presence of de-novo kidney injury

Patients that developed de-novo kidney injury were older than the no kidney injury group with a difference in median age of five years. This is likely explained by the increasing prevalence of comorbidities associated with increasing age; these can contribute to a decline in physiological reserve in addition to the normal decline in kidney function associated with ageing.

The odds of developing de-novo injury were noted to be 49% higher for males on multivariable analysis. This is in keeping with previous studies demonstrating a higher proportion of male patients with AKI in ICU, as well as a meta-analysis in 2018 which found that hospital acquired AKI was 2.2 times more likely to occur in males (143). The exact pathophysiology behind this association is not fully understood, but theoretical mechanisms have been extrapolated from animal models following ischaemia-reperfusion injury; it has been suggested that this may be due to the effect of sex hormones on various cellular processes involved in the development of kidney injury (143).

Surgical admissions to the ICUs accounted for more than half of the total study population at 57.3%. After adjusting for other influencing variables, surgical patients were statistically less likely to develop a de-novo injury than patients admitted from medical specialties (OR = 0.70, *p*-value < 0.001). These data suggesting that ICU admission from medical specialties confers an increased risk profile of kidney injury is consistent with the findings from a large retrospective study by Porter et al. which used an electronic alert system for identifying AKI in over 15,000 patients and documented a higher incidence of AKI within medical specialties compared with surgical specialties (144).

For patients with available APACHE II scores, the median values were significantly higher in the de-novo injury and pre-existing EKF groups when compared to the no kidney injury group. Admissions to critical care are often found to suffer from multiple organ dysfunction and various physiological markers form the basis for calculations of APACHE II scores (80). This may explain why APACHE II scores are higher for patients who develop kidney injuries; the more deranged the physiology, the more likely the kidneys will be injured as a result.

The most common reason for admission was found to be sepsis. This was the case for the entire patient population, as well as each of the subgroups. However, the proportion of patients admitted with sepsis was nearly twice that in the de-novo injury group compared to the no kidney injury group. When sepsis vs non-sepsis was included in the multivariable models, it was found to be strongly associated with the development of de-novo kidney injury (OR = 2.13). MODS commonly occurs in the context of sepsis, and it has previously been described at length how it is associated with high morbidity and mortality (145, 146). The pathophysiology associated with both MODS and sepsis involves significant arterial vasodilation leading to hypoperfusion of the kidneys as well as systemic release of inflammatory mediators which cause damage at a cellular level. Due to a combination of these factors, sepsis has also been shown to cause kidney injuries in up to one third of patients (147).

Pre-existing comorbidities were grouped based on presence of cardiovascular disease, respiratory disease, liver disease, diabetes and malignancy. Whilst similar rates of respiratory disease and pre-existing malignancy were seen in the

de-novo injury and no kidney injury groups, there was a significant association demonstrated between pre-existing cardiovascular comorbidities, liver disease and diabetes and the development of de-novo kidney injury. This is likely a direct consequence of the microvascular and macrovascular damage caused in the kidneys secondary to either hypertension or diabetes (referred to as hypertensive or diabetic nephropathy). Cardiovascular disease has been identified as being 50% more likely to occur in patients suffering from AKI compared to patients who did not suffer from any kidney injury (148). Furthermore, diabetes has been found to be one of the leading causes of EKF, with up to 40% of cases attributed to sequelae of diabetes (149); this link has been shown to contribute to higher risk of developing AKI during hospitalisation as well (150). The data from this study suggest that this underlying damage renders kidneys more susceptible to development of acute injury.

3.5.2 Features associated with severity of de-novo kidney injury

The de-novo injury subgroup was categorised as stage 1-3 based on KDIGO guidelines (16). Within this group, stage 3 injury was found to be the most common severity (43.5%).

Patient sex and age were similar amongst the different stages of severity. The most noticeable difference was with regards to APACHE II scores – these increased as severity of kidney disease increased. This would suggest that severity of illness estimated by APACHE II scores correlates well with severity of kidney injury. The proportion of patients admitted from medical specialties also increased as severity of injury increased. Whilst there is data relating to the relative prevalence of AKI across varying medical and surgical specialties (144), no data exist detailing the relative severity of kidney injury depending on admitting specialty. A potential explanation for this may be that the range of diseases treated in medical specialties is more likely to predispose patients to greater severity of kidney injury; this may be reflected by the differences between post-operative injury due to a surgical insult compared with a more acute, systemic underlying disease process.

Patients with stage 3 injury were also found to have significantly lower baseline eGFR when compared to stage 1 injury. This is representative of the well

documented link between underlying CKD and the likelihood of developing more severe acute kidney injury (150). The likely pathophysiology underlying this process is that the progressive deterioration of nephrons in the kidneys render them more susceptible to more severe injury (151). Pre-existing diabetes was also significantly higher in stage 3 patients when compared with stage 1. While this association has not been previously described, the underlying microvascular and macrovascular mechanisms that predispose the kidneys to damage are likely to be responsible for a greater risk of more severe injury (149).

Table 3.8 details the median time to kidney recovery for each of the severity groups. For this analysis, only ICU survivors were used to prevent death from being represented as "kidney recovery" and influencing results. The data showed that as severity increased, the median length of time until kidney recovery also increased. The progression to AKD was particularly marked in stage 3 disease: the majority of patients fell into this classification (51.0%) compared to only 4.0% of patients with stage 1 injury. This was further represented in multivariable analysis, where progression to stage 3 disease was by far the most important factor in determining risk of progression to AKD (OR = 8.57, p <0.001). Whilst outcomes for AKD as a separate defined group of AKI lasting seven days or longer have not been previously described, these results agree with previous data that suggest that increasing severity of kidney injury is a risk factor for prolonged kidney recovery (152).

3.5.3 Features associated with progression to AKD

A total of 1,620 DNKI patients survived to day 7 following the initial injury: 403 (24.9%) of these patients progressed to AKD.

Age had no association with progression to AKD on both univariable and multivariable analyses. It may be expected that older people would be more prone to a protracted injury, as increasing age is an independent risk factor in the development of kidney injury of any length (153). However, it is possible that any potential association is lost by older patients dying prior to day 7 which prevents their progression to AKD. Indeed, the data from this study show that the median age in the early mortality group is significantly higher than in the AKI and AKD groups.

Male sex was a significant factor in the development of AKD. Since minimal data exist around AKD, this relationship can only be hypothesised but it the underlying pathophysiology may be linked to effect of sex hormones on various cellular processes as was discussed above (143). However, admission type was not associated with length of kidney injury, with no statistically significant difference between those with AKD compared to patients with shorter-term AKI.

A higher proportion of patients within the AKD subgroup were admitted as a result of sepsis compared to the AKI group. When sepsis vs non-sepsis was included in the multivariable models, it was found to be strongly associated with progression to AKD. This is likely a further representation of the close link between sepsis and MODS (146). In addition, a previous study by Lai and colleagues reported that dialysis-requiring AKI was almost three times more likely to result in severe sepsis than patients who did not experience any kidney injury (154). These data would suggest that de-novo kidney injury following sepsis may be associated with a longer time to recovery than any other aetiology.

Reduced baseline eGFR was also a significant factor in progression to AKD following multivariable analysis. This observed association is likely a representation of the well-established link between underlying CKD and risk of subsequent AKI (155). The tubulointerstitial pathology and altered cell signalling in kidney tubular cells that predominate in CKD are likely to significantly contribute to prolonging the length of DNKI (156).

When included in a multivariable analysis looking at progression to AKD, none of the comorbidities were found to be significantly associated with risk of prolonged kidney injury. A possible association was identified between pre-existing diabetes and progression to AKD, but this was again found to be statistically insignificant (OR = 1.24, *p*-value = 0.072). This may be a result of the long-term pathophysiological effects of diabetic nephropathy being corrected for when baseline eGFR was also included in the model as a variable.

3.5.4 Requirement for organ support whilst admitted to ICU

Organ support was differentiated based on mechanical ventilation, vasopressor support and kidney replacement therapy. 88.9% of patients who suffered from a de-novo kidney injury received at least one of the above modalities of organ support. This was comparable to patients within the pre-existing EKF group, but significantly higher than patients admitted who did not suffer a kidney injury (57.5%). When looking at specific modalities, the data showed that patients with a de-novo injury received mechanical ventilation and vasopressors more often than patients with either no injury or pre-existing EKF. As might be expected, the proportion of patients in the pre-existing EKF group that received KRT was more than three-times that in the de-novo injury group: this is due to the fact that by definition a large proportion of this group were on long-term KRT and are likely to have required it during their ICU admission.

As length of de-novo injury increased, so too did the proportion of patients who received KRT. Similarly, a greater proportion of patients within the AKD group received either mechanical ventilation or vasopressors when compared to the AKI group. This is likely reflective of the association between longer length of injury and worsening severity of injury and MODS. It would stand to reason that a higher proportion of patients suffering from multiple organ dysfunction would require more modalities of organ support.

The patients suffering from de-novo injury were also separated into two groups based on receipt of KRT. The median age and proportion of male/female patients in these two groups were found to be similar, but the data demonstrated that the median APACHE II scores were significantly higher in the KRT group. The rate of kidney injury requiring KRT was found to be 9.4% of the entire study population. This is consistent with previously reported rates of 5-15% within the ICU population (17, 107, 111).

3.5.5 In-patient mortality of ICU patients based on length and severity of kidney injury

The raw in-ICU mortality for the patients admitted to the selected ICUs during the study period was found to be 17.3%; in-hospital mortality was 21.6%. The Scottish Intensive Care Society Audit Group (SICSAG) produce annual figures on

both in-ICU and in-hospital mortality for all intensive care units across Scotland (128): the crude in-hospital mortality for all of Scotland across the three years which the data for this study was gathered from varied between 18-20%. Whilst this doesn't account for several important variables such as combined high dependency and intensive care units and severity of case mix admitted to individual ICUs, it demonstrates the crude mortality rate for the two selected units was similar to the mean for the entire country across the study period.

Prior work by Forni and colleagues found that kidney injury of both increasing severity and length are independent risk factors for increased morbidity and mortality in both the critical care population and in hospital inpatients (152). This study's findings agreed with these conclusions: it found that the raw in-ICU and in-hospital mortality rates were three-times higher in patients with a de-novo kidney injury when compared to patients with no kidney injury. Furthermore, DNKI patients had higher mortality rates than the population with pre-existing established kidney failure: this has been described in the literature before by Clermont et al. (23% vs 11% in-ICU mortality) and is likely a representation that DNKI involves a more severe acute illness and is more likely to be indicative of MODS (114).

Within the de-novo injury subgroup, in-ICU mortality was found to increase from stages 1-3. The same was true for in-hospital mortality, with a similar trend seen when compared to in-ICU mortality. These data agree with results published by Lafrance and colleagues, who assessed a large cohort of hospitalised patients for presence and severity of AKI and found that a stepwise increase in stage of kidney injury conferred an approximate 10% increase in mortality (26). Whilst this data would suggest that increasing severity of kidney injury is associated with higher likelihood of dying in hospital, further analysis is required to determine if this is also seen in rates of long-term survival following de-novo kidney injury.

Before describing AKI and AKD subgroups, patients who died within 6 days of their initial kidney injury were removed; this was to prevent death from censoring the potential progression of disease to AKD. When divided into AKI and AKD subgroups, the ICU and hospital mortality rates were found to be highest in the AKD group (16.1% and 26.1%). Patients who suffered from AKD

also had a bigger increase from in-ICU to in-hospital mortality compared to the AKI subgroup. The reasons for this disparity may be multifactorial, but as no prior data on AKD exist, they must be hypothesised. One such reason may be that AKD represents a higher burden of acute disease resulting in a higher likelihood of death. In addition to this, earlier recovery of kidney injury (AKI) may be indicative of a self-defined population that are showing the ability to recover from acute physiological insults. Another such reason may be that the features associated with AKD, such as admission due to sepsis, confers an additional mortality risk: the association between sepsis and increased mortality has been detailed in a 2020 meta-analysis by Bauer et al (157). Due to such a significant disparity in short-term mortality between the AKI and AKD groups, further work is required to assess if this increased mortality risk is continued following hospital discharge.

When the data were analysed based on receipt of KRT, the results demonstrated that ICU and hospital mortality was significantly higher for patients suffering from de novo injury requiring KRT. When looking at changes between ICU and hospital mortality for both groups, there was a similar rise in mortality for both groups. These results are in keeping with multiple previous studies detailing the increased mortality in de-novo injury requiring KRT compared to patients with injury who do not require KRT (111, 117, 158). These studies were conducted on different cohorts of patients ranging from the ICU population to all hospitalised patients, but the reported 90-day mortality in all these studies was greater than 40%. This is similar to the in-hospital mortality demonstrated in this study (47.2%). One aspect of stratifying the severity of disease according to KDIGO guidelines is based on receipt of KRT: if KRT is required then the kidney injury is automatically classed as stage 3 regardless of creatinine levels at the time. This would again support the evidence that increasing severity of disease may be associated with increased mortality.

3.5.6 Strengths and weaknesses

This study details the demographics of all ICU patients and stratifies them according to presence, severity and length of kidney injury using a new definition of acute kidney disease. It utilises multiple different data sources to categorise each patient as accurately as possible and allows each patient group

to be described in detail based on their demographics, principle aetiology and degree of organ support delivered. The large sample size over a period of 3 years would indicate that this data is representative of patients who are admitted to ICU across the UK.

This study has two main limitations: the first is that only creatinine data was used to identify and categorise the varying degrees of kidney injury. KDIGO recommendations detail that this can also be done using urine output, however the available data regarding urine output during ICU admission was not in enough detail to stratify length and severity of injury for all patients during the study population. The second main limitation is that whilst kidney recovery is classified as the first point following initial injury where creatinine values return to baseline, it does not account for the possibility that values would then increase again indicating a recurrence of injury or continuation of the same injury after a one-off value below the pre-defined cut-off.

3.6 Conclusions

The definition of AKD is a fairly novel one and whilst the concept of a "persistent AKI" has been suggested for several years, very little data has been produced looking at the short- and long-term outcomes of these patients as a separate group. Patients admitted to ICU suffering from a severe or longer-term de-novo kidney injury were found to have higher predicted mortality on admission to ICU, and this was reflected in both the crude in-ICU and in-hospital mortality numbers for patients who were found to have acute kidney disease. Development of de-novo kidney of any type in the context of critical illness was associated with a significant increase in mortality when compared with both patients who suffered from no kidney injury, and the general ICU population over the total study period.

Chapter 4 Long-term survival and kidney outcomes following de-novo kidney injury in intensive care

4.1 Introduction

Since the term acute kidney injury (AKI) was defined, multiple studies have demonstrated it is associated with both an increase in mortality and a progression to chronic kidney disease (CKD) (33, 42, 107). Other evidence has been produced that shows that these outcomes are often worse when people develop acute kidney injury on the background of critical illness (110, 111). In recent years, it has been hypothesised that kidney disease should be treated as a continuum, and more work needs to be conducted into the significant period of time between a shorter injury lasting less than 7 days - referred to as AKI - and a new concept of injury lasting 7 days and beyond – referred to as acute kidney disease (AKD) (45). This study sought to determine factors associated with long-term survival rates and prolonged decline in kidney function in patients with varying lengths of kidney injury who were admitted to the intensive care unit (ICU) with critical illness.

4.2 Study aims

4.2.1 How do long-term survival rates vary between patients with de-novo kidney injury and those without and what factors influence this?

The population of ICU survivors will be described according to the total numbers alive at 30 days following hospital discharge. The long-term survival of these patients may also be expected to be decreased based on presence of kidney injury during their stay. These patients will be described according to their baseline demographics and stratified based on the presence of de-novo kidney injury. Their long-term survival will then be detailed, and a multivariable model constructed to determine how the presence of kidney injury in ICU impacts survival when accounting for other predictors of mortality risk.

4.2.2 How do rates of survival compare between patients with AKI and patients with AKD and what factors impact this?

The definition of AKD is a relatively new concept and one which is yet to be described in any great detail. Patients who suffered from a de-novo kidney injury in ICU and survived until at least 30 days post discharge will be classified based on length of kidney injury. Patients with protracted kidney injury and short-term injury will then be compared and a multivariable analysis performed to assess for the effect of AKD on long-term survival, as well as accounting for other variables within the two groups.

4.2.3 How do rates of prolonged decline in kidney function vary between patients with de-novo injury and those without?

As previously detailed, it has been proven that an episode of kidney injury is a risk factor for progression to CKD. Having examined the differences in long-term survival between patients with and without de-novo kidney injury, these groups will be compared for presence of decreased estimated glomerular filtration rate (eGFR) at 6-, 12- and 18-months post discharge. These will be stratified based on what stage of CKD these values would correspond to and will be also be analysed for factors contributing to a prolonged reduction in kidney function within each of the two groups.

4.2.4 How does long-term kidney function differ between patients with AKI and patients with AKD?

Whilst previous research has demonstrated that increased length of kidney injury is a risk factor for progression to CKD, it has never been examined in the context of a disparate group such as AKD. The previously defined group of patients classified as suffering from either AKI or AKD will be analysed for presence of decreased eGFR at 6-, 12- and 18-months following their discharge. These calculated eGFRs will be grouped using a known staging system for CKD and will also be assessed to determine potential factors which may contribute to a prolonged reduction in kidney function. Patients will then be assessed for development of major adverse kidney events (MAKEs) over the total follow up period.

4.3 Methods

For the purposes of this study, only ICU survivors were used from the original dataset. ICU survivors were defined as patients that had survived to 30-days following hospital discharge – this was to prevent patients who may have been discharged from ICU for end-of-life care being included in the long-term analysis. These groups were organised into three broad categories of no kidney injury, de-novo kidney injury and pre-existing established kidney failure (EKF). The term de-novo kidney injury was used to prevent confusion when referring to AKI and AKD patients within this group. As this study population is different from previous work using the entire dataset, these groups were then described in terms of total numbers and percentages for patient sex, hospital admitting specialty (described hereafter as either surgical or medical; specialties within each group are further detailed in Appendix B), baseline estimated glomerular filtration rate measured in millilitres per minute per 1.73 metres squared (eGFR), Acute Physiology and Chronic Health Evaluation (APACHE) II Score, comorbidities and primary diagnosis responsible for admission. Within surgical admission, patients admitted directly from surgery could be further classed as elective or emergency. Precipitating illness requiring ICU admission was identified based on admission diagnosis which has subsequently been grouped as indicated in Appendix B.

Patient age, APACHE II score and predicted mortality for each group was described in terms of median and interquartile ranges. The chances of survival over time were plotted using Kaplan Meier graphs for the pre-defined subgroups. Survival in each of the groups were then compared using a log-rank test. A multivariable analysis of all factors which could influence the probability of survival was then conducted using a Cox proportional hazards model; all variables with an initial p-value <0.2 on univariable analysis were included in the multivariable model. Schoenfeld residuals were calculated for each variable – if the differences between the observed and expected rates varied over time based on the calculated residuals, this variable was not included in the multivariable model. A mixed-effect, generalised linear model was constructed to determine prolonged reduction in kidney function over time; this was done to account for the variation in number of, and time periods between, creatinine measurements in individual patients following discharge. Major adverse kidney

events were defined as: eGFR drop of >30% from baseline, eGFR drop of >40% from baseline, doubling of baseline creatinine or initiation of chronic kidney replacement therapy (KRT). Time to event analyses were then conducted on each of these and the inter-group differences were compared.

4.4 Results

4.4.1 Patient characteristics in ICU survivors

Of the 5,312 patients who were included in the initial descriptive analyses in the prior study, 4,085 were still alive at 30 days post hospital discharge. Of these patients (Table 4.1), 1,347 (33.0%) suffered a de-novo kidney injury during their ICU admission. Of the remaining patients, 72 (1.7%) had established kidney failure prior to their admission to ICU; 2,666 (65.3%) patients alive 30 days post-discharge suffered no kidney injury during their admission.

Kidney injury	Total number – n (%)
No kidney injury	2,666 (65.3%)
De novo kidney injury	1,347 (33.0%)
Pre-existing established kidney failure	72 (1.7%)
Total patients	4,085 (100.0%)

Table 4.1: Proportion of day 30 survivors based on kidney injury

4.4.1.1 Key baseline demographics

Of the 4,085 patients identified as ICU survivors, 2,241 were male (54.9%); 814 of these patients suffered from a de-novo injury during their ICU admission (Table 4.2). This represented 36.3% of the total male population and demonstrated the comparatively higher proportion of male patients within the injury group compared to the no kidney injury group (60.4% vs 52.0% respectively; *p*-value <0.001). Within the pre-existing EKF group, 41 patients were found to male (56.9%). The median age of this study population was found to be 56.0 (43.0 – 69.0); the median age of the group to suffer from no kidney injury was significantly lower compared with patients who suffered a kidney injury during their admission (54.0 vs 59.0; *p*-value <0.001). Of the 2,563

patients admitted from surgical specialties, 793 were found to be in the de-novo injury group. This represented 58.9% of patients within this group, which was a lower proportion compared to the group who suffered from no kidney injury (65.1%; *p*-value <0.001).

Characteristic	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo injury (n = 1347)	Pre-existing established kidney failure (n = 72)
Age – median (IQR)	56.0 (43.0 – 69.0)	54.0 (41.0 – 68.0)	59.0 (47.0 – 71.0)	58.0 (50.5 – 67.5)
Male – n (%)	2241 (54.9%)	1386 (52.0%)	814 (60.4%)	41 (56.9%)
Admitted from surgical specialty – n (%)	2563 (62.7%)	1735 (65.1%)	793 (58.9%)	35 (48.6%)
Baseline eGFR – median (IQR)	91.8 (72.3 – 106.7)	95.6 (80.7 – 109.5)	83.9 (61.9 – 99.7)	8.9 (6.8 - 16.0)
APACHE II score – median[5] (IQR)	15.0 (10.0 – 20.0)	13.0 (9.0 – 17.0)	19.0 (15.0 – 24.0)	24.0 (19.0 – 29.0)
Comorbidities – n (%)				
Cardiovascular disease	1495 (36.6%)	880 (33.0%)	570 (42.3%)	45 (62.5%)
Respiratory disease	790 (19.3%)	523 (19.6%)	262 (19.5%)	5 (6.9%)
Liver disease	336 (8.2%)	207 (7.8%)	125 (9.3%)	4 (5.6%)
Diabetes	556 (13.6%)	282 (10.6%)	252 (18.7%)	22 (30.6%)
Malignancy	298 (7.3%)	202 (7.6%)	92 (6.8%)	4 (5.6%)

Table 4.2: Demographics comparison of ICU survivors based on presence of kidney injury

[5] Data unavailable for 134 patients – only 3951 patients used in these calculations (no kidney injury = 2566; de-novo injury = 1316; pre-existing EKF = 69)

Calculated APACHE II scores were not available for 134 patients. Median APACHE score at ICU admission for the remaining 3,938 patients who had survived ICU was found to be 15.0 (10.0 – 20.0). The median score for the entirety of the no kidney injury group (13.0) was significantly lower than the median calculated scores for the de-novo group and pre-existing EKF group (19.0 and 24.0 respectively; both *p*-values <0.001). Median baseline eGFR was calculated as 91.8 for all patients. Within the no kidney injury group, the median baseline eGFR was found to be significantly higher than in the group who suffered from a de-novo injury during their ICU stay (95.6 vs 83.9; *p*-value <0.001). The median baseline eGFR in the pre-existing EKF group was substantially lower than either of the other two groups at 8.9 (6.8 – 16.0; both *p*-values <0.001 when compared to the other two groups).

Proportion of comorbidities found within the entire study population varied dependent on organ system affected. Rates of pre-existing liver disease were low for the entire patient cohort and were comparable across the three groups. Respiratory comorbidities were seen in similar proportions in the de-novo injury group and group of patients with no kidney injury (*p*-value = 0.933) but were much lower in the pre-existing EKF group (*p*-value = 0.011 when compared with no kidney injury group and *p*-value = 0.013 when compared with de-novo injury group). A higher proportion of patients in the de-novo injury groups were found to have pre-existing diabetes compared to the group of patients without kidney injury (18.7% vs 10.6%; *p*-value <0.001). This trend was also seen when considering cardiovascular comorbidities, with 42.3% in the de-novo injury group compared to 33.0% in the no kidney injury group (*p*-value <0.001). However, rates of both these comorbidities were substantially higher in the pre-existing EKF group (all *p*-values <0.05 for these analyses).

4.4.1.2 Precipitating illness requiring admission

Precipitating illness	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo injury (n = 1347)	Pre-existing established kidney failure (n = 72)
Sepsis/Infection	800 (19.6%)	385 (14.4%)	397 (29.5%)	18 (25.0%)
Malignancy	498 (12.2%)	410 (15.4%)	84 (6.2%)	4 (5.6%)
Trauma	357 (8.7%)	266 (10.0%)	91 (6.8%)	-
Gastrointestinal (Other)	334 (8.2%)	239 (9.0%)	92 (6.8%)	3 (4.2%)
Drug Related	310 (7.6%)	262 (9.8%)	48 (3.6%)	-
Respiratory/Airway	254 (6.2%)	190 (7.1%)	62 (4.6%)	2 (2.8%)
Gastrointestinal Perforation	189 (4.6%)	118 (4.4%)	69 (5.1%)	2 (2.8%)
Seizures	169 (4.1%)	105 (3.9%)	63 (4.7%)	1 (1.4%)
Haemorrhage	142 (3.5%)	87 (3.3%)	55 (4.1%)	-
Neurological	141 (3.5%)	100 (3.8%)	38 (2.8%)	3 (4.2%)
Kidney	123 (3.0%)	20 (0.8%)	82 (6.1%)	21 (29.2%)
Hepatobiliary	117 (2.9%)	74 (2.8%)	42 (3.1%)	1 (1.4%)

Cardiac Arrest	103 (2.5%)	56 (2.1%)	45 (3.3%)	2 (2.8%)
Post-operative Complications	79 (1.9%)	57 (2.1%)	19 (1.4%)	3 (4.2%)
Cardiac (Other)	69 (1.7%)	50 (1.9%)	15 (1.1%)	4 (5.6%)
Vascular	67 (1.6%)	22 (0.8%)	43 (3.2%)	2 (2.8%)
Endocrine/Metabolic	61 (1.5%)	23 (0.9%)	36 (2.7%)	2 (2.8%)
Miscellaneous	55 (1.4%)	46 (1.7%)	8 (0.6%)	1 (1.4%)
Obstetrics/Gynaecology	51 (1.3%)	44 (1.7%)	7 (0.5%)	-
Burns Related	39 (1.0%)	30 (1.1%)	9 (0.7%)	-
Musculoskeletal	34 (0.8%)	29 (1.1%)	4 (0.3%)	1 (1.4%)
Cardiac Failure	32 (0.8%)	13 (0.5%)	19 (1.4%)	-
Hypersensitivity/Immunocompromise	29 (0.7%)	21 (0.8%)	6 (0.5%)	2 (2.8%)
Ischaemic Heart Disease	18 (0.4%)	12 (0.5%)	6 (0.5%)	-
Liver Disease	8 (0.2%)	4 (0.2%)	4 (0.3%)	-
Haematology/Coagulation	6 (0.2%)	3 (0.1%)	3 (0.2%)	-

Table 4.3: Precipitating illness leading to ICU admission based on presence of kidney injury

The precipitating illness leading to admission to ICU in each patient group is demonstrated in Table 4.3. The most common diagnosis across all patients to survive to 30 days post hospital discharge was sepsis/infection (19.6%). Whilst this was also the case in the group of patients to suffer from a de-novo injury (29.5%), it was the second most common diagnosis in the group of patients to suffer from no kidney injury and pre-existing EKF; the most common reason for ICU admission in these groups was malignancy and kidney disorders respectively. Within the de-novo injury group, the second most common reason for admission was gastrointestinal (other). Sepsis was a significantly more common reason for admission in the de-novo injury group than in the group who did not experience any kidney injury (*p*-value <0.001).

Of the 800 patients who were admitted with a primary diagnosis of sepsis, almost half suffered from a de-novo injury at any point during their stay (49.6%). This was a higher proportion compared to patients within the no kidney injury group (48.1%). However, this was contrasted with the second most common reason for admission: malignancy. A large proportion of the patients admitted with malignancy suffered from no kidney injury during their ICU stay (82.3%). This was also the case for patients admitted with trauma (74.5%), which was the third most common illness for the total study population.

4.4.1.3 Organ support during ICU admission

Organ support was separated into invasive mechanical ventilation (IMV), cardiovascular support (CVS) and kidney replacement therapy (KRT). Table 4.4 demonstrates the proportion of patients who received each of these modalities. Of all the patients included in the study, 2,622 (64.2%) of them underwent at least one of the above forms of organ support during their stay. When separated into specific modalities, invasive mechanical ventilation was the most common organ support amongst the total patients (50.5%). For all patients to undergo CVS, the majority went on to develop a de-novo kidney injury (52.0%); 43.1% of all patients requiring IMV developed a de-novo kidney injury during their ICU admission. A high proportion of the pre-existing EKF group underwent KRT at some point during their stay (70.8%) compared to 18.9% in the de-novo injury group.

When analysing the total study population, 1,272 patients were found to require multi-organ support during their admission; 725 (57.0%) were in the de-novo injury group. Conversely, among patients that received no organ support during their ICU stay, there was a high proportion that did not suffer from kidney injury (85.4%). When looking specifically at the de-novo injury group, only 14.9% of these patients went through their entire ICU stay without any form of organ support; 725 of the remaining patients who required one of the above modalities needed multi-organ support (53.8%). In the pre-existing EKF group, 81.9% of the patients required at least one form of organ support – 58.3% of the total patients within this group required multiple modalities of organ support during their total admission.

Intervention	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)	Pre-existing established kidney failure (n = 72)
Modalities – n (%)				
Invasive mechanical ventilation	2062 (50.5%)	1139 (42.7%)	889 (66.0%)	34 (47.2%)
Cardiovascular support	1707 (41.8%)	782 (29.3%)	887 (65.9%)	38 (52.8%)
Kidney replacement therapy	305 (7.5%)	-	254 (18.9%)	51 (70.8%)
Degree of organ support - n (%)				
None	1463 (35.8%)	1250 (46.9%)	200 (14.9%)	13 (18.1%)
Single	1350 (33.1%)	911 (34.2%)	422 (31.3%)	17 (23.6%)
Multi	1272 (31.1%)	505 (18.9%)	725 (53.8%)	42 (58.3%)

Table 4.4: Modalities of organ support based on presence of kidney injury

4.4.1.4 Demographics of patients with de-novo kidney injury

Characteristic	De-novo injury (n = 1347)	Acute kidney injury (n = 1059)	Acute kidney disease (n = 288)
Age – median (IQR)	59.0 (47.0 – 71.0)	59.0 (47.0 – 71.0)	59.0 (47.0 – 70.0)
Male - n (%)	814 (60.4%)	625 (59.0%)	189 (65.6%)
Admitted from surgical specialty – n (%)	793 (58.9%)	644 (60.8%)	149 (51.7%)
Baseline eGFR – median (IQR)	83.9 (61.9 – 99.7)	85.3 (65.0 – 101.2)	76.7 (52.7 – 96.4)
APACHE II score – median[6] (IQR)	19.0 (15.0 – 24.0)	18.0 (14.0 – 23.5)	23.0 (19.0 – 28.0)
Comorbidities – n (%)			
Cardiovascular disease	570 (42.3%)	443 (41.8%)	127 (44.1%)
Respiratory disease	262 (19.5%)	212 (20.0%)	50 (17.4%)
Liver disease	125 (9.3%)	103 (9.7%)	22 (7.6%)
Diabetes	252 (18.7%)	183 (17.3%)	69 (24.0%)
Malignancy	92 (6.8%)	75 (7.1%)	17 (5.9%)
Most common precipitating illnesses necessitating ICU admission	**1.** Sepsis **2.** Gastro (Other) **3.** Trauma	**1.** Sepsis **2.** Gastro (Other) **3.** Trauma	**1.** Sepsis **2.** Kidney **3.** Vascular

Table 4.5: Baseline demographics in patients with de-novo injury based on length of kidney injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission

[6] Data unavailable for 31 patients – only 1316 patients used in these calculations (AKI = 1035; AKD = 281)

Specific analysis of the 1,347 ICU survivors to suffer from de-novo injury showed that 288 patients had experienced a protracted kidney injury and were classified as AKD. The comparison of baseline characteristics between the AKI and AKD groups can be found in Table 4.5. No difference was seen in the median age of both groups (59.0 years in both). A higher proportion of male patients was seen within the AKD group when compared to the AKI group, but this difference did not meet significance (65.6% vs 59.0% respectively; *p*-value = 0.064). Conversely, the proportion of patients admitted from surgical specialties was found to be much higher in the AKI group (60.8% vs 51.7%; *p*-value = 0.008). Calculation of median baseline eGFR was found to be significantly lower in the AKD group compared to patients to suffer from AKI (76.7 vs 85.3; *p*-value <0.001).

As with the entire study population, a number of patients within this subgroup did not have an available APACHE score for analysis. As such, with regards to the analysis of APACHE II score, these 31 patients were excluded. The remaining 1,316 patients were classified as either AKI or AKD. Overall, when comparing the AKI group to patients who suffered from AKD, the median APACHE II score was higher in the AKD group than in the AKI group: 23.0 vs 18.0 respectively (*p*-value <0.001).

On analysis of precipitating illness necessitating admission to ICU, sepsis was found to be the most common diagnosis for all patients with de-novo injury, and both the AKI and AKD subgroups; however, the proportion of patients to be admitted due to sepsis was significantly higher within the AKD group (38.9% compared to 27.0%; *p*-value <0.001). The second and third most common reasons for admission also differed: kidney and vascular causes were found to be far more common within the AKD group whilst gastrointestinal (other) and trauma causes were more common in the AKI group.

Baseline comorbidities differed slightly between the AKI and AKD groups. Rates of the various pre-existing comorbidities were similar, but respiratory and liver comorbidities and pre-existing malignancy were slightly more common within the AKI group, whilst cardiovascular comorbidities were slightly more common within the AKD group. However, the only comorbidity to show any statistically

significant between group difference was pre-existing diabetes mellitus (*p*-value = 0.002) which was more prevalent within the AKD group.

4.4.2 Long-term mortality

4.4.2.1 Survival rates dependant on presence of kidney injury

The maximum follow-up period for patients involved in the study was 1,612 days: this was the amount of time from the first patient's 30-day post-discharge date on 2nd August 2015 until the final point of follow up on 31st December 2019. The minimum follow-up period for the study population was 355 days.

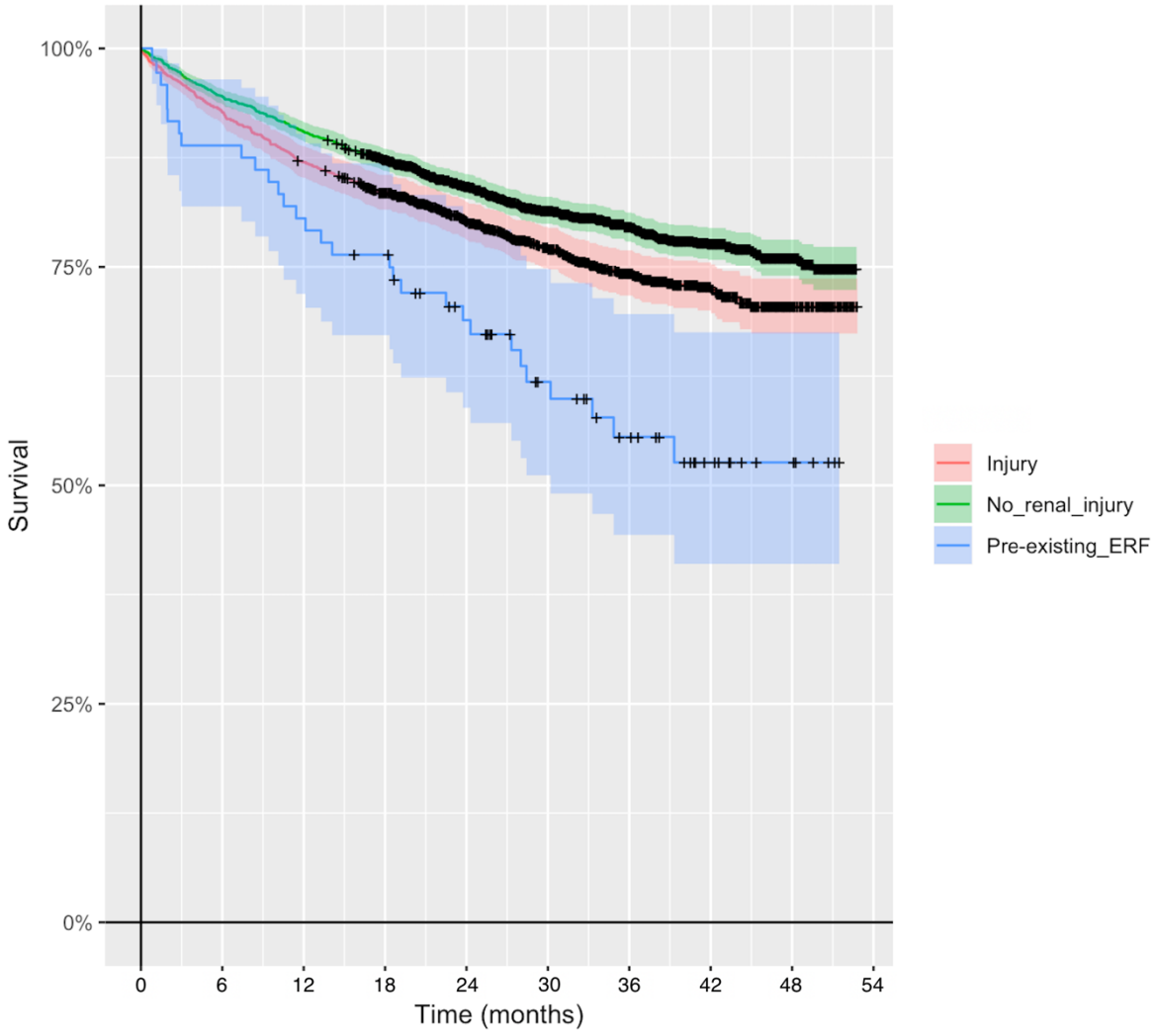


Figure 4.1: Kaplan Meier survival curves of ICU survivors based on presence of kidney injury. Time 0 represents day 30 following date of discharge from hospital (*p*-value <0.001)

Long-term survival for all ICU survivors over this time period is demonstrated by a Kaplan Meier survival curve based on presence of kidney injury in ICU or pre-existing EKF on admission to ICU (Figure 4.1). This demonstrated poorer long-

term survival over the total study period in patients with de-novo kidney injury compared to patients with no kidney injury. In addition, patients who were admitted to ICU with pre-existing EKF had poorer long-term survival than patients in the other two groups. Exact survival for varying time periods including 95% confidence intervals during follow up can be found in Table 4.6.

Time Period	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)	Pre-existing established kidney failure (n = 72)
3 months – Survival (95% C.I.)	96.6% (96.0% - 97.2%)	97.1% (96.4% - 97.7)	96.0% (95.0% - 97.1%)	90.1% (83.5% - 97.3%)
6 months – Survival (95% C.I.)	93.9% (93.2% - 94.6%)	94.6% (93.7% - 95.4%)	92.9% (91.5% - 94.3%)	88.7% (81.7% - 96.4%)
12 months – Survival (95% C.I.)	89.1% (88.2% - 90.1%)	90.5% (89.3% - 91.6%)	87.0% (85.2% - 88.8%)	80.3% (71.5% - 90.1%)
18 months – Survival (95% C.I.)	85.8% (84.7% - 86.9%)	87.2% (86.0% - 88.5%)	83.5% (81.5% - 85.5%)	76.1% (66.8% - 86.7%)
2 years – Survival (95% C.I.)	82.6% (81.4% - 83.8%)	84.2% (82.8% - 85.6%)	80.3% (78.1% - 82.5%)	68.5% (58.4% - 80.4%)
3 years – Survival (95% C.I.)	77.3% (75.9% - 78.7%)	79.5% (77.8% - 81.2%)	74.2% (71.7% - 76.9%)	55.2% (44.0% - 69.3%)
4 years – Survival (95% C.I.)	73.7% (72.0% - 75.4%)	75.9% (73.9% - 78.0%)	70.4% (67.3% - 73.6%)	52.3% (40.7% - 67.2%)

Table 4.6: Predicted survival in ICU survivors over varying time periods based on presence of kidney injury

Survival rates in patients within the de-novo injury group were lower than patients within the no kidney injury group throughout the follow up period (log-rank test: $p < 0.001$). Follow-up from 12 months onwards demonstrated a statistically significant difference in survival between the de-novo injury and no

kidney injury groups at 12 months, 18 months, 2 years, 3 years and 4 years ($p < 0.001$). Survival rates in the de-novo injury group were also lower at 3 months and 6 months, but these were not shown to be statistically significant. Survival rates within the pre-existing EKF group was lower than the other groups at all time periods, but this difference was not shown to be statistically significant for the first 18 months when compared with the no kidney injury group; however, there was a statistically significant difference from 2 years onwards.

4.4.2.2 Survival rates based on length of kidney injury

Minimum and maximum follow-up periods were identical for the subset of ICU survivors to suffer from a de-novo kidney injury during their ICU admission: 355 days to 1,612 days. The 1,347 ICU survivors to suffer from de-novo injury were separated into AKI and AKD groups: the Kaplan Meier analysis of the survival of these two groups is shown in Figure 4.2. Throughout the entire follow-up period, survival of AKD patients was shown to be consistently lower than patients to suffer from a shorter-term kidney injury. However, on log-rank analysis of the two survival curves over the total follow-up period, this difference was shown to not be statistically significant ($p = 0.200$).

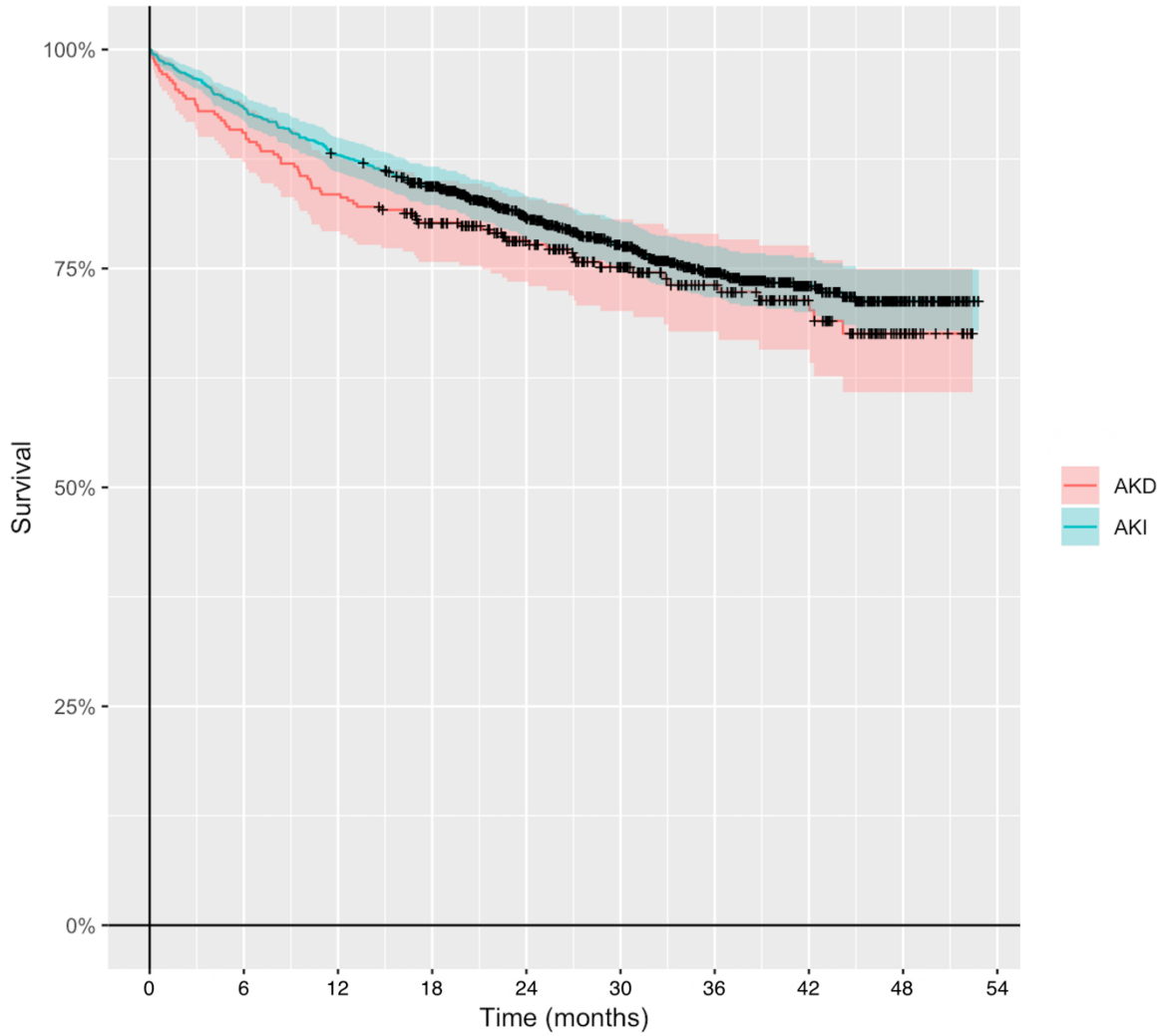


Figure 4.2: Survival of ICU survivors based on development of AKD. Time 0 represents day 30 following date of discharge from hospital. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission

Time Period	De-novo kidney injury (n = 1347)	Acute kidney injury (n = 1059)	Acute kidney disease (n = 288)
3 months – Survival (95% C.I.)	96.0% (95.0% - 97.1%)	96.7% (95.6% - 97.8%)	93.7% (90.9% - 96.5%)
6 months – Survival (95% C.I.)	92.9% (91.5% - 94.3%)	93.5% (92.1% - 95.0%)	90.5% (87.1% - 94.0%)
12 months – Survival (95% C.I.)	87.0% (85.2% - 88.8%)	87.9% (86.0% - 89.9%)	83.5% (79.2% - 87.9%)
18 months – Survival (95% C.I.)	83.5% (81.5% - 85.5%)	84.4% (82.2% - 86.6%)	80.2% (75.7% - 85.0%)
2 years – Survival (95% C.I.)	80.3% (78.1% - 82.5%)	80.8% (78.5% - 83.3%)	78.2% (73.5% - 83.2%)
3 years – Survival (95% C.I.)	74.2% (71.7% - 76.9%)	74.5% (71.7% - 77.5%)	73.2% (67.8% - 79.0%)
4 years – Survival (95% C.I.)	70.4% (67.3% - 73.6%)	71.3% (67.9% - 74.8%)	67.6% (60.9% - 75.0%)

Table 4.7: Predicted survival in ICU survivors dependant on progression to AKD

Calculated survival can be seen at various time periods during the follow-up period in Table 4.7. This correlates with Figure 4.2, demonstrating that raw survival at each measured time point was lower in the AKD group compared to the AKI group; it also demonstrates that confidence intervals overlap between the two groups at every set point throughout the four years. When follow-up time was capped at pre-specified points, log-rank analyses on the time periods documented in Table 4.7 showed no statistically significant difference was seen between the two survival curves for any time-period.

4.4.3 Risk factors associated with mortality

4.4.3.1 Risk factors associated with survival for total study population

For the purposes of this analysis, the 72 patients admitted to ICU with pre-existing EKF were excluded. For the remaining 4,013 patients, age, sex, baseline eGFR, admission from surgical specialties, admission diagnosis of sepsis or not, comorbidities and presence of kidney injury during ICU admission were all included and underwent initial univariable analysis using the Cox-proportional hazards model; the resulting hazard ratios (HRs) and corresponding *p*-values can be found in Table 4.8. APACHE II score was excluded to avoid co-linearity as its calculation utilises age and comorbidities. Furthermore, the calculation of the acute physiology score includes a measure of kidney function embedded within it and would therefore confound results when the key variable of interest also incorporates kidney function. Receipt of multi-organ support was also excluded as this would also lead to co-linearity; as one of the three modalities was KRT, only patients to suffer from de-novo injury would have received it.

The initial univariable analysis of the selected variables demonstrated that presence of de-novo injury, increasing age, reduced baseline eGFR, cardiovascular comorbidities, diabetes and pre-existing malignancy were all associated with an increased risk of death across the total follow up period (*p*-value <0.001). Schoenfeld residuals were calculated for each variable individually: all were found to have a *p*-value >0.2 with the exception of pre-existing respiratory comorbidities (*p*-value = 0.002) and pre-existing liver disease (*p*-value = 0.103); these were therefore excluded from the multivariable model and the univariable HRs were not reported. All other variables were assessed to have met the proportionality assumption and were suitable for inclusion in the multivariable model.

Characteristic	Univariable HR (95% C.I.)	*p*-value	Multivariable HR (95% C.I.)	*p*-value
Presence of DNKI				
Nil	Ref	-	Ref	-
Present	1.28 (1.11 – 1.47)	<0.001	1.16 (1.01 – 1.35)	0.042
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.93 (1.57 – 2.37)		1.82 (1.47 – 2.25)	<0.001
>65 years	3.35 (2.74 – 4.09)	<0.001	2.97 (2.39 – 3.71)	<0.001
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.38 (1.14 – 1.68)	<0.001	0.98 (0.80 – 1.20)	0.847
<30 ml/min/1.73m^2	1.71 (1.22 – 2.39)	0.002	1.36 (0.96 – 1.92)	0.082
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	0.90 (0.75 – 1.05)	0.182	0.86 (0.71 – 1.02)	0.089
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.50 (1.31 – 1.72)	<0.001	1.00 (0.86 – 1.16)	0.953
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.60 (1.34 – 1.90)	<0.001	1.31 (1.10 – 1.57)	0.003
Malignancy				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.13 (1.74 – 2.60)	<0.001	1.77 (1.44 – 2.17)	<0.001
Sex				
Female	Ref	-	-	-
Male	1.04 (0.91 – 1.19)	0.597		
Admitting specialty				
Medical	Ref	-	-	-
Surgical	1.02 (0.89 – 1.18)	0.753		
Respiratory comorbidities				
Nil	-	-	-	-
Pre-existing diagnosis				
Liver disease				
Nil	-	-	-	-
Pre-existing diagnosis				

Table 4.8: Risk factors associated with mortality following ICU survival

Presence of de-novo injury during ICU admission was found to be a statistically significant factor in increased long-term mortality (HR = 1.16; *p*-value = 0.042). Other factors which retained statistical significance when included in the multivariable model were increasing age (HR = 1.82 and HR = 2.97), pre-existing diabetes (HR = 1.31) and pre-existing malignancy (HR = 1.77): these factors were all associated with an increased risk of mortality. Whilst baseline eGFR and pre-existing cardiovascular comorbidities were shown to have an effect on long-term survival on their own, this was found to not be statistically significant when incorporated into the multivariable model. Male sex and admission from surgical specialties were shown to not be statistically significant on initial univariable analyses (*p*-values 0.597 and 0.753 respectively). Schoenfeld residuals were also calculated for the multivariable model which returned *p*-values > 0.2 for each variable individually as well as a global value of 0.280; this suggested that the proportionality assumption held true for the multivariable model as well.

4.4.3.2 Factors associated with mortality in de-novo injury patients

The 1,347 patients to suffer from a de-novo kidney injury whilst in ICU were analysed separately. As with the total study population above, the same baseline demographics were used within the multivariable model: age, sex, baseline eGFR, surgical admission, comorbidities and admission diagnosis of sepsis or not. In addition, presence of AKD was included instead of presence of kidney injury of any length. The results of the univariable analyses can be found in Table 4.9.

The univariable analyses demonstrated an increased risk of mortality associated with increasing age (HR = 1.46 for 45-65 years and HR = 2.38 for >65 years; *p*-value = 0.030 and *p*-value <0.001) and pre-existing malignancy (HR = 2.00; *p*-value <0.001); admission due to sepsis was associated with a decreased risk of mortality (HR = 0.77; *p*-value = 0.042). Progression to AKD was not found to be significantly associated with increased risk of mortality, but as the variable of interest it was included in the multivariable model regardless of a *p*-value = 0.237. The univariable analyses of all other variables did not show any significant association with changes in mortality. However, with the exception of sex, all these variables were found to have a *p*-value <0.2 and were therefore included in the multivariable model to determine if any became significant when

other variables were corrected for. Prior to this, Schoenfeld residuals were calculated individually for each variable: cardiovascular comorbidities and respiratory comorbidities returned p-values of 0.012 and 0.002 respectively and were therefore removed from the multivariable model. All remaining variables were found to have *p*-values > 0.2 which suggested the proportional hazards (PH) assumption held true and they were all suitable for inclusion in the model.

The multivariable model demonstrated that increasing age was still associated with an increase in mortality (HR = 1.48 for 45-65 years and HR = 2.48 for >65 years; *p*-value = 0.025 and *p*-value < 0.001), whilst admission from surgical specialties was found to be associated with a decrease in mortality which was now statistically significant (HR = 0.72; *p*-value = 0.008). Admission with sepsis also resulted in a decrease in long-term mortality (HR = 0.72; *p*-value = 0.013). Pre-existing liver disease (HR = 1.48) and pre-existing malignancy (HR = 1.90) were also found to have a statistically significant association with increased mortality once included in the multivariable model (p-value = 0.029 and *p*-value <0.001 respectively). Whilst presence of AKD was suggestive of an increase in mortality, it was not found to be significant as part of the multivariable model (HR = 1.18; *p*-value = 0.215). Schoenfeld residuals were recalculated for this model and again all *p*-values were >0.2 with a global value of 0.778; this again suggested that all these variables met the proportionality assumption and were therefore appropriate for inclusion in the model.

Characteristic	Univariable HR (95% C.I.)	*p*-value	Multivariable HR (95% C.I.)	*p*-value
Presence of AKD				
Nil	Ref	-	Ref	-
Present	1.17 (0.90 – 1.51)	0.237	1.18 (0.91 – 1.54)	0.215
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.46 (1.04 – 2.04)	0.030	1.48 (1.05 – 2.08)	0.025
>65 years	2.38 (1.72 – 3.30)	<0.001	2.48 (1.77 – 3.48)	<0.001
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.83 (0.67 – 1.04)	0.104	0.72 (0.56 – 0.93)	0.008
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.11 (0.83 – 1.49)	0.476	0.92 (0.68 – 1.25)	0.605
<30 ml/min/1.73m^2	1.41 (0.96 – 2.08)	0.080	1.32 (0.89 – 1.97)	0.165
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	0.77 (0.60 – 0.99)	0.042	0.72 (0.56 – 0.93)	0.013
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.35 (0.96 – 1.90)	0.090	1.48 (1.04 – 2.09)	0.029
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.29 (0.99 – 1.68)	0.054	1.13 (0.86 – 1.48)	0.382
Malignancy				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.00 (1.42 – 2.82)	<0.001	1.90 (1.34 – 2.70)	<0.001
Sex				
Female	Ref	-	-	-
Male	1.10 (0.88 – 1.38)	0.391		
Cardiovascular comorbidities				
Nil	-	-	-	-
Pre-existing diagnosis				
Respiratory comorbidities				
Nil	-	-	-	-
Pre-existing diagnosis				

Table 4.9: Factors associated with increased risk of mortality in de-novo injury patients

4.4.4 Rates of reduced kidney function in ICU survivors

For the purposes of these analyses, the 72 ICU survivors who suffered from EKF prior to admission to ICU were excluded, due to the significant alterations in serum creatinine values influenced by their treatments with KRT. The remaining 4,013 patients were then assessed for serum creatinine tests performed at the defined follow-up periods of 6 months, 12 months and 18 months. Pre-ICU baseline glomerular filtration rate for these patients can be found in Table 4.10.

Estimated baseline glomerular filtration rate	Total patients (n = 4013)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)
>60.0	3449 (85.9%)	2414 (90.5%)	1035 (76.8%)
45.0 – 60.0	292 (7.3%)	163 (6.1%)	129 (9.6%)
30.0 – 44.9	160 (4.0%)	68 (2.6%)	92 (6.8%)
15.0 – 29.9	79 (2.0%)	17 (0.6%)	62 (4.6%)
<15.0	33 (0.8%)	4 (0.2%)	29 (2.2%)

Table 4.10: Estimated baseline glomerular filtration rates in patients before admission to ICU

4.4.4.1 Long-term kidney function in ICU survivors

Over the total follow up period, 1,881 patients from the no kidney injury group had at least one eGFR value available for 6, 12 or 18 months: this corresponded to 70.6% of the 2,666 ICU survivors who fell into this group. A similar proportion of patients in the de-novo injury group had at least one available value: 1,020 out of 1,347 ICU survivors (75.7%).

A total of 2,129 patients had an available serum creatinine for 6-month follow up. These patients were initially assessed for calculated eGFR based on presence of kidney injury whilst in ICU: the results of this analysis are available in Table 4.11. This showed that higher proportions of the de-novo kidney injury group were seen in the lower eGFR ranges compared to patients who suffered

from no kidney injury whilst admitted to ICU. By contrast, a high proportion of the patients with no injury were found to have an eGFR of >60 at the 6-month follow up point (86.7%). Whilst the relative numbers of patients within the eGFR ranges of 15.0 -29.0 and <15.0 were low, there were higher proportions found in the de-novo injury group.

At the 12-month follow-up time point 1,851 patients had an available serum creatinine value. The results of the analysis on these patients are available in Table 4.12. This analysis showed similar patterns to the one performed on patients at the 6-month period: a high proportion of patients from the no kidney injury group were found to have an eGFR of >60 compared to patients within the de-novo injury group (83.9% vs 65.4%). The same pattern was also seen in eGFR ranges below 30, however there was a higher proportion of patients in the 30- 60 eGFR range in the de-novo injury group at 12 months compared to that found at 6 months.

Estimated glomerular filtration rate at 6 months	Total patients (n = 2129)	No kidney injury (n = 1334)	De-novo kidney injury (n = 795)
>60.0	1690 (79.4%)	1156 (86.7%)	534 (67.2%)
45.0 – 60.0	214 (10.1%)	99 (7.4%)	115 (14.5%)
30.0 – 44.9	130 (6.1%)	55 (4.1%)	75 (9.4%)
15.0 – 29.9	73 (3.4%)	21 (1.6%)	52 (6.5%)
<15.0	22 (1.0%)	3 (0.2%)	19 (2.4%)

Table 4.11: Estimated glomerular filtration rates in patients at 6 months

Estimated glomerular filtration rate at 12 months	Total patients (n = 1851)	No kidney injury (n = 1177)	De-novo kidney injury (n = 674)
>60.0	1428 (77.2%)	987 (83.9%)	441 (65.4%)
45.0 – 60.0	205 (11.1%)	114 (9.7%)	91 (13.5%)
30.0 – 44.9	139 (7.5%)	51 (4.3%)	88 (13.1%)
15.0 – 29.9	63 (3.4%)	21 (1.8%)	42 (6.2%)
<15.0	16 (0.9%)	4 (0.3%)	12 (1.8%)

Table 4.12: Kidney function in ICU survivors at 12 months

Estimated glomerular filtration rate at 18 months	Total patients (n = 1730)	No kidney injury (n = 1110)	De-novo kidney injury (n = 620)
>60.0	1335 (77.2%)	934 (84.1%)	401 (64.7%)
45.0 – 60.0	198 (11.4%)	104 (9.4%)	94 (15.2%)
30.0 – 44.9	116 (6.7%)	51 (4.6%)	65 (10.5%)
15.0 – 29.9	60 (3.5%)	17 (1.5%)	43 (6.9%)
<15.0	21 (1.2%)	4 (0.4%)	17 (2.7%)

Table 4.13: 18-month follow-up of kidney function in ICU survivors

Exploration of the values available at 18 months revealed 1,730 patients available for analysis: these results are available in Table 4.13. These numbers were again very similar to the 6- and 12-month follow up periods, with the majority of patients found to have an eGFR <15 having suffered from a de-novo injury during their stay in ICU (81.0%).

4.4.4.2 Changes in kidney function from baseline

To attain a more accurate reflection of changes in kidney function following admission to ICU, available eGFR at 6, 12 and 18 months were compared with each patient's baseline eGFR and the change was calculated. Median and IQR were then reported for each time period dependant on presence of kidney injury during admission. In addition, the median eGFR for each patient across the three defined time points was taken and compared to the baseline; this was used to determine the most accurate reflection of the effect of kidney injury in ICU over the total follow-up period. The results of these analyses can be found in Table 4.14: negative numbers denote a reduction in eGFR from baseline and positive numbers represent an increase.

The analyses based on time period demonstrated that at the three defined points during the follow up period the median change in eGFR showed a reduction in both the no kidney injury and de-novo injury groups. The observed reduction in eGFR from baseline increased in magnitude in both groups of patients as the length of time following hospital discharge increased. At all defined time points, the reduction in eGFR was greater in the de-novo injury group compared with the patients who survived ICU without suffering from a kidney injury: -1.78 difference at 6 months, -2.36 difference at 12 months and -3.01 difference at 12 months. When comparing the change from baseline eGFR to median eGFR values across the total follow-up period, the calculated change showed a larger reduction in the de-novo group compared to the no kidney injury group. For analyses of total follow-up period and the pre-defined follow up points, the observed difference in medians between the two groups was found to be statistically significant. In addition, an eGFR slope (Figure 4.3) comparing patients with no kidney injury to those with de-novo injury during admission demonstrated that patients with de-novo injury have a faster decline in eGFR over the total follow up period, with a Wald test *p*-value of <0.001. The decline for patients in the de-novo kidney injury (DNKI) group was found to be 0.00193 ml/min/1.73m^2/day greater than patients in the no kidney injury group: this correlated with a 0.704 ml/min/1.73m^2 greater decrease in eGFR every year.

Time Period	No kidney injury	De-novo kidney injury	*p*-value
6 months			
Number of patients	1334	795	0.011
Median change in eGFR	-1.41	-3.19	
Interquartile range	-8.95 to +4.65	-13.55 to +5.48	
12 months			
Number of patients	1177	674	<0.001
Median change in eGFR	-2.13	-4.49	
Interquartile range	-9.41 to +4.72	-14.74 to +3.66	
18 months			
Number of patients	1110	620	<0.001
Median change in eGFR	-2.25	-5.26	
Interquartile range	-10.41 to +4.32	-16.15 to +3.64	
Total follow up period			
Number of patients	1881	1020	<0.001
Median change in eGFR	-1.99	-4.18	
Interquartile range	-9.10 to +4.15	-13.94 to +3.89	

Table 4.14: Changes in eGFR from baseline over total follow-up period

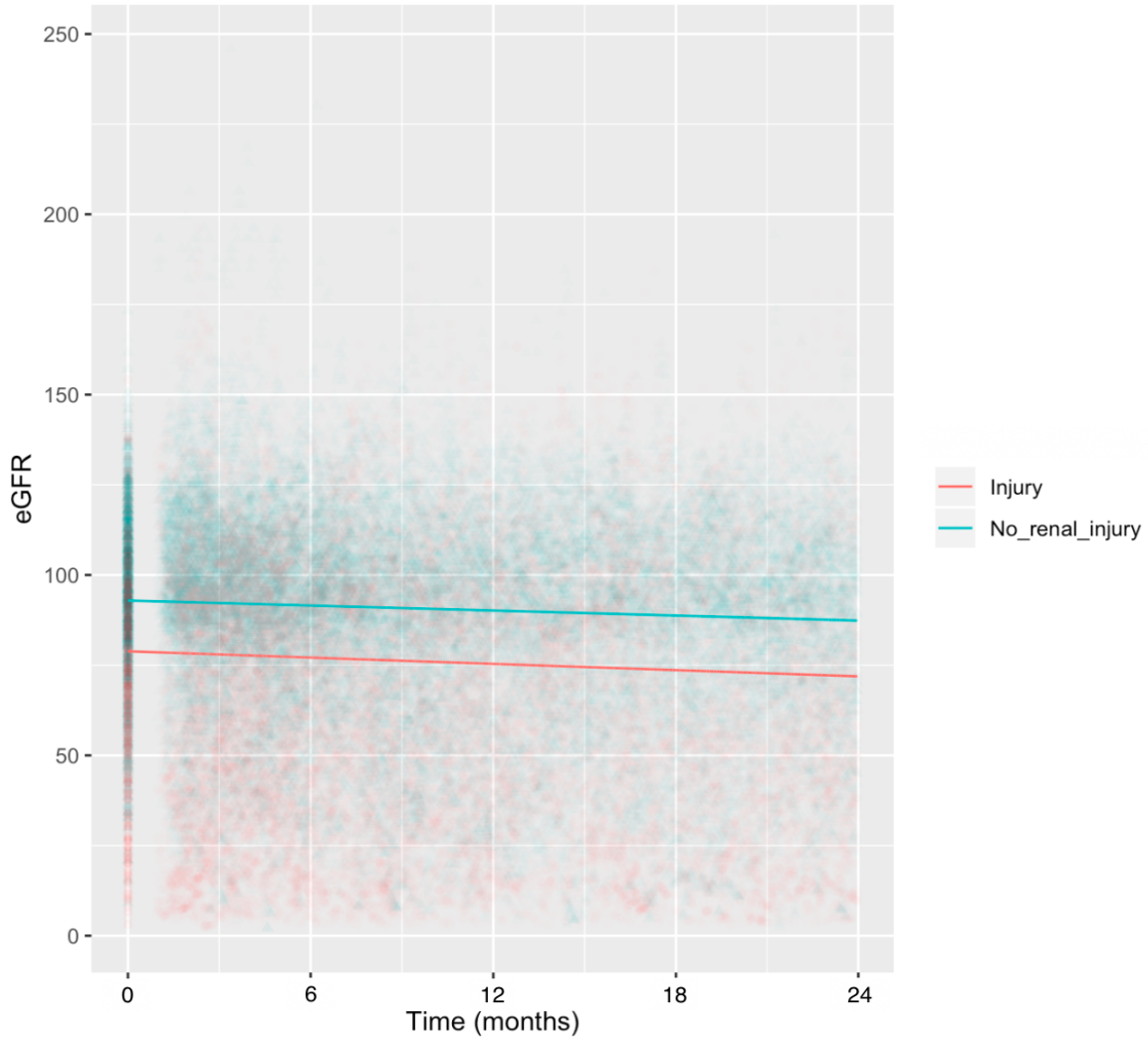


Figure 4.3: eGFR slope comparing patients based on presence of kidney injury whilst admitted to ICU. Slope is generated from serum creatinine values taken following hospital discharge. Time 0 represents date of admission to ICU and the value plotted for each individual patient at this point is pre-admission baseline eGFR to incorporate the change.

Further analyses were then conducted on the group of ICU survivors to suffer from a de-novo injury based on the length of their kidney injury whilst admitted to ICU. In total 1,020 of these patients had a least one follow-up value available; this corresponded to 803 out of 1,055 ICU survivors with AKI (76.11%) and 217 out of 288 ICU survivors with AKD (75.35%). The analyses of this subset of patients demonstrated a reduction in eGFR for both AKI and AKD patients at 6, 12 and 18 months and across the total time period. In addition, the change in eGFR was shown to be of greater magnitude as the time after discharge from hospital increased. AKD patients were also shown to have a larger reduction in eGFR compared to AKI patients at all time points and across the study period as a whole: -3.35 difference at 6 months, -4.39 difference at 12 months. -5.60 at 18 months and -4.05 for median values across the total follow up period. For all of the above analyses, the median difference in eGFR change was shown to be

statistically significant between the AKI and AKD groups (*p*-values <0.025). This was also seen in an eGFR slope (Figure 4.4) comparing AKI patients with AKD patients over the total follow up period: eGFR in patients with AKD was found to decline at a faster rate than patients with AKI with a Wald test *p*-value of 0.036. The eGFR decline in AKD patients was 0.00240 ml/min/1.73m^2/day greater than in AKI patients which translated to a 0.876 ml/min/1.73m^2 greater decrease in eGFR every year.

Time Period	Acute kidney injury	Acute kidney disease	*p*-value
6 months			
Number of patients	622	173	0.009
Median change in eGFR	-2.33	-5.68	
Interquartile range	-11.99 to +5.75	-20.82 to +4.73	
12 months			
Number of patients	530	144	0.003
Median change in eGFR	-3.56	-7.95	
Interquartile range	-13.56 to +3.75	-19.77 to +1.73	
18 months			
Number of patients	489	131	0.012
Median change in eGFR	-4.30	-9.90	
Interquartile range	-14.43 to +3.76	-22.91 to +2.72	
Total follow up period			
Number of patients	803	217	0.021
Median change in eGFR	-3.40	-7.45	
Interquartile range	-12.54 to +3.85	-18.85 to +3.80	

Table 4.15: eGFR changes from baseline based on length of kidney injury

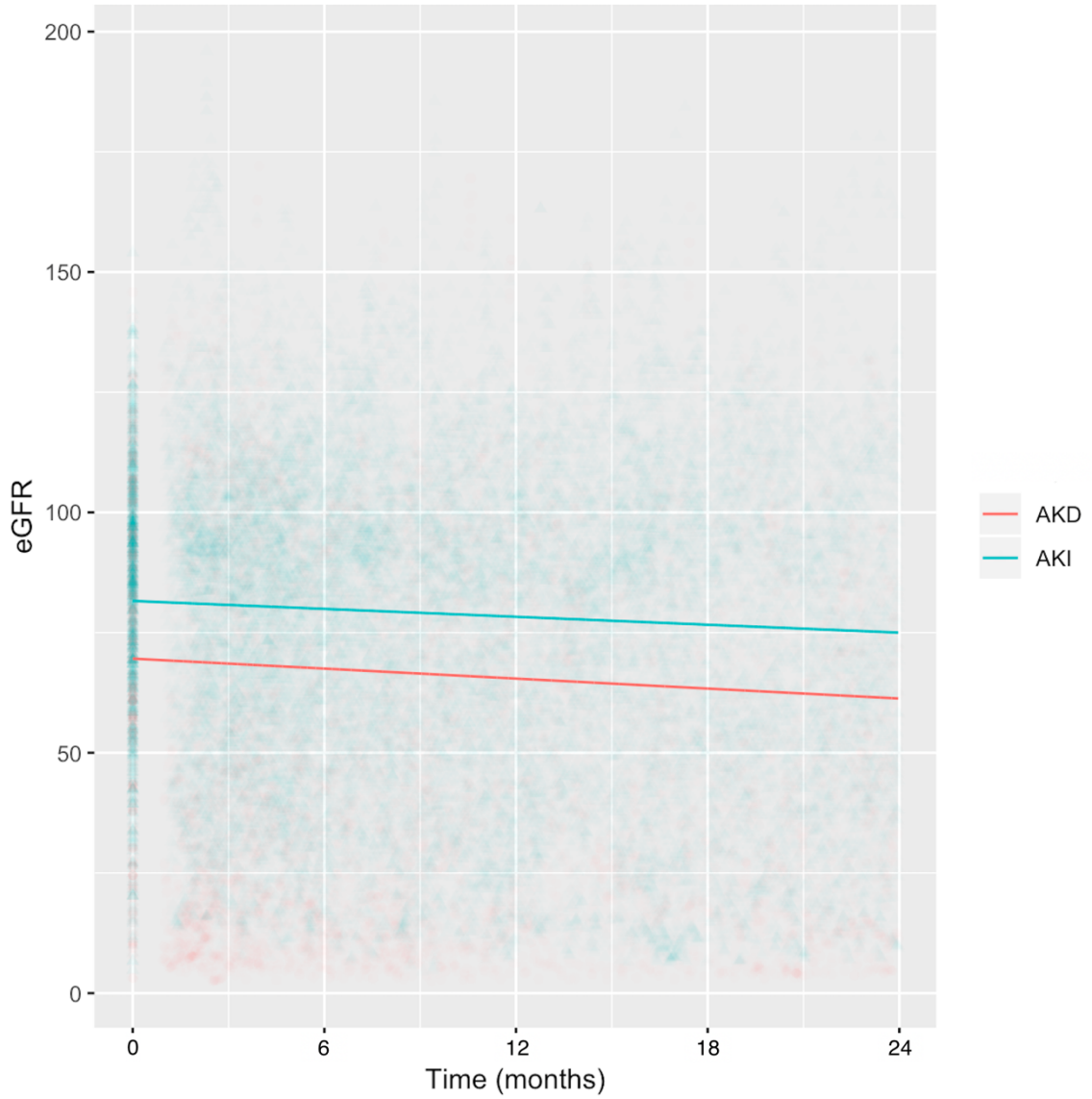


Figure 4.4: eGFR slope dependent on presence of AKD during ICU admission. Slope is generated from serum creatinine values taken following hospital discharge. Time 0 represents date of admission to ICU and the value plotted for each individual patient at this point is pre-admission baseline eGFR to incorporate the change.

4.4.5 Major adverse kidney events following ICU admission

4.4.5.1 Relative rates of major adverse kidney events based on presence and length of injury

Due to the nature of the outcome measure, pre-existing EKF patients were automatically excluded from these analyses. In total, of the remaining 4,013 patients, 1,249 (31.1%) suffered from a major adverse kidney event (MAKE) during the total follow up period. The total numbers of patients suffering from each individual MAKE can be found represented in Table 4.16.

Major adverse kidney event	Total patients (n = 4013)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)	*p*-value
eGFR drop <30% from baseline – n (%)	1240 (30.9%)	651 (24.4%)	589 (43.7%)	<0.001
eGFR drop <40% from baseline- n (%)	892 (22.2%)	432 (16.2%)	460 (34.2%)	<0.001
Serum creatinine doubled from baseline- n (%)	521 (13.0%)	246 (9.2%)	275 (20.4%)	<0.001
Initiation long-term KRT- n (%)	12 (0.3%)	-	12 (0.9%)	-
Any MAKE – n (%)	1249 (31.1%)	652 (24.5%)	597 (44.3%)	<0.001

Table 4.16: Rates of MAKEs based on presence of kidney injury during ICU. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission

The most common MAKE to occur over the total follow up period was found to be a drop in eGFR of 30% or more from baseline prior to ICU admission. In total, 30.9% of all patients were found to have at least a 30% drop in eGFR; a higher proportion of patients within the de-novo injury group suffered from this event compared to patients within the no kidney injury group (43.7% vs 24.4%; *p*-value <0.001). Similarly, a higher proportion of patients within the de-novo injury group were found to have any MAKE during the total follow-up period compared to the no kidney injury group (44.3% vs 24.5%; *p*-value <0.001). The representation of the development of MAKEs over time be seen represented in Figure 4.5. The log-rank test between the curves demonstrated a statistically significant difference (*p*-value <0.001).

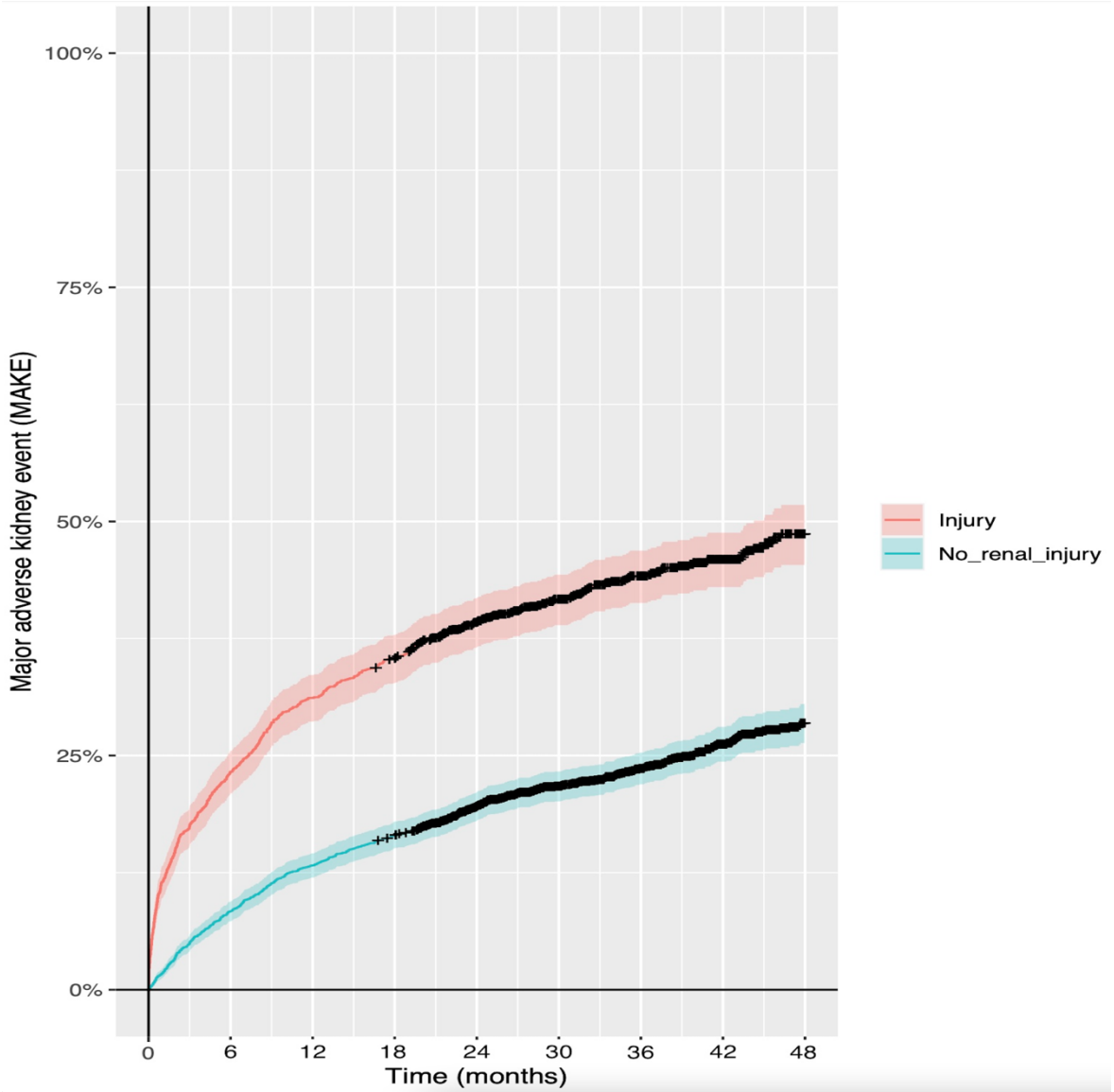


Figure 4.5: Development of major adverse kidney events over time in ICU survivors

Sub-group analysis of AKI vs AKD patients revealed a similar pattern to that seen on comparison of patients without kidney injury to those with de-novo injury during ICU admission: the most common MAKE seen in both groups was an eGFR drop of 30% or more from baseline prior to ICU admission. This occurred in a higher proportion of the AKD group compared to the AKI group (50.4% vs 41.9% respectively; *p*-value = 0.009). When comparing individual MAKEs, all were found to be more common in the AKD group compared to the AKI group; in addition, when comparing development of any MAKE, a higher proportion was seen in the AKD group compared to the AKI group (54.2% vs 41.9% respectively; *p*-value <0.001). Figure 4.6 shows the development of MAKEs in ICU survivors as time progresses following hospital discharge separated into AKI and AKD groups. The log-rank test comparing the event curves between these two groups was also found to be statistically significant (*p*-value <0.001).

Major adverse kidney event	Total patients (n = 1347)	Acute kidney injury (n = 1059)	Acute kidney disease (n = 288)	*p*-value
eGFR drop <30% from baseline - n (%)	589 (43.7%)	444 (41.9%)	145 (50.4%)	0.009
eGFR drop <40% from baseline- n (%)	460 (34.2%)	335 (31.6%)	125 (43.4%)	<0.001
Serum creatinine doubled from baseline- n (%)	275 (20.4%)	199 (18.8%)	76 (26.4%)	0.005
Initiation long-term KRT- n (%)	14 (1.0%)	6 (0.6%)	8 (2.8%)	0.003
Any MAKE - n (%)	600 (44.5%)	444 (41.9%)	156 (54.2%)	<0.001

Table 4.17: Relative rates MAKEs based on length of injury

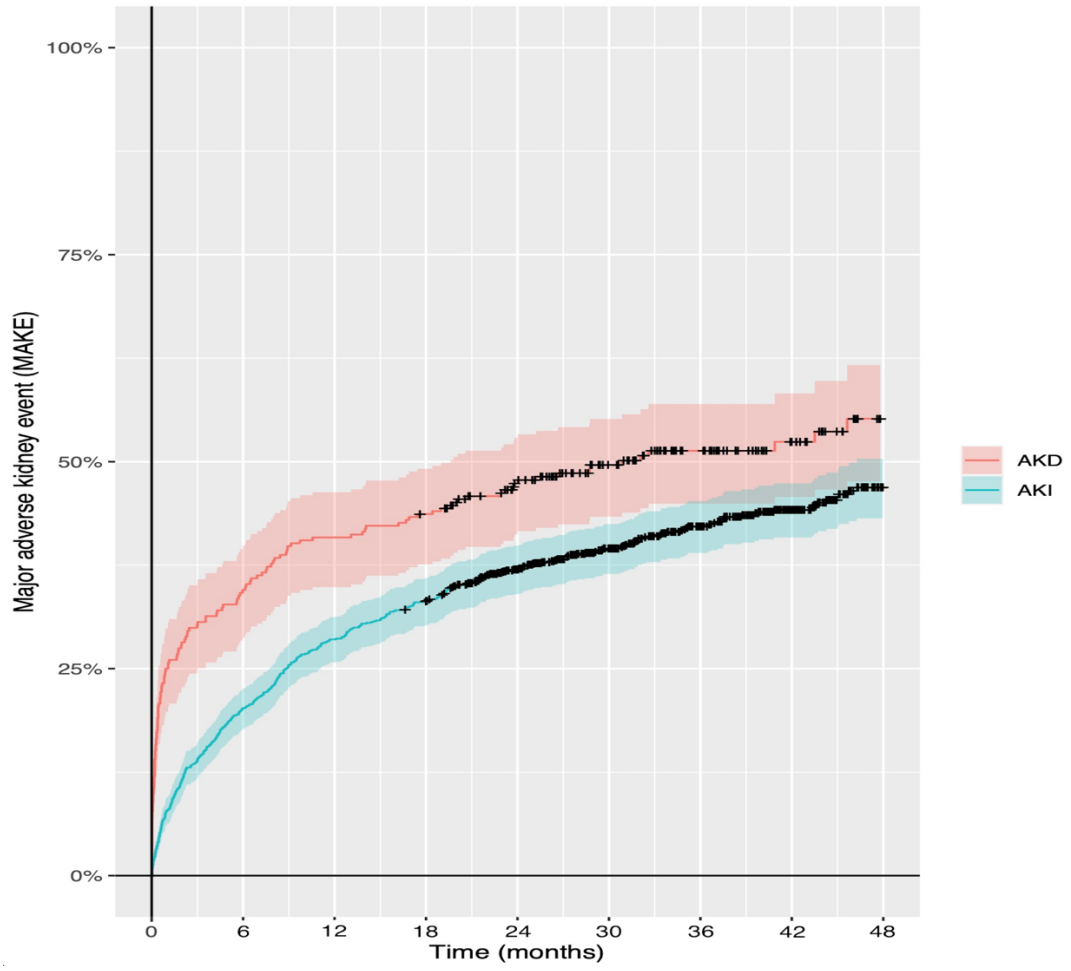


Figure 4.6: Proportion of MAKEs developed over time based on length of injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission

4.4.5.2 Risk factors associated with MAKEs

To ascertain if presence of kidney injury in ICU was an important factor in reduction in kidney function over the follow up period, a multivariable analysis was conducted to correct for differences caused by differing baseline demographics. As with previous multivariable analyses using this cohort of patients, all key baseline demographics initially underwent a univariable analysis independently before inclusion in the multivariable model. Whilst there was a recognition that baseline eGFR was likely to have a strong influence on an outcome which involved drops in eGFR, it was included in the model so that it was corrected for when determining the significance of other variables. Again, the risk of co-linearity was avoided by exclusion of several variables: APACHE II score as this is calculated using measure of kidney function embedded within it which would likely confound results, and recipients of multi-organ support as KRT was one of the three modalities used. When tests for proportionality were assessed, it was apparent that far more events occurred in the DNKI group earlier in the follow-up period and therefore the PH assumption failed; therefore, odds ratios (ORs) and associated 95% CIs were calculated.

Table 4.18 demonstrates the univariable and multivariable ORs for MAKEs during the total follow up period. Initial univariable analyses of the selected variables demonstrated that presence of de-novo injury, increasing age, decreasing baseline eGFR, admission due to sepsis and all pre-defined comorbidities were significantly associated with development of a MAKE during the total follow up period. The only variable which did not show a significant effect on univariable analysis was admitting specialty. Presence of de-novo injury had a greater than double increase in odds of developing a MAKE (OR = 2.28; *p*-value <0.001). Increasing age, pre-existing cardiovascular disease, liver disease and diabetes also showed a significant association with the development of MAKE during the follow-up period when they were included in the multivariable model. Unlike prior analyses, male sex was associated with a reduced risk of a major adverse kidney event (OR = 0.74; *p*-value <0.001). When other variables were accounted for, baseline eGFR, admission due to sepsis, respiratory comorbidities and pre-existing malignancy were not found to be statistically significant. On both univariable and multivariable analyses, admitting specialty was not found to be statistically significant.

Characteristic	Univariable OR (95% C.I.)	*p*-value	Multivariable OR (95% C.I.)	*p*-value
Presence of DNKI				
Nil	Ref	-	Ref	-
Present	2.42 (2.11 – 2.79)	<0.001	2.28 (1.96 – 2.66)	<0.001
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.94 (1.62 – 2.33)	<0.001	1.54 (1.27 – 1.88)	<0.001
>65 years	3.08 (2.56 – 3.71)	<0.001	2.19 (1.77 – 2.72)	<0.001
Sex				
Female	Ref	-	Ref	-
Male	0.76 (0.66 – 0.86)	<0.001	0.74 (0.64 – 0.85)	<0.001
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	2.00 (1.64 – 2.45)	<0.001	1.23 (0.99 – 1.53)	0.060
<30 ml/min/1.73m^2	1.22 (0.81 – 1.81)	0.336	0.65 (0.45 – 1.02)	0.082
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	1.38 (1.17 – 1.62)	<0.001	1.12 (0.94 – 1.34)	0.211
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.05 (1.79 – 2.36)	<0.001	1.41 (1.21 – 1.65)	<0.001
Respiratory comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.31 (1.11 – 1.54)	0.002	1.17 (0.98 – 1.39)	0.080
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.54 (1.22 – 1.94)	<0.001	1.84 (1.44 – 2.36)	<0.001
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.27 (1.88 – 2.73)	<0.001	1.67 (1.37 – 2.03)	<0.001
Malignancy				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.34 (1.04 – 1.71)	0.021	1.18 (0.91 – 1.52)	0.218
Admitting specialty				
Medical	Ref	-	-	-
Surgical	1.02 (0.89 – 1.17)	0.795		

Table 4.18: Analysis of variables associated with long-term development of MAKEs

A separate analysis was carried out only on the patients to suffer from de-novo injury during admission: these results can be found in Table 4.19. As was the case for the entire study population, the model failed the proportionality assumption so ORs were reported instead of HR. The same variables underwent both individual univariable and multivariable analyses with the exception of presence of de-novo injury; this was replaced with presence of AKD. The results demonstrated a similar pattern to the previous analyses which compared DNKI patients to those who did not experience a kidney injury: presence of AKD, increasing age, reduced baseline eGFR, cardiovascular comorbidities, respiratory comorbidities and diabetes mellitus were all statistically significant factors in the development of a major adverse kidney event on univariable analyses. When considering the multivariable analysis, presence of AKD was found to significantly increase the odds of developing a MAKE by 25% (*p*-value = 0.022) when the other variables were accounted for. Increasing age, pre-existing liver disease and diabetes were all statistically significant factors in the development of MAKE following the multivariable analysis. As was the case for the analyses comparing patients with DNKI to those who did not experience a kidney injury during their ICU admission, male sex was found to be a protective factor in the subsequent development of MAKE when considering the multivariable analysis (OR = 0.84; *p*-value = 0.045). When other variables were corrected for, baseline eGFR, cardiovascular comorbidities and respiratory comorbidities were not significant factors in the future development of MAKEs.

Characteristic	Univariable OR (95% C.I.)	*p*-value	Multivariable OR (95% C.I.)	*p*-value
Presence of AKD				
Nil	Ref	-	Ref	-
Present	1.43 (1.10 – 1.86)	0.007	1.25 (1.03 – 1.51)	0.022
Age				
<45 years	Ref	-	Ref	-
45-65 years	1.59 (1.25 – 2.03)	<0.001	1.47 (1.15 – 1.90)	0.003
>65 years	1.86 (1.47 – 2.38)	<0.001	1.67 (1.29 – 2.19)	<0.001
Sex				
Female	Ref	-	Ref	-
Male	0.80 (0.68 – 0.95)	0.009	0.84 (0.72 – 0.99)	0.045
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.25 (1.01 – 1.52)	0.033	1.08 (0.87 – 1.33)	0.486
<30 ml/min/1.73m^2	0.82 (0.56 – 1.16)	0.184	0.71 (0.49 – 1.01)	0.068
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.32 (1.12 – 1.55)	<0.001	1.13 (0.95 – 1.35)	0.169
Respiratory comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.22 (1.00 – 1.48)	0.042	1.11 (0.91 – 1.35)	0.276
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.22 (0.94 – 1.57)	0.121	1.36 (1.04 – 1.75)	0.019
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.37 (1.13 – 1.65)	0.001	1.25 (1.03 – 1.52)	0.022
Admitting specialty				
Medical	Ref	-	-	-
Surgical	0.94 (0.80 – 1.11)	0.486		
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	-	-
Sepsis	1.11 (0.93 – 1.31)	0.256		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.12 (0.81 – 1.50)	0.476		

Table 4.19: Risk factors associated with development of MAKEs following de-novo injury. Modified from *"Short- and long-term outcomes of intensive care patients with acute kidney disease"* Andonovic et al. EClinicalMedicine (2022) with permission

4.5 Discussion

4.5.1 Baseline demographics of ICU survivors

Data from the results of this study demonstrated that of the 5,312 patients admitted to ICU during the study period, 4,085 (76.9%) survived at least 30 days after they were discharged from hospital. Of these 4,085 patients, approximately one in every three (33.0%) was found to have had a de-novo kidney injury at some point during their ICU admission. This was a slightly lower proportion than the previous study looking specifically at short-term outcomes from the entire study population (40.3%). This correlates with data from the total study population showing higher in-hospital mortality rates in patients with de-novo injury compared to those who suffered from no kidney injury.

An initial analysis was performed with the goal of comparing baseline demographics of ICU survivors to that of the total study population as documented in the prior study looking at short-term outcomes. This analysis found that the demographics of the ICU survivors were very similar to the population admitted to ICU. Of note, increasing age and male sex were found to be associated with de-novo injury, as has been previously demonstrated in the literature (143, 153). Increasing age is linked to higher rates of comorbidities and declined physiological reserve in kidney function (153). As discussed in the previous study, it has been postulated that the association between male sex and increased prevalence of kidney injury may be due to the effect of sex hormones on various cellular processes (143).

Admission from medical specialties was also significantly more common in the de-novo injury group compared with the group without kidney injury. This agrees with previous data from Porter and colleagues, who have previously documented a much higher prevalence of kidney injury in patients from medical specialties compared to surgical specialties (144). Median baseline eGFR was also significantly lower in the DNKI group: this is a representation of the well documented link between CKD and AKI as a result of the tubulointerstitial pathology found in CKD (155, 156). A significantly greater proportion of DNKI patients suffered from pre-existing diabetes. Diabetic nephropathy is a well-

recognised complication of diabetes and it has been shown to increase the risk of developing kidney injury during hospitalisation (150).

Patients who suffered from DNKI during their ICU admission also had a significantly higher median APACHE II score, and a significantly higher rate of multi-organ support. Given that APACHE II scores represent an increased severity of illness, both of these factors are an illustration of the increased risk of kidney injury within the critically unwell (17).

Apart from age, which was similar between the two groups, all of the above discussed factors were also associated with progression to AKD when compared specifically to the group of patients found to have AKI. The underlying pathology behind this mechanism must be hypothesised due to the lack of prior data on AKD, however the pathophysiological processes discussed above for development of DNKI likely play a similar role in the progression to AKD.

4.5.2 Long-term survival based on presence and length of kidney injury

All mortality data was analysed from the first date of the study period (1st July 2015) until the 31st December 2019. Follow-up time differed for each patient based on their date of discharge from hospital: the range of follow-up for mortality was 355 days to 1,612 days.

Once separated into groups based on presence of kidney injury, the long-term survival was significantly decreased in patients who had suffered from a de-novo injury during their ICU admission compared to those who had not. This was confirmed by systematic time-period analyses of the two groups demonstrating that patients within the de-novo group had a lower rate of survival at all time points throughout the documented follow-up period. This is consistent with previous literature, which states that de-novo injury is associated with a long-term increased risk of mortality and poorer prognosis (26, 27, 30, 34, 110). The pathophysiology behind this mechanism is likely multifactorial and is partly dependant on aetiology of the initial kidney injury, however the link between this and mortality is a reflection of the integral role that the kidneys play in maintaining normal homeostasis within the body. This is supported by the even

poorer survival rates seen in the admittedly small group (n = 72) of ICU survivors admitted with pre-existing EKF throughout the study period.

Subgroup analysis was conducted on the de-novo injury patient group: these patients were separated into AKI and AKD groups. The Kaplan Meier estimate of these groups showed a consistently lower survival rate in the AKD group throughout the follow-up period. However, in spite of this sustained difference between the groups, the log-rank test found the difference in the two survival curves to not be statistically significant. This may be due to the fact that the sample size of ICU survivors who suffered from AKD during their admission was reasonably small (n = 288) which resulted in wide confidence intervals over the follow-up period.

Whilst the concept of AKD as a separate entity is a fairly novel concept and therefore limited evidence on the subject is available, some prior studies have examined the effect that longer term kidney injury has on mortality in specific subsets of patients (47, 159). The results of these studies would support the data produced in this study that longer-term injury is associated with an increased risk of long-term mortality. Coca and colleagues specifically assessed patients with post-operative kidney injury, and they reported an adjusted hazard ratio of 2.01 for long-term kidney injury lasting over 7 days when compared with patients without kidney injury (47). Brown et al. also assessed postoperative AKI following cardiac surgery, and they reported an adjusted HR of 3.40 for injury lasting 7 days or more (159). It should be noted that both of these studies assessed a postoperative cohort of patients compared to the ICU population in this study, were both inclusive of short-term mortality and the reported hazard ratios were compared to patients without kidney injury. Further study with greater numbers would be beneficial in determining if the novel concept of AKD does confer a significant increase in long-term mortality in comparison to a shorter-term kidney injury.

4.5.3 Factors associated with long term survival

Multivariable analysis showed that de-novo injury represented a statistically significant difference in long-term survival, with a HR of 1.16 (95% C.I. = 1.00 – 1.35; *p*-value = 0.042). This supported the Kaplan Meier estimate showing a

difference between the survival curves of de-novo injury patients and no kidney injury patients. Not only did this confirm that the increased risk of mortality seen in the prior study analysing short-term outcomes was sustained over a much longer-term but was consistent with the results of previously published literature on the subject (26, 30, 34). These three studies reported increased long-term mortality risks associated with AKI ranging from 26-41%. Whilst these reported hazard ratios are higher than those seen in our study, the sample size achieved in these previous studies was larger and predominantly used all hospitalised patients rather than an ICU cohort.

The data also demonstrated that increasing age, pre-existing diabetes and pre-existing malignancy were associated with an increase in long-term mortality whereas admission from surgical specialties showed a reduction in risk of long-term mortality. This link between increasing age and pre-existing malignancy can be easily explained, as older patients and patients with an underlying cancer diagnosis are at greater risk of dying compared with younger patients or patients with no underlying malignancy. Furthermore, underlying diabetes mellitus has recently been reported as having an age-, sex- and ethnicity-adjusted hazard ratio of 1.29 in a national cohort of adults (160). Whilst this is not a specific critical care population, it confirms the data from this study which showed underlying diabetes confers an increased long-term mortality risk.

Since admission specialty was dichotomised into medical and surgical specialties, an associated reduction in risk following admission from surgical specialties indicates that an independent risk factor for long term mortality was admission from medical specialties. Again, this correlation has been previously documented as an independent risk factor for both sustained reduction in kidney function and reduced long-term survival (51). This associated increase in risk was also observed within the subset of patients to suffer from de-novo injury. This may be a reflection of the more complex and comorbid patient population who are admitted from medical specialties; it may also suggest that post-operative patients who have been admitted following a definitive surgical procedure to fix a specific pathology are then more likely to survive longer-term.

While there was an observed difference in survival between AKI and AKD patients, this difference was no longer found to be significant after adjustment was made for other prognostic variables. As postulated above, the lack of statistical significance is possibly due to a reduced sample size of ICU survivors in the AKD group. Due to the lack of previous data in this field, it is challenging to anticipate the expected effect of AKD on long-term outcomes. The only study of similar methodology focused on differences in the rates of kidney recovery between late reversal kidney injury when compared to rapid reversal injury (51). This retrospective study of almost 17,000 critically unwell patients by Kellum et al, described five distinct phenotypes associated with reversal of kidney injury: patients with late reversal, relapse after reversal or failure to reverse had significantly lower adjusted survival estimates at 1-year ranging from 30%-80% when compared to patients with early reversal kidney injury. However, this analysis was inclusive of short-term mortality and therefore less comparable to the results demonstrated in this study.

4.5.4 Sustained reduction in kidney function

Initial analysis was carried out to determine crude rates of patients within certain eGFR ranges at various time points throughout the follow-up period; these ranges were based on internationally recognised definitions for stages of CKD but cannot be classified as such in this study as this required two distinct eGFR values within this range over a 3-month period. The crude rates within each range offered a simple representation of possible trends within the dataset but should be interpreted with caution as prior eGFR values for each patient were not taken into account. Nonetheless, this data showed two patterns: proportions of patients within the eGFR ranges corresponding to more clinically significant stages of CKD (3A – 5) increased as time from hospital discharged increased, and rates of eGFR values equivalent to worse CKD were higher in the de-novo injury group compared to the no kidney injury group. Whilst absolute numbers in the eGFR <15 group (corresponding to CKD stage 5) were small, the majority of patients within this small subset were found to have suffered a de-novo kidney injury during their ICU admission: 86.4% at 6 months, 75.0% at 12 months and 81.0% at 18 months. Given patients with pre-existing eGFR <60 ml/min/1.73m^2 were removed prior to this analysis, such a rapid decline is likely to correlate with the acute insult suffered during ICU admission.

To try and differentiate effect of both presence and length of kidney injury whilst admitted to intensive care, absolute differences in eGFR from baseline to follow up were calculated for each patient. This eliminated the potential effect of pre-existing kidney dysfunction influencing rates of patients with certain eGFR values during follow up. Time period analyses showed similar trends to that seen when assessing crude rates of eGFR ranges: the trend of median eGFR values showed a greater magnitude of change as time from hospital discharged increased, and a bigger drop in eGFR values was seen in the de-novo injury group as opposed to the no kidney injury group. Both these patterns were reflected within the AKI and AKD subgroups, with long-term kidney injury associated with a greater drop in eGFR using each patient's median value over the total 18-month follow up period. Whilst these absolute changes in eGFR may be of negligible difference clinically due to the drop from baseline being relatively small, the data suggests that AKD as a separate entity is associated with worse kidney function post hospital discharge.

A mixed-effect generalised linear model was constructed to account for the variability in both number of serum creatinine measurements and differing timeframes between these measurements for individual patients. Slopes showing the progression of eGFR over a prolonged time-period have previously been described in the literature as being an accurate measure for determining the progression of kidney function over time; this is particularly relevant in patients with high baseline eGFR (161). This eGFR slopes for DNKI vs no kidney injury groups demonstrated that different numbers of creatinine measurements and different timeframes between measurements were accounted for, the decline in eGFR seen in the de-novo injury group was significantly faster than in the no kidney injury group at a rate of 0.704 ml/min/1.73m^2 every year. This is in keeping with the data described above and supports the hypothesis that de-novo injury is associated with a prolonged reduction in eGFR.

Patients with AKD also demonstrated a sharper decline in eGFR in the months following critical illness, when compared to patients with a shorter-term injury (AKI) at a rate of 0.876 ml/min/1.73m^2/year. This would suggest that damage sustained on initial injury may accelerate further loss of functional units within the kidneys and their ability to filter and concentrate urine. Nojima et al. have

previously found that one-year eGFR decline rate is associated with poorer long-term kidney outcomes (162). Whilst the above results would appear to be a small change, previous research has stated that a progressive eGFR loss of 3.3% or more per year was associated with progressive kidney function decline defined by progression of microalbuminuria (163). Given that eGFR naturally declines at a rate of 1 ml/min/1.73m^2/year, this additional 0.876 ml/min/1.73m^2/year would cause an eGFR drop of >3.3% in patients with a starting eGFR of 57 ml/min/1.73m^2 or less. Furthermore, a decline which is 87% greater year on year would result in patients with a baseline eGFR of 100 ml/min/1.73m^2 developing CKD stage 3A in 22 years rather than 40 years.

4.5.5 Factors associated with major adverse kidney events

The definition of major kidney endpoints has been a matter of some debate in the recent literature. Multiple different measures have been postulated, most of which refer to a sustained drop in eGFR from baseline, increasing in albuminuria, progression to established kidney failure or death due to kidney disease (133). Whilst a 40% drop in eGFR from baseline is considered a more sensitive marker of a major adverse kidney event, a drop of 30% or more has also been suggested as a valid surrogate endpoint (133). Due to the lack of data on patients' urinalysis for possible albuminuria, this endpoint was excluded from this study. Whilst death due to kidney disease is considered a valuable MAKE, the absolute numbers of this are very small and lack of data on cause of death prevented it from being used for the purposes of this study. Four well defined endpoints of drop in eGFR of 30% or more, 40% or more, doubling of serum creatinine or initiation of long-term KRT were used in the analysis (134).

When these selected MAKEs were plotted as events occurring over time, there was a stark difference between patients who had suffered from a de-novo injury of any length and patients who had no kidney injury; the data demonstrated in a sharp divergence in number of events up until 18 months, at which point the two groups increase at a similar rate. Comparison of these two curves over the total follow-up period showed a statistically significant difference and further supported the above data showing significant differences in eGFR change following ICU admission. However, it was also noted that in the population that did not suffer from kidney injury in ICU, 24.5% of the patients went on to have a

major adverse kidney event in the next four years. This may represent consequences of the pathophysiological mechanisms underlying the multi-organ dysfunction syndrome (MODS) which is commonly seen in critically ill patients: these patients have significant inflammation which can result in scarring of the glomeruli and progression to CKD and EKF (164), and chronic low-grade inflammation which is considered a hallmark of CKD (165). Furthermore, endothelial dysfunction is a significant problem in critically unwell patients (166), and this has also been shown to predominate in kidney disease due to the accelerated progression of atherosclerosis and reduced expression of endogenous mediators such as endothelial nitric oxide synthase (167).

Multivariable analysis was conducted to determine the significance of presence of kidney injury during admission: baseline demographics were incorporated to correct for their effect and assess if the characteristics associated with kidney injury in ICU had any association with prolonged kidney injury. Initial analysis of the total patient population demonstrated age and presence of de-novo injury were associated with a new major adverse kidney event in ICU survivors; conversely, male sex was a protective factor. Increasing age has also been associated with significant increased risk of developing not just CKD of any stage, but severe CKD (168, 169). This had been described as a consequence of the interplay between the higher prevalence of comorbidities in the elderly which directly affect the kidneys, and the normal structural and physiological changes seen in the kidneys during aging (170). This was also supported by the independent increased risk of pre-existing cardiovascular comorbidities, liver disease and diabetes.

Unlike prior data looking at short-term outcomes and long-term survival of this study cohort, male sex was found to be associated with a reduced risk of adverse kidney events in the long-term. This is possibly a consequence of male sex being associated with decreased short- and long-term survival: a higher proportion of higher risk men within this study population may have died before potentially suffering from an adverse kidney event. The data from this study also showed that presence of de-novo injury of any length was associated with a greater than two-fold increase in the odds of any major adverse kidney event over the total follow up period (OR = 2.28). The link between acute kidney injury of any

length and potential kidney events leading to progression to CKD has been well established in the literature (34, 171-173) . A meta-analysis found that the pooled hazard ratio for developing CKD was 8.8 in patients to suffer an AKI compared to those who had not (33). In this study population, de-novo injury was associated with a near doubling in odds of suffering from an adverse kidney event.

AKD patients were found to be at significantly higher risk of a MAKE than AKI patients over the follow-up period with an additional burden of 25% higher rates of MAKEs demonstrated. Again, this further strengthens the hypothesis generated from the above data on eGFR trends and suggests that protracted kidney injury is indeed associated with worse long-term kidney outcomes. Using development of CKD as a surrogate marker for MAKEs, this relationship correlates well with previous evidence published regarding increased risk of developing CKD following an episode of AKI (171): this study only utilised patients requiring KRT for AKI and found that these patients were greater than three times more likely to require long-term KRT compared to patients who did not suffer from a kidney injury during their hospitalisation. Furthermore, a prior meta-analysis found that increased length of injury is an independent risk factor for progression to CKD (48), with kidney injury of 10 days or more associated with approximately three times the risk of developing new incident CKD stage 3A or worse compared to patients without a kidney injury. However, these results were heavily skewed by a single study looking at post-operative kidney injury following cardiac surgery, which reported an adjusted OR of 13.5 for new incident CKD in longer-term kidney injury. The data produced from this study agrees with these two studies but reports increased odds of only 25%. This is probably due to results only including MAKEs rather than new CKD and comparing short-term injury with longer-term injury rather than patients without kidney injury.

Multivariable analysis of the de-novo injury group showed that the previously seen relationship between increasing age, pre-existing liver disease and diabetes resulting in development of a MAKE was also maintained; this was also the case for the protective association seen with male sex. As discussed above, this may be secondary to the decreased short- and long-term survival found in male

patients. The association between increasing age and underlying comorbidities and future MAKEs is also likely to be indicative of the normal structural changes seen in the kidneys as a result of the aging process (170) and the pathophysiological changes that occur in diabetic nephropathy including generation of reactive oxygen species and activation of protein kinase C which contribute to progressive cellular damage and reduction in kidney function (174).

4.5.6 Strengths and weaknesses

This study utilises a large database of ICU survivors to detail their demographics and how their long-term outcomes vary based on the presence of kidney injury during admission. In addition, it explores the long-term outcomes of patients with a novel concept referred to as AKD – an area in which very little data is currently available. It makes use of a number of different data sources to attain as complete a follow up picture as possible; this is then incorporated into a multitude of different analyses to mitigate for confounding factors and try to ascertain which variables have a significant effect on ICU survivors' outcomes. As this data is produced over a three-year period from two large ICUs, it is likely that the results are generalisable across the normal patient population admitted to ICUs in the UK.

The main limitations in this study relate to the categorisation of initial kidney injury and kidney recovery. Kidney Disease Improving Global Outcomes (KDIGO) recommendations suggest categorisation based on either serum creatinine or urine output – hourly urine output values for this period were not felt to be reliable enough and therefore only serum creatinine values were used. Secondly, there is not a unified definition for kidney recovery, but the most commonly used is once the definition for AKI of any stage is no longer met. This dataset also uses this definition but does not account for potential relapses which may be of greater length than the initial kidney injury. Therefore, this data may slightly underestimate the number of patients who progress to AKD. In addition, since kidney recovery is based on serum creatinine, which is dependent on muscle mass, rates of recovery may be influenced by reduction in lean body mass frequently seen in critically unwell patients.

4.6 Conclusions

Whilst “persistent AKI” has been considered as a concept since the term was defined and has been studied as an independent risk factor associated with poorer long-term outcomes, the idea of AKD specifically defining an injury lasting 7 days or more is so new that little data has been produced on both its short- and long-term outcomes. This study showed that patients with de-novo injury had poorer long-term survival and suffered from prolonged reduction in kidney function compared to patients who did not experience any kidney injury during admission. Patients with AKD had greater reduction in kidney function compared to AKI patients and progression to AKD was found to be a significant independent risk factor. Whilst there was an association between progression to AKD and reduced long-term survival, no significant difference was seen between the AKD and AKI survival curves. More studies utilising larger cohorts of patients are required in this area to further assess the relationship between AKD and long-term survival.

Chapter 5 Long-term cardiovascular outcomes following kidney injury whilst admitted to intensive care

5.1 Introduction

Chronic kidney disease (CKD) has long been documented as being a significant risk factor in the development of cardiovascular disease. Prior studies have quantified the increased risk of developing cardiovascular disease to be two to four times greater in patients with CKD (121). The pathophysiological mechanism underlying this is thought to be multifactorial, with mild to moderate CKD thought to contribute to hypertension, dyslipidaemia, sodium overload and chronic low-grade inflammation throughout the cardiovascular system; more severe CKD is also implicated in hormonal imbalances, anaemia, soft tissue calcification and resistance to erythropoietin (121). The results of these factors all contribute to increased stimulation of inflammatory pathways and underlying chronic inflammation which in turn lends itself to increased risk of developing cardiovascular disease. This increased risk profile has also been documented in patients following acute kidney injury (AKI), with acute myocardial infarction and development of heart failure noted as two events which are significantly more likely following an episode of AKI (122). This study sought to determine the potential long term cardiovascular effects of kidney injury during admission to the intensive care unit (ICU) and whether acute kidney disease (AKD) had any consequence in the risk of these events occurring.

5.2 Study aims

5.2.1 How does presence of kidney injury and progression to AKD during ICU admission impact on myocardial injury?

The population of ICU survivors will be described according to the total numbers alive at day 30 following hospital discharge. Based on prior evidence, the underlying changes to the cardiovascular system following an episode of AKI may be expected to result in an increased risk of the development of acute myocardial infarction (MI) following hospital discharge. As the most common measure for determining myocardial infarction includes an increase of cardiac muscle specific enzymes in blood such as troponin, this is often used as a

surrogate marker of acute MI. The patient cohort will be described according to presence of troponin positive events in ICU survivors stratified by presence of kidney injury as well as differences between AKI and AKD patients. These will then be detailed according to time to event and a multivariable analysis conducted to determine how each variable influences the likelihood of myocardial injury following hospital discharge.

5.2.2 Does kidney injury during ICU admission have an effect on long-term requirement for angiography and percutaneous coronary interventions?

Patients with symptoms suggestive of underlying coronary artery disease will often undergo medical investigations to determine the underlying cause. Coronary angiography is a radiological investigation used to assess coronary arteries for narrowing which may increase the risk of subsequent MI. All angiography results following hospital discharge will be retrieved and the report assessed for reference to coronary artery narrowing. In addition, any recommendation for further intervention such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in the report will be documented. These results will then be detailed according to proportion by kidney injury group, followed by time to event analysis and subsequent multivariable analysis to assess the effect of certain variables on development of coronary artery disease.

5.2.3 How does presence and length of kidney injury impact on cerebrovascular events?

Cerebrovascular events can be categorised as either an infarction or haemorrhage and are most commonly diagnosed using radiological imaging of the brain – either using computed tomography (CT) or magnetic resonance imaging (MRI). All cerebral imaging for each patient following ICU discharge will be retrieved and the official report for each will be examined by a doctor who specialises in interpreting these images (radiologist). This doctor will document on each image if there was evidence of either an infarction or haemorrhage – these will then be described based on presence of event for each kidney injury group. In addition, time to event for each group will be detailed and an analysis of the effect of certain baseline variables will be conducted.

5.3 Methods

For the purposes of this study, only ICU survivors were used from the original dataset. ICU survivors were defined as patients who had survived to 30-days following hospital discharge – this was to allow for patients who may have been discharged from ICU for end-of-life care being included in the long-term analysis. These groups were organised into three broad categories of no kidney injury, de-novo kidney injury and pre-existing established kidney failure (EKF); de-novo injury was used to define all patients with a new injury during admission (with the exception of ERF patients) and was termed as such to prevent confusion when comparing AKI and AKD patients within this group. For subgroup analyses looking at only de-novo kidney injury patients, these were then separated into AKI and AKD groups based on whether the length of kidney injury lasted seven days or longer.

All high sensitivity cardiac troponin values following ICU discharge were collected and analysed – a myocardial injury was registered if the plasma concentration for troponin I was found to be higher than the standard upper limit for normal used in laboratories within the region: 14 nanograms per litre (ng/l). The first positive value was taken as time to event for each patient, and chances of event occurring over time were plotted using Kaplan Meier graphs based on presence of kidney injury during ICU admission. Chances of event occurring were compared using a log-rank test to determine if there were any differences between the groups. This was then repeated for radiological evidence of time to first coronary angiography and time to first cerebrovascular event. To allow a specialty doctor in radiology to interpret the imaging reports, the dataset was linked using patient specific details before being de-identified so that it contained no patient identifiable information before being disseminated.

Regression analysis was used to identify factors associated with subsequent myocardial injury, coronary artery interventions, or cerebrovascular events. Initial univariable analyses were performed on each collected variable except for APACHE II score: this avoided co-linearity as a measure of kidney function is used in the APACHE calculation. Univariable *p*-values of less than <0·2 were included in any multivariable model. For myocardial injury, analyses of variables were

conducted using a Cox proportional hazards model which were reported as hazard ratio (HR) and 95% CI. To ascertain if each variable met the proportionality assumption, Schoenfeld residuals were calculated for each individual variable as well as for the multivariable model. If the *p*-value of the residuals calculated on any variable was found to be <0.2, it was removed from the multivariable model as it was presumed to not obey the proportionality assumption. If this was found to be the case, logistic regression was used to calculate adjusted odds ratios (OR) and 95% CIs at a time point which all patients had complete follow up period. For all analyses, a statistical significance was set at a two-sided *p*-value of <0.05.

5.4 Results

The demographics of the 4,085 patients who survived to day 30 post hospital discharge can be found documented in the prior study looking at long-term survival and reduction in kidney function: 2,666 (65.3%) were found to have no kidney injury, 1,347 (33.0%) patients were found to have suffered from de-novo injury during admission and 72 (1.8%) patients were admitted to ICU suffering from pre-existing established kidney failure (EKF). Minimum and maximum follow-up periods for ICU survivors were 355 days and 1,465 days respectively; the median follow-up time was 848 days.

5.4.1 Myocardial injury events following ICU admission

5.4.1.1 Myocardial injury events based on presence of kidney injury during admission

Of the 4,085 ICU survivors, 1,977 (48.4%) had at least one troponin value measured following hospital discharge: 1,228 patients (62.1%) had not suffered kidney injury in ICU, 701 patients (35.5%) had experienced de-novo injury and 48 patients (2.4%) had pre-existing EKF. These numbers corresponded to similar proportions of each group within the total cohort of ICU survivors at 65.3%, 33.0% and 1.7% respectively. Of patients who had a troponin value available for analysis, 482 (24.4%) had a myocardial injury. Within the no kidney injury group, 240 out of 1,228 patients had a myocardial injury (19.5%); 210 out of 701 patients had a positive event in the de-novo injury group (30.0%); and 32 out of 48 patients had a positive event in the pre-existing EKF group (66.7%). The

demographics of the patients based on presence of a troponin measurement over the total follow up period and whether this was positive can be found in Table 5.1; patients with an available measurement were grouped based on if they had at least one positive value.

The median age from all patients with at least one troponin value available was found to be 59.0. Patients from the group with at least one positive troponin value were found to have a higher median age compared to those who had normal troponin values (64.5 vs 57.0; *p*-value <0.001) and those with no troponin values (64.5 vs 56.0; *p*-value <0.001). Proportions of male patients were similar between the group with all negative troponins and the group with at least one positive value: 56.6% of patients with a positive troponin were male compared to 53.2% in the group with no positive events (*p*-value = 0.212). The proportion of male patients within the group with no troponin value were also comparable to these two groups (55.6%). There was a significantly lower proportion of patients admitted from surgical specialties in the group who presented with at least one positive troponin value following ICU admission when compared with the group without troponins and the group with all negative values (both *p*-values <0.001); they were also found to have a lower median baseline eGFR when compared with these two groups (both *p*-values <0.001). Median APACHE II score was significantly higher in the positive troponin group compared to the other two groups (both *p*-values <0.001). Similarly, higher rates of the pre-defined comorbidities were seen in the group with at least one positive troponin when compared to the group with all negative values: this was the case for pre-existing cardiovascular disease (*p*-value <0.001), respiratory disease (*p*-value = 0.002) and diabetes (*p*-value = 0.007), but similar rates of pre-existing liver disease (p-value = 0.159) and pre-existing malignancy (p-value = 0.667) were seen between the two groups. The most common reason for admission to ICU across the entire patient cohort was sepsis. This was also the case for patients with no troponin values, patients with at least one positive value, and the group of patients with all normal troponin values.

Characteristic	Total patients (n = 4085)	No troponin value (n = 2108)	Negative troponins (n = 1495)	Positive troponin (n = 482)
Age – median (IQR)	56.0 (43.0 – 69.0)	56.0 (42.0 - 68.0)	57.0 (44.0 – 69.0)	64.5 (53.0 – 74.0)
Male - n (%)	2241 (54.9%)	1172 (55.6%)	796 (53.2%)	273 (56.6%)
Admitted from surgical specialty – n (%)	2563 (62.7%)	1333 (63.2%)	970 (64.9%)	260 (53.9%)
Baseline eGFR – median (IQR)	91.8 (72.3 – 106.7)	92.6 (74.3 – 107.1)	91.8 (74.0 – 106.7)	79.5 (53.1 – 96.0)
APACHE II score – median[7] (IQR)	15.0 (10.0 – 20.0)	14.0 (10.0 – 19.0)	15.0 (10.0 – 19.0)	18.0 (13.0 – 23.0)
Comorbidities – n (%)				
Cardiovascular disease	1495 (36.6%)	662 (31.4%)	574 (38.4%)	259 (53.7%)
Respiratory disease	790 (19.3%)	366 (17.4%)	296 (19.8%)	128 (26.6%)
Liver disease	336 (8.2%)	155 (7.4%)	135 (9.0%)	46 (9.5%)
Diabetes	556 (13.6%)	230 (10.9%)	224 (15.0%)	102 (21.2%)
Malignancy	298 (7.3%)	153 (7.3%)	107 (7.2%)	38 (7.9%)
Most common precipitating illnesses necessitating ICU admission	**1.** Sepsis **2.** Malignancy **3.** Trauma	**1.** Sepsis **2.** Trauma **3.** Malignancy	**1.** Sepsis **2.** Malignancy **3.** Gastro (Other)	**1.** Sepsis **2.** Resp **3.** Gastro (Other)

Table 5.1: Demographics of patients with at least one troponin value following hospital discharge

[7] Data unavailable for 134 patients – only 3951 patients used in these calculations (no troponin value = 2040; no positive events = 1441; positive event = 470)

Characteristic	Total patients (n = 482)	No kidney injury (n = 240)	De-novo injury (n = 210)	Pre-existing established kidney failure (n = 32)
Age – median (IQR)	64.5 (53.0 – 74.0)	64.0 (53.0 – 75.0)	66.0 (55.0 – 75.0)	60.0 (52.5 – 67.0)
Male - n (%)	273 (56.6%)	132 (55.0%)	125 (59.5%)	16 (50.0%)
Admitted from surgical specialty – n (%)	260 (53.9%)	152 (63.3%)	100 (47.6%)	8 (25.0%)
Baseline eGFR – median (IQR)	79.5 (53.1 – 96.0)	87.9 (70.5 – 100.8)	72.5 (52.4 – 92.9)	9.0 (6.9 – 16.3)
APACHE II score – median[8] (IQR)	18.0 (13.0 – 23.0)	15.0 (11.0 – 19.0)	21.0 (16.0 – 26.0)	24.0 (22.0 – 29.0)
Comorbidities – n (%)				
Cardiovascular disease	259 (53.7%)	115 (47.9%)	122 (58.1%)	22 (68.8%)
Respiratory disease	128 (26.6%)	62 (25.8%)	63 (30.0%)	3 (9.4%)
Liver disease	46 (9.5%)	22 (9.2%)	21 (10.0%)	3 (9.4%)
Diabetes	102 (21.2%)	42 (17.5%)	48 (22.9%)	12 (37.5%)
Malignancy	38 (7.9%)	15 (7.1%)	22 (9.2%)	1 (3.1%)
Most common precipitating illnesses necessitating ICU admission	**1.** Sepsis **2.** Resp **3.** Gastro (Other)	**1.** Sepsis **2.** Resp **3.** Gastro (Other)	**1.** Sepsis **2.** Gastro (Other) **3.** Resp	**1.** Kidney **2.** Sepsis **3.** Cardiac (Other)

Table 5.2: Demographics of patients with a myocardial injury based on presence of kidney injury

[8] Data unavailable for 12 patients – only 470 patients used in these calculations (no kidney injury = 231; de-novo injury = 210; pre-existing EKF = 29)

The demographics of patients with at least one instance of myocardial injury based on presence of kidney injury are described in Table 5.2. Median age was similar in both the no kidney injury group and de-novo injury group (64.0 and 66.0 years, respectively; *p*-value = 0.457). Similar proportions of male patients were also observed in the de-novo injury group when compared with the no kidney injury group (59.5% vs 55.0%; *p*-value = 0.383). As was seen in the prior analysis on the demographics of all ICU survivors, lower median pre-ICU baseline eGFR and higher median APACHE II score were seen in the de-novo injury group compared to the patients who did not suffer from a kidney injury during their ICU admission (both *p*-values <0.001). In addition, patients with de-novo injury were less likely to have been admitted from surgical specialties as opposed to patients with no kidney injury (47.6% vs 63.3% respectively; *p*-value <0.001). Significantly higher rates of pre-existing cardiovascular disease (*p*-value = 0.039) were seen in the de-novo injury group when compared with the group who did not experience any kidney injury. The proportion of patients with pre-existing respiratory disease, liver disease, diabetes mellitus and malignancy were similar between these two groups. As was the case with the total cohort of patients with myocardial injury, sepsis was the most common precipitating illness necessitating ICU admission in both the de-novo injury and no kidney injury groups. The group of patients with pre-existing EKF was small (n = 32), but when compared with the group who did not experience any kidney injury during their ICU admission, median APACHE II score (*p*-value <0.001), proportion of patients with pre-existing cardiovascular disease (*p*-value = 0.043) and pre-existing diabetes (*p*-value = 0.015) were all significantly higher than in the pre-existing EKF group. Rates of admission from surgical specialties and baseline eGFR were both significantly lower in the pre-existing EKF group (both *p*-values <0.001).

Rates of myocardial injury were charted over time for the entire follow up period; the first episode of myocardial injury was charted for each individual patient. For the purposes of this analysis, all ICU survivors were used with the exception of pre-existing ERF patients. The results of this analysis are available in Figure 5.1. This demonstrated that rates of myocardial injury were consistently higher in the de-novo injury group compared to the no kidney injury group throughout the follow up period. Analysis of the time to event curves

showed that differences between the curves for each group were shown to be statistically significant when log-rank test was used (*p*-value <0.001).

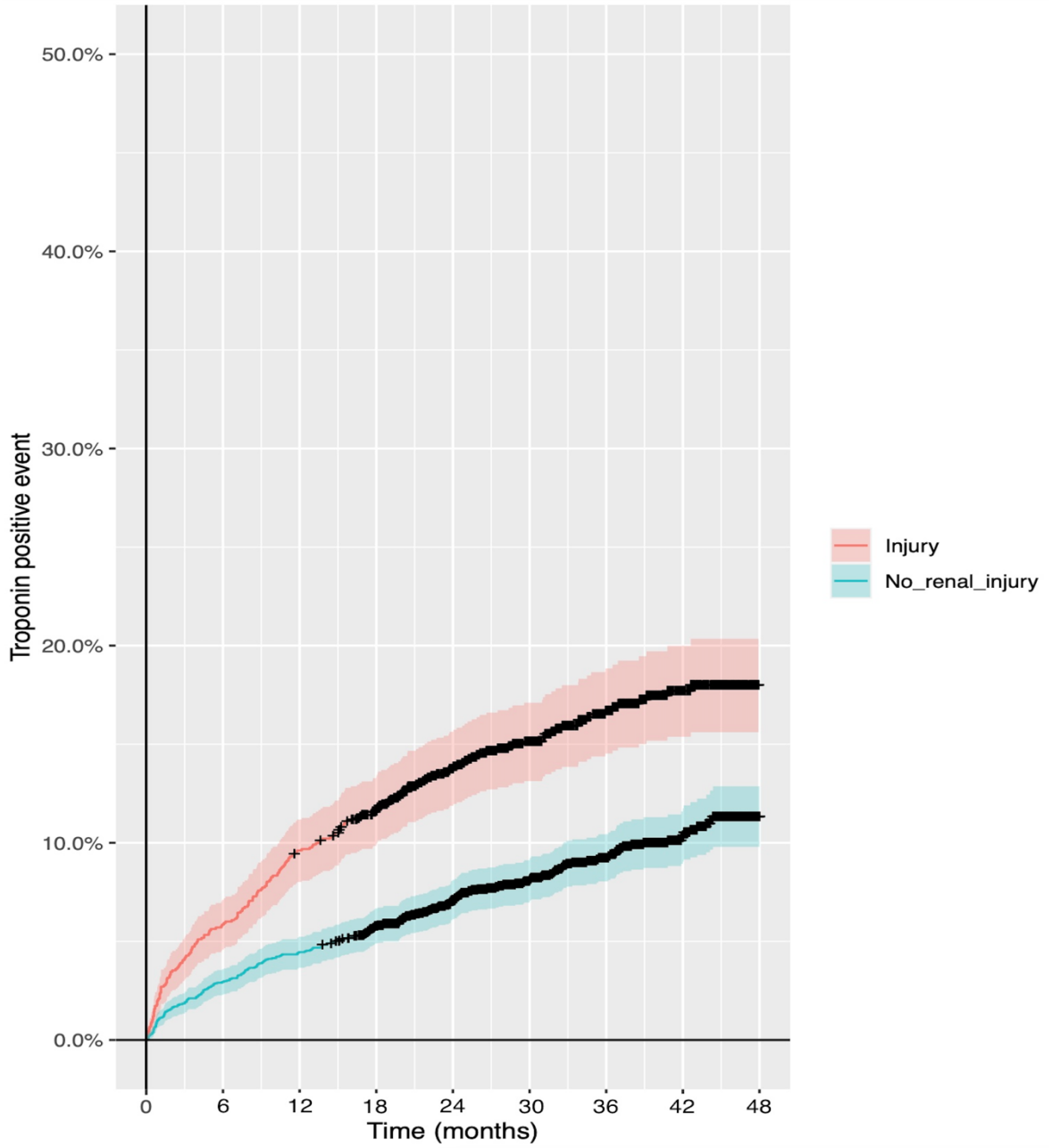


Figure 5.1: Rates of myocardial injury based on presence of kidney injury. Time 0 is taken from day 30 following hospital discharge. *p*-value <0.001

To assess if presence of de-novo kidney injury was a risk factor for future myocardial injury, the 72 patients in the pre-existing EKF group were removed from this analysis. Results of both initial univariable analyses and the multivariable Cox proportional hazards analysis are represented in Table 5.3.

Characteristic	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
Presence of de-novo kidney injury				
Nil	Ref	-	Ref	-
Present	1.84 (1.53 – 2.22)	<0.001	1.46 (1.20 – 1.77)	<0.001
Age				
<40 years	Ref	-	Ref	-
40-70 years	2.48 (1.77 – 3.48)	<0.001	2.03 (1.43 – 2.88)	<0.001
>70 years	4.64 (3.28 – 6.58)	<0.001	3.41 (2.33 – 4.99)	<0.001
Sex				
Female	Ref	-	Ref	-
Male	1.13 (0.94 - 1.36)	0.189	1.22 (1.01 – 1.47)	0.021
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.72 (0.60 – 0.86)	<0.001	0.63 (0.52 – 0.77)	<0.001
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	2.28 (1.81 – 2.88)	<0.001	1.56 (1.22 – 1.99)	<0.001
<30 ml/min/1.73m^2	2.53 (1.69 – 3.76)	<0.001	1.66 (1.10 – 2.51)	0.016
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	1.17 (0.93 – 1.46)	0.183	0.93 (0.74 – 1.18)	0.559
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.05 (1.70 – 2.47)	<0.001	1.42 (1.16 – 1.73)	<0.001
Respiratory comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.65 (1.34 – 2.03)	<0.001	1.58 (1.28 – 1.94)	<0.001
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.24 (0.91 – 1.70)	0.180	1.31 (0.95 – 1.80)	0.099
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.71 (1.36 – 2.16)	<0.001	1.17 (0.92 – 1.49)	0.198
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.14 (0.81 – 1.59)	0.459		

Table 5.3: Risk factors associated with development of an episode of myocardial injury

Univariable analyses of the selected variables revealed that increasing age was the variable most strongly associated with an episode of myocardial injury during the total follow up period (HR = 2.48 for 40–70 year olds and HR = 4.64 for >70 year olds). Presence of de-novo injury was found to be a significant factor in the development of a myocardial injury over the total follow up period (HR = 1.84; *p*-value <0.001). Pre-existing cardiovascular comorbidities were also strongly associated with development of myocardial injury (HR = 2.05; *p*-value <0.001). Other comorbidities such as pre-existing respiratory disease and diabetes were found to be significantly associated with an increased risk of injury (HR = 1.65 and HR = 1.71 respectively). Decreased pre-ICU baseline eGFR was also found to be strongly associated with an increased risk of future myocardial injury (HR = 2.28 for baseline eGFR of 30-60 ml/min/1.73m^2 and HR = 2.53 for a baseline eGFR of <30 ml/min/1.73m^2; *p*-values <0.001 for both). However, patients admitted from surgical specialties had a decreased risk of future myocardial injury (HR = 0.72; *p*-value <0.001). The only variables not found to be significantly associated with risk of myocardial injury were male sex (*p*-value = 0.189), admission due to sepsis (*p*-value = 0.183), pre-existing liver disease (*p*-value = 0.180) and pre-existing malignancy (*p*-value = 0.459). With the exception of pre-existing malignancy, all of these variables met the predefined criteria (of *p*-value <0.2) allowing them to be included in the multivariable model.

Multivariable analysis revealed that the presence of de-novo injury was still statistically significantly associated with subsequent myocardial injury; patients with this risk factor were found to have a 46% increased chance of a myocardial injury following admission to ICU compared to the no kidney injury group (*p*-value < 0.001). Increased age, decreased baseline eGFR, pre-existing cardiovascular comorbidities and respiratory comorbidities all remained significantly associated with an increased risk of a myocardial injury in the multivariable analysis. Similarly, admission from surgical specialties was still significantly associated with reduced risk of future myocardial injury. Whilst not found to be significant in the univariable analysis, male sex (HR = 1.22; (*p*-value = 0.021) was associated with increased risk of an episode of myocardial injury once the other selected variables were accounted for. Conversely, pre-existing diabetes was no longer found to be a statistically significant factor; admission

due to sepsis and pre-existing liver disease were also still not associated with development of subsequent myocardial injury. Schoenfeld residuals were calculated for all variables individually: all *p*-values were found to be >0.2 with a global value for the multivariable model of 0.361. The proportionality assumption was therefore felt to hold true, and the model was considered appropriate.

5.4.1.2 Myocardial injury in de-novo injury patients based on progression to AKD

The 1,347 ICU survivors who suffered a de-novo injury during ICU admission were grouped based on progression to AKD and underwent further analysis. The demographics of the patients who were found to have at least one episode of myocardial injury during the total follow up period can be found in Table 5.4: 170 of these patients were from the AKI group, and 40 were from the AKD group.

Patients within the AKI group were also found to have a higher pre-ICU baseline eGFR than those in the AKD group (77.5 and 59.1 respectively; *p*-value = 0.004). Patients within the AKI group had a higher median age than those within the AKD group but this was not found to be statistically significant (69.0 vs 62.0 respectively; *p*-value = 0.063). Of the de-novo patients who suffered from myocardial injury following hospital discharge, a lower proportion had been admitted from surgical specialties in the AKD population (37.5%) compared to AKI patients (50.0%), but this difference was not statistically significant (*p*-value = 0.212); in addition, similar proportions of patients in the two groups were male. As was seen in the prior analysis of ICU survivors within the de-novo injury group, AKD patients in this cohort were found to have a higher median APACHE II score than patients in the AKI group (*p*-value <0.001). Rates of pre-existing comorbidities in these patients were similar across the two groups, with no statistically significant difference seen for any pre-existing comorbidity. Within both groups of patients, sepsis was the most common precipitating illness necessitating admission to ICU.

Characteristic	Total patients (n = 210)	Acute kidney injury (n = 170)	Acute kidney disease (n = 40)	*p*-value
Age – median (IQR)	66.0 (55.0 – 75.0)	69.0 (56.0 – 76.0)	62.0 (53.0 – 69.0)	0.063
Male - n (%)	125 (59.5%)	99 (58.2%)	26 (65.0%)	0.433
Admitted from surgical specialty – n (%)	100 (47.6%)	85 (50.0%)	15 (37.5%)	0.212
Baseline eGFR – median (IQR)	72.5 (52.4 – 92.9)	77.5 (57.3 – 93.5)	59.1 (24.5 – 85.0)	0.004
APACHE II score - median (IQR)	21.0 (16.0 – 26.0)	20.0 (15.0 – 25.0)	24.0 (20.0 – 30.0)	<0.001
Comorbidities - n (%)				
Cardiovascular disease	122 (58.1%)	97 (57.1%)	25 (62.5%)	0.530
Respiratory disease	63 (30.0%)	52 (30.6%)	11 (27.5%)	0.701
Liver disease	21 (10.0%)	17 (10.0%)	4 (10.0%)	0.998
Diabetes	48 (22.9%)	39 (22.9%)	9 (22.5%)	0.952
Malignancy	15 (7.1%)	14 (8.2%)	1 (2.5%)	0.205
Most common precipitating illnesses necessitating ICU admission	**1.** Sepsis **2.** Gastro (Other) **3.** Respiratory	**1.** Sepsis **2.** Gastro (Other) **3.** Respiratory	**1.** Sepsis **2.** Kidney **3.** Cardiac Arrest	-

Table 5.4: Demographics of de-novo injury patients with a myocardial injury based on progression to AKD

Rates of myocardial injury over the follow up period for all ICU survivors with de-novo injury during ICU admission can be found in Figure 5.2. This showed that rates of myocardial injury were very similar in both the AKI and AKD groups throughout the follow up period. Log rank test comparing the two curves confirmed that there was no statistically significant difference between the two groups (*p*-value = 0.400). Further analysis was conducted to determine if there were any risk factors associated with a myocardial injury within this subset of patients.

All variables used in the prior analysis of all ICU survivors were assessed initially using univariable analyses in the population with confirmed de-novo injury; in this instance, presence of AKD was substituted for presence of de-novo injury. The results of both the univariable analyses and the multivariable analysis can be found in Table 5.5.

Progression to AKD during ICU admission was not associated with having an episode of myocardial injury following discharge (*p*-value = 0.373). Both pre-existing cardiovascular and respiratory comorbidities were strongly associated with myocardial injury in ICU survivors with de-novo injury (HR = 1.98 and HR = 1.92 respectively). Increasing age was also associated with subsequent myocardial injury (HR = 2.19 for 40-70 year olds and HR = 3.76 for >70 year olds); this was similarly the case for decreasing baseline eGFR (HR = 1.81 for baseline eGFR of 30-60 ml/min/1.73m^2 and HR = 1.82 for a baseline eGFR of <30 ml/min/1.73m^2). Admission from surgical specialties (HR = 0.61; *p*-value <0.001) was found to be associated with a reduced risk of having a myocardial injury. All other variables were not found to reach statistical significance in the development of future myocardial injury. However, all variables with a univariable p-value <0.2 were included in the multivariable model to assess if their effect achieved significance.

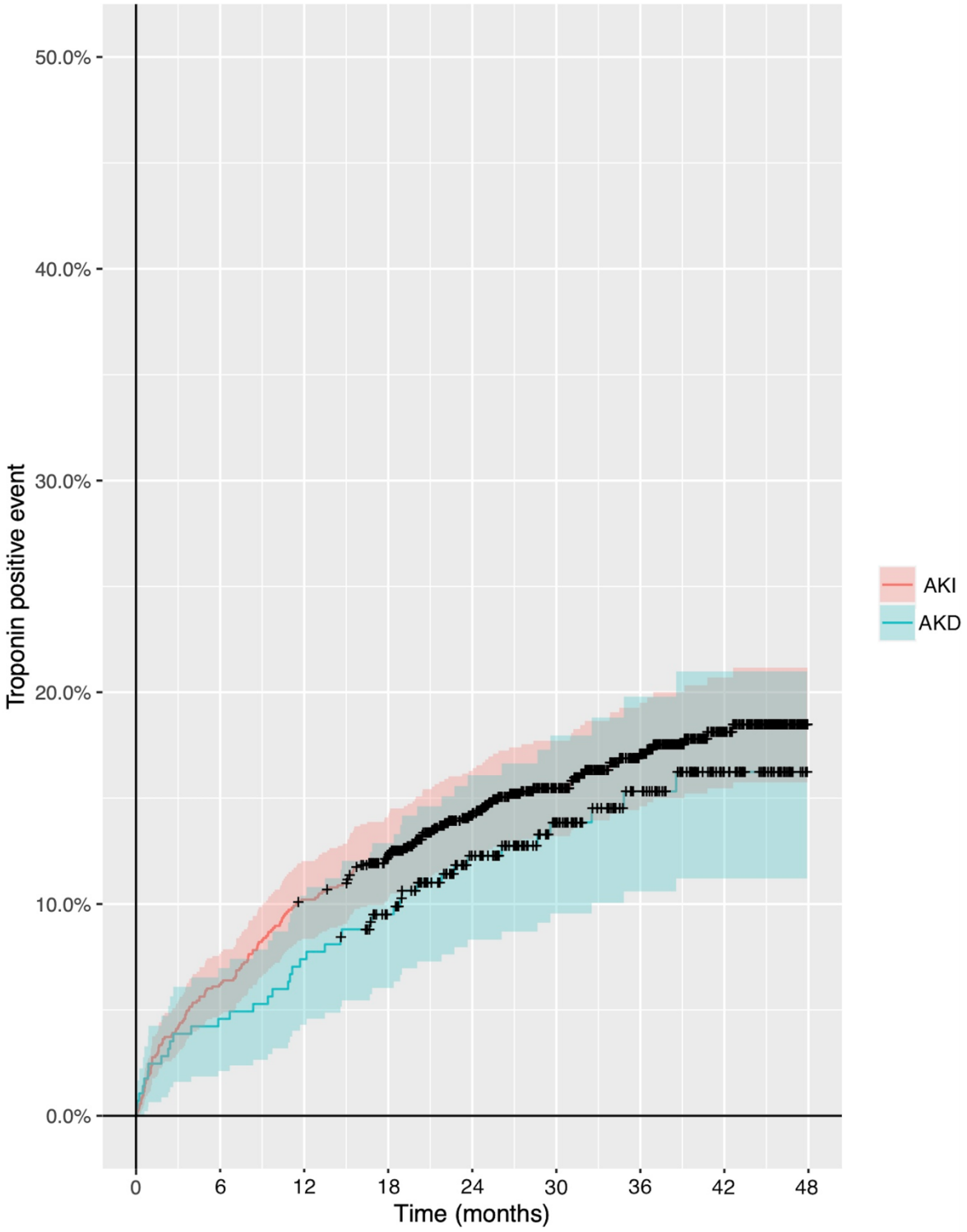


Figure 5.2: Rates of myocardial injury in ICU survivors with de-novo injury based on length of injury. Time 0 is taken from day 30 following hospital discharge. *p*-value = 0.400

Characteristic	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
Progression to AKD				
Nil	Ref	-	Ref	-
Present	0.86 (0.61 – 1.21)	0.373	0.81 (0.57 – 1.15)	0.231
Age				
<40 years	Ref	-	Ref	-
40-70 years	2.19 (1.28 – 3.75)	0.004	1.71 (0.98 – 2.97)	0.058
>70 years	3.76 (2.17 – 6.51)	<0.001	2.69 (1.50 – 4.84)	<0.001
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.61 (0.47 – 0.80)	<0.001	0.51 (0.38 – 0.68)	<0.001
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.81 (1.31 – 2.50)	<0.001	1.50 (1.08 – 2.10)	0.017
<30 ml/min/1.73m^2	1.82 (1.16 – 2.86)	0.009	1.67 (1.05 – 2.65)	0.029
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	0.80 (0.59 – 1.10)	0.167	0.73 (0.53 – 1.01)	0.054
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.98 (1.51 – 2.61)	<0.001	1.61 (1.20 – 2.16)	0.002
Respiratory comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.92 (1.43 – 2.58)	<0.001	1.71 (1.27 – 2.31)	<0.001
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.31 (0.95 – 1.80)	0.105	0.96 (0.68 – 1.34)	0.788
Sex				
Female	Ref	-	-	-
Male	0.98 (0.74 - 1.29)	0.881		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.11 (0.71 – 1.75)	0.645		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.07 (0.63 – 1.81)	0.806		

Table 5.5: Risk factors for myocardial injury in de-novo injury patients

The results of the multivariable analysis demonstrated that the five variables which were significantly associated with a change in risk of a myocardial injury on univariable analysis remained so following correction for the other variables. Progression to AKD remained statistically insignificant in determining risk of a myocardial injury (*p*-value = 0.231). Admission from surgical specialties was still strongly associated with a reduction in risk of subsequent myocardial injury following ICU admission (HR = 0.51). This was also the case for decreased baseline eGFR (HR = 1.50 for baseline eGFR of 30-60 ml/min/1.73m^2 and HR = 1.67 for a baseline eGFR of <30 ml/min/1.73m^2). Increasing age (HR = 1.71 for 40-70 year olds and HR = 2.69 for >70 year olds), and pre-existing cardiovascular (HR = 1.61) and respiratory comorbidities (HR = 1.71) all remained associated with an increased risk of a positive event. Admission due to sepsis and pre-existing diabetes remained statistically insignificant with regards to risk of developing a myocardial injury. Schoenfeld residuals for all variables were found to have a *p*-value >0.2 and were therefore included in the model; the global *p*-value for this multivariable model was 0.257.

5.4.2 Angiography and coronary artery interventions

5.4.2.1 Risk factors associated with requiring angiography and intervention

Event	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)	Pre-existing established kidney failure (n = 72)
Angiography following hospital discharge – n (%)	119 (2.9%)	60 (2.3%)	50 (3.7%)	9 (12.5%)
Subsequent coronary artery intervention – n (%)	53 (1.3%)	25 (0.9%)	24 (1.8%)	4 (5.6%)
Percutaneous coronary intervention – n (%)	41 (1.0%)	17 (0.6%)	21 (1.6%)	3 (4.2%)
Coronary artery bypass grafting – n (%)	12 (0.3%)	8 (0.3%)	3 (0.2%)	1 (1.4%)

Table 5.6: Angiography and coronary artery intervention based on kidney injury group

The absolute rates of angiography performed in ICU survivors following hospital discharge can be found in Table 5.6. From the total study population, 119 patients underwent investigation with angiography (2.9%); of these patients, 53 (44.5%) went on to require further coronary artery intervention either via percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). A higher proportion of the de-novo injury group received angiography following hospital discharge than those who suffered from no kidney injury during ICU admission (3.7% vs 2.3%; *p*-value = 0.007); this was also the case for subsequent intervention, with 1.8% of all patients in the de-novo group requiring coronary artery intervention compared with 0.9% in the no kidney injury group (*p*-value = 0.028). A higher proportion of interventions in the de-novo injury group were percutaneous compared to the group without kidney injury, but this difference was not statistically significant (87.5% and 68.0% respectively; *p*-value = 0.102). The group of pre-existing EKF patients had a much higher relative rate of angiography (*p*-values compared with both other groups <0.001) and subsequent intervention than the other two groups (*p*-value <0.001 compared with no kidney injury and *p*-value = 0.024 compared with de-novo injury group).

Variables associated with coronary intervention are reported in Table 5.7. Initial analysis of Schoenfeld residuals when constructing a multivariable model for risk factors associated with subsequent angiography and intervention, all *p*-values returned were <0.001. On log-log plot analysis, this revealed that the vast majority of interventions occurred at the beginning of the follow up period (median time to angiography = 134 days), with very few events beyond the first 18 months. Since the proportionality assumption was not met for all variables, odds ratios at 12 months were reported instead of hazard ratios. The results of the initial univariable analyses and subsequent multivariable analysis are represented in Table 5.7.

Presence of de-novo injury during ICU admission was shown to be associated with coronary artery intervention on initial analysis (OR = 1.92; *p*-value = 0.024). This was also the case for increasing age, although due to very small numbers in the reference group the confidence intervals were extremely wide; nevertheless, both 40-70 year olds (*p*-value = 0.010) and >70 year olds (*p*-value = 0.013) had significantly higher odds of receiving coronary artery interventions

compared with <40 year olds. Pre-existing cardiovascular comorbidities were strongly associated with requirement for intervention over the total follow up period (OR = 2.83; *p*-value <0.001), whilst admission from surgical specialties reduced the risk of subsequent coronary intervention (OR = 0.34; *p*-value <0.001). All other variables did not display a statistically significant effect on the risk of requiring coronary artery intervention following ICU admission, although male sex and admission due to sepsis were found to have *p*-values <0.2 and were therefore included in the multivariable model.

The multivariable analysis demonstrated that whilst de-novo kidney injury during admission suggested an increased risk of future coronary intervention, it did not have a statistically significant effect (OR = 1.64; *p*-value = 0.093). Increasing age and pre-existing cardiovascular comorbidities remained significant factors in increased risk of interventions once the other variables were accounted for. Similarly, the reduced odds of future intervention associated with admission from surgical specialties remained statistically significant (OR = 0.25; *p*-value <0.001). On adjusted analysis, admitting diagnosis of sepsis was associated with a statistically significant reduced risk of coronary intervention (OR = 0.29; *p*-value = 0.010). As was the case on initial univariable analysis, male sex was not found to have a significant effect on the risk of coronary artery intervention once other variables were accounted for.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Kidney injury				
Nil	Ref	-	Ref	-
Present	1.92 (1.09 – 3.38)	0.024	1.64 (0.92 – 2.93)	0.093
Age				
<40 years	Ref	-	Ref	-
40-70 years	13.62 (2.94 – 242.31)	0.010	12.18 (2.55 – 218.71)	0.015
>70 years	13.24 (2.63 – 240.86)	0.013	11.50 (1.72 – 214.16)	0.022
Sex				
Female	Ref	-	Ref	-
Male	1.42 (0.80 – 2.60)	0.195	1.42 (0.80 – 2.62)	0.242
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.34 (0.18 – 0.60)	<0.001	0.25 (0.13 – 0.45)	<0.001
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	0.47 (0.16 – 1.07)	0.108	0.29 (0.10 – 0.67)	0.010
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.83 (1.60 – 5.13)	<0.001	2.36 (1.30 – 4.39)	0.006
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	-	-
30-60 ml/min/1.73m^2	1.50 (0.65 – 3.04)	0.302		
<30 ml/min/1.73m^2	-	-		
Respiratory disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.19 (0.58 – 2.27)	0.609		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.47 (0.08 – 1.52)	0.294		
Diabetes				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.09 (0.45 – 2.29)	0.834		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.82 (0.20 – 2.26)	0.744		

Table 5.7: Risk factors associated with requirement for coronary artery intervention in ICU survivors

5.4.2.2 Factors associated with coronary interventions in de-novo injury patients

The rates of angiography and subsequent coronary artery interventions in the subset of de-novo injury patients grouped by length of kidney injury is available in Table 5.8. Of the 50 patients with de-novo kidney injury during their ICU stay who subsequently underwent coronary angiography, 46 were found to be in the AKI group (92.0%) compared to 4 in the AKD group (8.0%). Of the angiography performed in each group, similar proportions of patients required subsequent coronary intervention: 47.8% in the AKI group compared to 50.0% in the AKD group. On direct comparison, a high proportion of the interventions performed in the AKI group were done percutaneously (90.9%) compared to zero percutaneous interventions in the AKD group.

Event	De-novo kidney injury (n = 1347)	Acute kidney injury (n = 1059)	Acute kidney disease (n = 288)	*p*-value
Angiography following hospital discharge – n (%)	50 (3.7%)	46 (4.3%)	4 (1.4%)	0.019
Subsequent coronary artery intervention – n (%)	24 (1.8%)	22 (2.1%)	2 (0.7%)	0.134
Percutaneous coronary intervention – n (%)	21 (1.6%)	21 (2.0%)	-	-
Coronary artery bypass grafting – n (%)	3 (0.2%)	1 (0.1%)	2 (0.7%)	0.555

Table 5.8: Angiography and coronary intervention in de-novo injury patients

As was the case when assessing the entire study cohort for coronary artery interventions, Schoenfeld residuals were <0.1 for all selected variables due to the majority of events occurring early in the follow up period (median time to angiography = 98 days). Consequently, odds ratios at 12 months were reported for these analyses rather than hazard ratios.

The results of both initial univariable analyses and multivariable analysis are shown in Table 5.9. Progression to AKD suggested an association with a reduced risk of future coronary interventions, but this was not found to be statistically

significant (OR = 0.33; *p*-value = 0.134). As was seen with the total study cohort of ICU survivors, admission from surgical specialties was associated with a reduced risk of further intervention over the entire follow up period (OR = 0.34; *p*-value = 0.014). The strongest association seen on univariable analysis was pre-existing cardiovascular comorbidities: this found that these patients had a greater than four times the odds of receiving coronary artery intervention (OR = 4.19; *p*-value = 0.002). All other variables were not found to exert a statistically significant effect on risk of requiring future coronary intervention on univariable analysis.

Multivariable analysis demonstrated that progression to AKD was still not shown to have a significant effect on requiring a coronary intervention during the follow up period (OR = 0.33; *p*-value = 0.133). The observed association between admission from surgical specialties and reduction in need for future coronary intervention on univariable analysis was maintained once the other variables were corrected for (OR = 0.24; *p*-value = 0.001). Similarly, the association between cardiovascular comorbidities and increased risk was also maintained (OR = 4.04; *p*-value 0.006). In addition to this, admission due to sepsis was also found to exert a statistically significant effect on reducing the risk of coronary events (OR = 0.29; *p*-value = 0.045). However, age was still found to have no significant effect on the overall risk of receiving future coronary artery intervention in ICU survivors who suffered from a de-novo injury during their ICU admission (*p*-value = 0.450).

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Progression to AKD				
Nil	Ref	-	Ref	-
Present	0.33 (0.05 – 1.13)	0.134	0.33 (0.05 – 1.12)	0.133
Age				
Reference	Ref	-	Ref	-
Increase of 1 year	1.02 (1.00 – 1.05)	0.112	1.01 (0.98 – 1.04)	0.450
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.34 (0.14 – 0.78)	0.014	0.24 (0.10 – 0.56)	0.001
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	0.34 (0.08 – 1.01)	0.079	0.29 (0.07 – 0.84)	0.045
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	4.19 (1.75 – 11.62)	0.002	4.04 (1.56 – 11.97)	0.006
Sex				
Female	Ref	-	-	-
Male	1.09 (0.48 – 2.62)	0.836		
Baseline eGFR				
Reference	Ref	-	-	-
Increase of 1ml/min/1.73m^2	1.00 (0.98 – 1.01)	0.814		
Respiratory comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.82 (0.24 – 2.20)	0.726		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.42 (0.02 – 2.02)	0.397		
Diabetes				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.62 (0.15 – 1.81)	0.439		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.98 (0.46 – 5.88)	0.277		

Table 5.9: Factors associated with coronary intervention in de-novo injury patients. Age and baseline eGFR were treated as linear variables for this specific analysis as all events fell within one age group and one baseline eGFR group

5.4.3 Cerebrovascular events

5.4.3.1 Risk of cerebrovascular events dependant on presence of kidney injury during ICU admission

All radiological imaging of the brain carried out on ICU survivors following hospital discharge was assessed by a specialty doctor in radiology for either an intra-cerebral haemorrhage or infarct. Of the 4,085 survivors, 650 (15.9%) were found to have undergone cerebral radiology following hospital discharge: 420 from the 2,666 patients with no kidney injury during ICU admission (15.8%), 217 from the 1,347 de-novo injury patients (16.1%), and 13 from the pre-existing EKF patients (18.1%). Of the cerebral imaging which was performed, CT was the modality used in 497 (76.5%) of scans, whereas MRI was the modality used in the remaining 153 (23.5%) of scans.

Event	Total patients (n = 4085)	No kidney injury (n = 2666)	De-novo kidney injury (n = 1347)	Pre-existing established kidney failure (n = 72)
Head radiology following hospital discharge – n (%)	650 (15.9%)	420 (15.8%)	217 (16.1%)	13 (18.1%)
Positive result – n (%)	73 (1.8%)	48 (1.8%)	24 (1.8%)	1 (1.4%)
Intra-cerebral haemorrhage – n (%)	34 (0.8%)	26 (1.0%)	8 (0.6%)	-
Intra-cerebral infarct – n (%)	39 (1.0%)	22 (0.8%)	16 (1.2%)	1 (1.4%)

Table 5.10: Summary of cerebrovascular events based on presence of kidney injury

A summary of the proportion of patients from each kidney injury group with available head radiology, positive results and differentiation based on infarct or haemorrhage is available in Table 5.10. Of the head radiology results retrieved, 73 of the 650 scans returned a positive result (11.2%). The proportion of positive results was similar in each of the kidney injury groups: 48 out of 420 results were positive in the no kidney injury group (11.4%), 24 out of 217 in the de-novo group (11.1%), and 1 out of 13 in the pre-existing EKF group (7.7%). When each kidney

injury group was compared with each other, the difference in proportion of positive results was not statistically significant (all *p*-values >0.05). When differentiated based on infarct or haemorrhage, the proportion of positive results varied according to the presence of kidney injury during ICU admission. Intra-cerebral haemorrhage was more common in the no kidney injury group (54.2%) whereas it was less common in the de-novo injury group (33.3%); there was no statistically significant difference when comparing these two groups (*p*-value = 0.095). The only positive result in the pre-existing EKF group was as a result of an intra-cerebral infarct.

Analyses were conducted to determine if any risk factors were associated with radiologically confirmed cerebrovascular events following ICU admission. All collected variables were initially assessed using univariable analysis; these results are available in Table 5.11. De-novo injury suffered during ICU admission was not found to have a statistically significant effect on risk of developing a cerebrovascular event (OR = 0.99; *p*-value = 0.958). Pre-existing liver disease was associated with increased risk of future cerebrovascular events (OR = 2.47; *p*-value = 0.003). This was also the case for pre-existing diabetes (OR = 1.88; *p*-value = 0.027). Conversely, admission to ICU from any surgical specialty was associated with a reduced risk of any cerebrovascular event occurring over the total follow up period (OR = 0.55; *p*-value = 0.012). When using a baseline eGFR of >60 ml/min/1.73m^2 as a reference, a baseline eGFR of <30 ml/min/1.73m^2 was associated with significantly increased odds of a subsequent cerebrovascular event (OR = 2.64; *p*-value = 0.038). All other assessed variables did not meet statistical significance: however, age was also included in the multivariable model as it was considered a clinically significant variable.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Presence of de-novo kidney injury				
Nil	Ref	-	Ref	-
Present	0.99 (0.60 – 1.61)	0.958	0.79 (0.47 – 1.33)	0.380
Age				
<40 years	Ref	-	Ref	-
40-70 years	0.86 (0.49 – 1.50)	0.596	0.86 (0.49 – 1.52)	0.602
>70 years	0.88 (0.49 – 1.58)	0.670	0.96 (0.51 – 1.82)	0.908
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.55 (0.35 – 0.88)	0.012	0.60 (0.37 – 0.96)	0.034
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.03 (0.49 – 2.16)	0.936	1.04 (0.48 – 2.25)	0.929
<30 ml/min/1.73m^2	2.64 (1.06 – 6.57)	0.038	2.48 (0.94 – 6.53)	0.065
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	2.47 (1.35 – 4.50)	0.003	2.25 (1.22 – 4.16)	0.010
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.88 (1.08 – 3.27)	0.027	1.85 (1.03 – 3.31)	0.040
Sex				
Female	Ref	-	-	-
Male	1.30 (0.81 – 2.09)	0.280		
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	-	-
Sepsis	0.66 (0.34 – 1.29)	0.229		
Cardiovascular comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.19 (0.74 – 1.91)	0.463		
Respiratory comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	0.90 (0.50 – 1.65)	0.741		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.36 (0.62 – 2.97)	0.437		

Table 5.11: Risk factors associated with cerebrovascular events

Once other variables were corrected for, the multivariable analysis showed that de-novo kidney injury at any point during ICU admission was not associated with a change in risk of developing a cerebrovascular event (OR = 0.79; *p*-value = 0.380). Pre-existing liver disease (OR = 2.25; *p*-value = 0.010) and pre-existing diabetes mellitus (OR = 1.85; *p*-value = 0.040) both remained associated with an increased risk of future cerebrovascular events. This was also the case for admission from surgical specialties, which remained associated with a decreased risk of a future event (OR = 0.60; *p*-value = 0.034). Whilst there was still a suggestion that a baseline eGFR of <30 ml/min/1.73m^2 was associated with increased risk, this was no longer found to be statistically significant on multivariable analysis (*p*-value = 0.065). As was the case on initial univariable analysis, age was not a statistically significant variable for future cerebrovascular events. In a similar vein to coronary artery interventions, Schoenfeld residuals were <0.2 for all selected variables owing to the majority of events occurring early in the follow up period (median time to radiology = 76 days). Consequently, odds ratios at 12 months were reported for these analyses rather than hazard ratios.

5.4.3.2 Factors associated with cerebrovascular events based on progression to AKD

Event	De-novo kidney injury (n = 1347)	Acute kidney injury (n = 1059)	Acute kidney disease (n = 288)	*p*-value
Head radiology following hospital discharge – n (%)	217 (16.1%)	150 (14.2%)	67 (23.3%)	<0.001
Positive result – n (%)	24 (1.8%)	14 (1.3%)	10 (3.5%)	0.019
Intra-cerebral haemorrhage – n (%)	8 (0.6%)	6 (0.6%)	2 (0.7%)	0.802
Intra-cerebral infarct – n (%)	16 (1.2%)	8 (0.8%)	8 (2.8%)	0.005

Table 5.12: Rates of cerebrovascular events in de-novo injury patients based on progression to AKD

The rates of cerebrovascular events occurring in ICU survivors following a de-novo injury are described in Table 5.12. These demonstrated that of the 217 patients who underwent head radiology, 150 were from the AKI group (69.1%) whilst 67 were from the AKD group (30.9%); given the smaller numbers in the AKD group, a higher proportion of these patients received a cerebral radiological scan vs AKI patients over the total follow up period (23.3% vs 14.2% respectively; *p*-value <0.001). Of the scans undertaken, 14 out of 150 returned a positive result in the AKI group (9.3%) compared to 10 out of 67 patients in the AKD group (14.9%) (*p*-value = 0.019). A much higher proportion of positive results in the AKD group were due to identification of an intra-cerebral infarct (80.0%) compared to 57.1% found in the AKI group (*p*-value = 0.005).

Initial univariable analyses for risk factors was conducted on each collected variable: the results of these analyses can be seen in Table 5.13. The only variable which displayed any statistically significant association with development of any cerebrovascular event was progression to AKD (OR = 2.65; *p*-value = 0.019). One or more age or baseline eGFR groups were observed to have a *p*-value <0.2 on univariable analyses and were therefore included in the multivariable model.

The multivariable model demonstrated similar results to those seen in the individual univariable analyses: only progression to AKD showed a statistically significant association with a change in risk of developing a cerebrovascular event over the total follow up period (OR = 2.41; *p*-value = 0.038). Neither age nor baseline eGFR were found to be statistically significant factors once factored into the multivariable model. Due to potential for over-saturation of the multivariable model due to small number of events, a sensitivity analysis was conducted with age as a linear variable: the overall results were similar with no changes to significant variables (Table 5.14). In a similar fashion to the analysis of cerebrovascular events in the total patient cohort, Schoenfeld residuals were <0.05 for all selected variables median time to radiology = 52 days). Consequently, odds ratios at 12 months were reported for these analyses rather than hazard ratios.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Progression to AKD				
Nil	Ref	-	Ref	-
Present	2.65 (1.18 – 5.96)	0.019	2.41 (1.05 – 5.55)	0.038
Age				
<40 years	Ref	-	Ref	-
40-70 years	0.56 (0.21 – 1.49)	0.192	0.60 (0.23 – 1.60)	0.308
>70 years	0.62 (0.20 – 1.92)	0.407	0.72 (0.23 – 2.27)	0.577
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	0.26 (0.03 – 1.93)	0.187	0.25 (0.03 – 1.88)	0.177
<30 ml/min/1.73m^2	3.23 (1.20 – 8.70)	0.020	2.59 (0.93 – 7.20)	0.067
Sex				
Female	Ref	-	-	-
Male	1.32 (0.56 – 3.08)	0.523		
Admitting specialty				
Medical	Ref	-	-	-
Surgical	0.82 (0.37 – 1.84)	0.635		
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	-	-
Sepsis	0.63 (0.23 – 1.68)	0.350		
Cardiovascular comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.16 (0.52 – 2.58)	0.723		
Respiratory comorbidities				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.09 (0.41 – 2.91)	0.867		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.39 (0.42 – 4.68)	0.590		
Diabetes				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.15 (0.43 – 3.07)	0.785		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.24 (0.29 – 5.29)	0.768		

Table 5.13: Risk factors associated with cerebrovascular events based on progression to AKD

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Progression to AKD				
Nil	Ref	-	Ref	-
Present	2.65 (1.18 – 5.96)	0.019	2.38 (1.03 – 5.48)	0.042
Age				
Reference	Ref	-	Ref	-
Increase of 1 year	0.98 (0.96 – 1.00)	0.194	0.99 (0.96 – 1.01)	0.299
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	0.26 (0.03 – 1.93)	0.187	0.27 (0.04 – 2.08)	0.210
<30 ml/min/1.73m^2	3.23 (1.20 – 8.70)	0.020	2.74 (0.98 – 7.63)	0.054
Sex				
Female	Ref	-	-	-
Male	1.32 (0.56 – 3.08)	0.523		
Admitting specialty				
Medical	Ref	-	-	-
Surgical	0.82 (0.37 – 1.84)	0.635		
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	-	-
Sepsis	0.63 (0.23 – 1.68)	0.350		
Cardiovascular comorbidities			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.16 (0.52 – 2.58)	0.723		
Respiratory comorbidities			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.09 (0.41 – 2.91)	0.867		
Liver disease				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.39 (0.42 – 4.68)	0.590		
Diabetes				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.15 (0.43 – 3.07)	0.785		
Malignancy				
Nil	Ref	-	-	-
Pre-existing diagnosis	1.24 (0.29 – 5.29)	0.768		

Table 5.14: Sensitivity analysis of factors associated with cerebrovascular events based on progression to AKD using age as a linear variable

5.5 Discussion

5.5.1 Subsequent episodes of myocardial injury in ICU survivors

5.5.1.1 Key demographics of patients with myocardial injury

The data generated from this study demonstrated that approximately half of the patients who survived to 30 days after discharge from hospital had at least one troponin value available for analysis. One quarter of tested individuals had registered at least one value above the pre-determined upper limit of 14 nanograms per litre and were therefore defined as having a myocardial injury. Whilst previous reviews of the available evidence have described raised troponin levels as being very common in the critically ill population with approximately 40-50% of patients affected (175), minimal evidence exists regarding persistently raised troponin assays following discharge from ICU. However, in a small study by Ammann et al., short term mortality in ICU was found to be significantly higher (22.4% vs 5.2%) in patients with a raised troponin level which was not attributed to an acute coronary syndrome (176). In a large meta-analysis looking at all patients with raised troponin values due to acute coronary syndrome, the odds of death at 30-days were greater than four times higher (OR = 4.19) in patients who had at least one positive troponin value (177).

Plasma troponin assays are a well-established method of assessing patients for myocardial injury, and trends in individual patients are often used as a sensitive measure of diagnosing acute myocardial infarction (178). Whilst it is not possible to diagnose myocardial infarction using a single elevated plasma troponin level, it is useful as a surrogate marker of potential cardiac injury. Although raised troponin values may be secondary to alternative pathologies, negative tests are highly sensitive for ruling out myocardial damage (179).

Patients with at least one troponin value following ICU discharge showed a higher median age in the patients with a myocardial injury (64.5 vs 57.0; *p*-value <0.001). These patients also had a significantly higher rate of concurrent comorbidities such as pre-existing cardiovascular disease, respiratory disease and diabetes compared to patients whose troponin values were all within normal limits; median pre-ICU baseline eGFR was also lower in patients with an episode of myocardial injury. These associations are in keeping with well-established

evidence linking increased age and pre-existing comorbidities with increased likelihood of suffering from an acute myocardial infarction (180, 181).

ICU survivors who had suffered a de-novo kidney injury had a higher proportion of myocardial injury compared to patients who did not experience a kidney injury during their ICU admission (15.6% vs 9.0%; *p*-value <0.001). This is in keeping with a prior meta-analysis of over 250,000 patients by Odutayo and colleagues: this found that the risk of suffering from an acute myocardial infarction following an episode of AKI was increased by 40% (RR = 1.40) compared to patients without AKI (122). The analysis of patients with myocardial injury based on kidney injury group found similar demographic differences to those seen in the prior study looking at the entire study population.

When separating de-novo patients based on length of kidney injury, results were difficult to interpret due to low numbers of AKD patients with an episode of myocardial injury (n = 40). The raw rates of myocardial injury were found to be similar when comparing the AKI group with the AKD group (16.1% vs 13.9% respectively; *p*-value = 0.369). Similar patterns seen in the previous chapter which detailed demographic differences between all ICU survivors in the AKI and AKD groups were represented in patients with myocardial injury when separated into AKI and AKD groups.

5.5.1.2 Risk factors associated with myocardial injury

This study evaluated the influence of demographic features, comorbidities, and kidney injury, on the risk of myocardial injury in ICU survivors. The pre-existing EKF group had the highest rate of troponin positive events compared to the other two groups. Whilst the small numbers in this group (n = 72) result in wide confidence intervals and uncertainty over the precision of the effect, these higher rates are in keeping with the higher reported rates of acute myocardial infarction amongst the EKF population; a large observational study of 50,000 patients showed significantly increased odds of acute MI in patients with CKD stage 3A and greater (OR = 7.97 for CKD stage 5) (182).

When comparing patients who had suffered de-novo injury in ICU to those with no kidney injury, the rates of myocardial injury during the total follow up period were consistently higher in the de-novo group. This is consistent with prior literature regarding increased risk of cardiovascular events following AKI (183): this study was performed on a very different cohort of elective cardiac surgery patients, but their reported analyses still found a statistically significant increased risk of acute MI in AKI patients when compared to patients without AKI over a 5-year follow up period (HR=1.50).

The absolute rates of positive events described above were further analysed using a multivariable model to determine the significance of certain variables. This analysis confirmed that presence of de-novo injury of any length was a significant risk factor for future occurrence of an episode of myocardial injury (HR = 1.46; *p*-value <0.001). The meta-analysis by Odutayo et al. (122) found that pooled rates of major cardiovascular events following AKI in the general population were very similar to this and reported a risk ratio of 1.38 (RR = 1.40 specifically for acute MI). No long-term data exist regarding secondary cardiovascular outcomes in critically unwell patients; however this study's results suggest that the risk of acute MI following AKI in ICU is similar when compared with these pooled outcomes. The mechanism behind this association is poorly understood, but previous animal models showed that following an acute kidney injury there is an increase in cellular apoptosis, capillary vascular congestion and circulating levels of inflammatory mediators in the heart (184).

Pre-existing cardiovascular comorbidity was associated with increased risk of post-ICU myocardial injury; this has been previously established as a risk factor in a large epidemiological study over 17 years which described increasing numbers of cardiovascular comorbidities as being associated with increased mortality rates at 30 days and 1 year (180). Whilst conducted in patients admitted with initial MI, further work by Wang et al. reported hypertension, coronary heart disease and dyslipidaemia were significant risk factors for recurrent MI following discharge from hospital (185). The pathophysiology of this is due to the underlying cardiovascular changes such as atherosclerosis and cardiac remodelling as a result of the mechanical stress on the vasculature because of chronic health conditions such as hypertension (186). Whilst diabetes

mellitus was strongly associated with myocardial injury on univariable analysis (*p*-value <0.001), it was not-significant in the Cox proportional hazard model. This may be partially explained by a co-linear effect with pre-existing cardiovascular disease: this was supported when cardiovascular disease was removed from the Cox model and the *p*-value for pre-existing diabetes became borderline for significance (*p*-value = 0.057). Another possible cause may be that reduced correcting for pre-ICU baseline eGFR partially accounts for the effect of diabetic nephropathy: again, a sensitivity analysis which removed baseline eGFR from the Cox model supported this as the *p*-value for pre-existing diabetes mellitus dropped towards significance (*p*-value = 0.069).

Other significant factors in the development of myocardial injury included increasing age and male sex: whilst this may be indicative of the higher increased risk of underlying cardiovascular comorbidities and frailty, other associations between differences in levels of sex hormones and their relative decline due to aging have been suggested (181). The significant association between reduced pre-ICU baseline eGFR and subsequent myocardial injury can be linked to the higher rates of acute MI seen in patients with CKD as discussed above (182). Whilst admission from surgical specialties was significantly associated with reduced odds of a future episode of myocardial injury, no previous studies looking at long term risk of MI based on admitting specialty have been published to support or refute this data. The reason behind this association may be linked to the underlying aetiologies commonly seen in medical or surgical cohorts of patients, as only presence or absence of sepsis was corrected for in the multivariable model.

Subgroup analysis of the de-novo injury patients showed no difference was seen in the event curves between AKI patients and AKD patients nor in the multivariable Cox proportional hazards model. Considering how new the definition of AKD is and the paucity of data available, there is no way to compare this with prior results; however, based on this study, progression to AKD does not appear to influence the risk of suffering future myocardial injury. Given the smaller numbers in the AKD group, this result should be interpreted with some caution, and further study with greater numbers is required to validate these findings.

5.5.2 Requirement for angiography and coronary artery interventions

While troponin assay can be useful to detect myocardial injury of multiple aetiology, coronary angiography provides detailed information about coronary vasculature. Unlike the relationship between requested cerebral radiology and potential cerebrovascular events, angiography is far more suggestive of likely symptomatic coronary artery disease; nevertheless, results on risk factors were only interpreted with relation to documented coronary artery intervention.

Whilst an association between de-novo kidney injury and requirement for coronary artery intervention was identified, this was not found to be statistically significant once it was factored into a multivariable model (OR = 1.64; *p*-value = 0.093). Wu et al. has previously documented an association between AKI and subsequent coronary events, with AKI requiring KRT found to confer a 67% increase in risk of developing a subsequent coronary event (123). Whilst statistical significance was not met in this data, an association was suggested which was in keeping with this evidence; the lack of statistical significance may be due to the absolute small number of events which occurred in this study population. In addition, the previous study by Wu and colleagues included all hospitalised patients rather than ICU-patients, and this will not include the possible survivorship bias in our study whereby patients who are more likely to suffer from complications have died as a result of their acute illness (123). Interpretation of this relationship may also be complicated as patients with AKI and subsequent CKD are less likely to undergo angiography and interventions due to higher complication rates (187).

Other risk factors identified in this study included increasing age, admission from medical specialties, cardiovascular comorbidities and admission due to pathology other than sepsis. The documented link between cardiovascular comorbidities and increasing age, and future coronary events has been described in detail above (181, 183), as has potential reasons behind admission from medical specialties being associated with an increased risk. However, very little literature is available on the possible association between admission due to sepsis and the apparent reduction in risk of future cardiovascular events. As postulated in the previous chapter looking at long-term survival, this may be

explained by the pathophysiology behind sepsis. These mechanisms result in people becoming acutely unwell over a short period of time with a high risk of dying. If patients can survive the initial insult, it may confer less long-term risks than other pathologies. This may also be because the constructed models do not include measures of illness severity and survivors of sepsis had less severe illness resulting in a reduced long-term risk profile. Alternatively, it may be that the patients admitted with precipitating causes other than sepsis have higher cardiovascular risk profiles. However, it is important to note that these results are at odds with the established literature, which has described survivors of sepsis as being at significantly higher risk of adverse cardiovascular events (124). Also of note is that these results have similar associations with the above data produced on myocardial injury; this would suggest that a single troponin positive event used as evidence of myocardial injury is a valid surrogate marker of future coronary events.

Analysis of de-novo patients separately demonstrated no significant link between progression to AKD and the need for future coronary interventions (OR = 0.33; *p*-value = 0.133). Again, this may be secondary to very small numbers of absolute events across this patient cohort. The associations between admission from medical specialties, admissions not due to sepsis and cardiovascular comorbidities were all still found to be statistically significant amongst this cohort of patients. Due to the small number of events within this subgroup, caution should be exercised when interpreting the results as the number of variables included in the multivariable analysis potentially oversaturate the model. Given that the sample size of these patients was found to be relatively small and may have contributed to this, and that certain aspects such as the relative risks in the septic population were in conflict to prior literature, further study is required in this area to determine the significance of these results.

5.5.3 Future cerebrovascular events

All cerebral radiology from the follow up period was retrieved for every ICU survivor. Whilst having radiological investigation could in theory be interpreted as a surrogate marker of a potential cerebrovascular event, there are multiple other reasons, such as head trauma, which may lead to cerebral radiology being requested by clinicians. Consequently, just the presence of a result of such a

radiological investigation is not a particularly sensitive measure of a potential cerebrovascular event. To improve the accuracy of the results generated, a specialty doctor in radiology manually interpreted the reports to determine if an event had occurred.

Cerebrovascular events occurred in fewer than one in fifty ICU survivors during the follow up period. Because the absolute number of cerebrovascular events in the study population was small, demographics were not described in detail. Instead, a multivariable analysis was conducted to determine if any of the collected variables had a significant effect on development of future cerebrovascular events. Variables found to be associated with increased risk were, admission from medical specialties, reduced baseline eGFR, pre-existing liver disease and pre-existing diabetes mellitus. Whilst there is a lack of data available on rates of acute cerebrovascular events based on admitting specialty in the hospital, there is prior work describing the link between chronic kidney disease and increased risk of a subsequent stroke (188). Furthermore, there has also been a documented link described in patients with pre-existing cirrhotic liver disease and development of cerebrovascular events which further supports the results found in this study (189). There is also a significant body of evidence highlighting the link between pre-existing diabetes mellitus and risk of future cerebrovascular events (190, 191). The association between presence of de-novo kidney injury and an event was not found to be statistically significant (OR = 0.79; *p*-value = 0.380). This data is not in keeping with the current published literature regarding increased risk of stroke following an episode of AKI (192); however this may be due to the absolute small number of events seen in this study population.

When specifically analysing the de-novo injury patients based on progression to AKD, multivariable analysis demonstrated that progression to AKD was the only factor which had a statistically significant effect on the development of future events (OR = 2.41; *p*-value = 0.038). This observation was driven by a higher rate of ischaemic stroke in the AKD population (80.0% in AKD group vs 57.1% in AKI group). This may be due to the protracted inflammatory and endovascular injury, however, the small number of events which occurred (n = 10) and the wide confidence intervals should lead to caution when interpreting these results.

A limitation of this methodology is that fatal events may occur without imaging, and this cohort of patients will not be captured in these data. Similarly, due to small numbers of events, there was potential for oversaturation of the multivariable model; however, a sensitivity analysis to reduce the number of variables to a more acceptable level agreed with the above results. Despite the small number of events, given multiple other variables were both accounted for and did not have a statistically significant effect of their own, this may highlight a very important area for further research with regards to the novel concept of AKD.

5.5.4 Strengths and weaknesses

This study details a large cohort of ICU survivors to identify the links between kidney injury on the background of critical illness and future cardiovascular events. It utilises a number of different data sources to ensure full data capture and correlates clinical outcomes with data from initial ICU admission. In addition, it makes use of clinicians with specialist knowledge in the relevant fields to interpret the results as accurately as possible and determine where events have occurred. The large and unselected sample size and long observation period are additional strengths. Furthermore, this study is the first of its kind to describe the effect that the reasonably new definition of acute kidney disease may have on secondary cardiovascular events; this data is also likely transferable to the general patient population admitted to ICU in the UK.

This study shares the same limitations described in the previous chapters regarding identification of de-novo kidney injury according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines: only serum creatinine values were used as urine output values were not reliable enough. Additionally, the limitations in using return of serum creatinine to baseline also applies to this study, as numbers in the AKD subgroup may be underrepresented due to artificial falls in serum creatinine levels not related to kidney recovery. The small absolute numbers of events in this study may also make it difficult to draw definitive conclusions. Furthermore, the small number of events identified in some analyses may lead to the potential over-saturation of their associated multivariable models; however, where possible, this potential weakness has been tested using sensitivity analyses. Odds ratios at 12 months were reported

for angiography and cerebrovascular events as the proportionality assumption failed: this was done to select a time-point at which all patients had an entire follow-up rather than assuming no event occurred in the intervening period between their individual loss to follow up and the maximum follow up time. However, it will have resulted in a loss of data for events which occurred over the longer term.

5.6 Conclusions

Although existing literature has described association between an episode of AKI and future risk of cardiovascular disease and significant events, no data is available on AKD or if any differences exist in this subset of patients. Whilst a single raised troponin value does not represent a coronary event, the data produced in this study is consistent with the established link between de-novo kidney injury and acute myocardial infarction. Whilst a continued association with patients requiring coronary artery intervention following hospital discharge was suggested by this data, it was not found to convey a statistically significant increase in risk. Although progression to AKD did not appear to influence rates of events due to coronary artery disease, it was the only risk factor identified in de-novo injury patients which had a statistically significant effect on increased risk of future cerebrovascular events. Given the absolute small numbers of events which occurred in this study, more research using a larger patient cohort is required to determine the potential significance of this important, identified relationship.

Chapter 6 Characterisation of oliguric vs non-oliguric kidney injury in intensive care

6.1 Introduction

Kidney injury can be defined in terms of either raised serum creatinine levels or reduced urine output according to internationally accepted guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) (16). Whilst both criteria can be used to identify acute kidney injury (AKI), prior work has been conducted to compare patients with AKI who develop a low urine output (known as oliguria) compared to those who do not; these studies reported differences in short-term outcomes, with oliguric AKI reported to have higher morbidity and mortality in the general population (193, 194). Previously, Mandelbaum and colleagues assessed patients in the intensive care unit (ICU) with AKI for in-hospital outcomes based on presence or absence of oliguria (195): they demonstrated that oliguric AKI had a higher in-hospital mortality compared with non-oliguric AKI. In addition, two studies assessed ICU patients who received kidney replacement therapy (KRT) for outcomes based on presence or absence of oliguria (131, 132): both of these studies found that short-term mortality was significantly higher in patients with oliguric injury. However, to date, minimal research has been performed comparing outcomes of oliguric vs non-oliguric beyond 28 days in the ICU population. In addition, no evidence has been produced to determine if an isolated episode of oliguria differs from a prolonged period of oliguria. Considering a single 24-hour period of oliguria may be due to additional factors such as requirement for initial fluid resuscitation, differences may be observed between one-off episode (point oliguria) compared to oliguria which persists (persisting oliguria). This study sought to ascertain the factors associated with development of oliguric kidney injury, as well as the differences in short- and long-term mortality and development of major adverse kidney events (MAKEs) depending on oliguric vs non-oliguric injury or point vs persisting oliguria.

6.2 Study aims

6.2.1 Which features are associated with the development of oliguric kidney injury?

Various features may influence the development of oliguric kidney injury when compared with non-oliguric injury. The population of all patients within the study will be described according to the type of kidney injury they suffered and how this varies between patients when accounting for patient age, sex, hospital admitting specialty, precipitating illness and baseline kidney function. An analysis will then be conducted to determine if any of these features influence the development of oliguric kidney injury and quantify to what degree each is important.

6.2.2 How does urine output in ICU patients with kidney injury vary based on severity of injury and progression to AKD?

Given that KDIGO guidelines define kidney injury and its severity based on both urine output and serum creatinine values, there should be significant association between more severe kidney injury diagnosed on serum creatinine levels and increased rates of oliguria. The median 24-hourly urine output for patients with kidney injury will be described and rates of oliguric vs non-oliguric injury depending on KDIGO staging of kidney injury and progression to AKD will be compared.

6.2.3 Does development of oliguric kidney injury influence ICU and hospital mortality?

It will be explored whether oliguric injury is a marker of more severe injury than non-oliguric kidney injury and whether this may influence short-term outcomes. The in-ICU and in-hospital mortality rates of patients with oliguric and non-oliguric injury will be compared.

6.2.4 How does development of oliguria during kidney injury affect long-term survival?

It may be expected that any potential increased risk in short-term mortality seen in either oliguric or non-oliguric kidney injury might also impact on long-term survival. Patients who suffered from any type of kidney injury in ICU and survived until at least 30 days post hospital discharge will be classified based on the presence of oliguria during their initial kidney injury. The mortality rates of both groups of patients during the follow up period will then be compared, and a multivariable analysis performed to assess for the effect of oliguria on long-term survival.

6.2.5 How does long-term kidney function differ between patients with oliguric injury and non-oliguric injury?

As previous research has never focussed on long-term outcomes of oliguric vs non-oliguric kidney injury, the impact of oliguric injury on future adverse kidney events has not previously been described. The previously defined group of patients who survived to day 30 following hospital discharge will be assessed for development of MAKEs and compared depending on presence or absence of oliguric kidney injury. In addition, a multivariable analysis will be conducted to assess if oliguric injury is a significant factor in the development of MAKEs.

6.2.6 What features are associated with development of persisting oliguria compared to point oliguria, and do short- and long-term outcomes vary between these groups?

As a single 24-hour period of oliguria may result following short-term mechanisms less suggestive of a severe kidney injury, outcomes between patients with a one-off episode of oliguria may differ from persisting oliguria. Features of patients with persisting oliguria will be described compared to patients with a single, one-off episode of oliguria. Furthermore, a comparison of short-term and long-term mortality rates in patients with persisting oliguria and patients with point oliguria will be made. Additionally, rates of MAKEs in point oliguric injury compared with persisting oliguric injury during the follow-up period will be compared.

6.3 Methods

Patients with kidney injury according to KDIGO guidelines (16) were identified using only serum creatinine values: the subset of these patients with available data on urine output throughout their ICU admission were included in this study. Patients with pre-existing established kidney failure (EKF) were excluded from this study. These patients were assessed for the presence of oliguria using daily urine output data and admission weight: if admission weight was not recorded, the patient was excluded from the study as body weight predicted using height may vary markedly from true body weight thus significantly altering the oliguric threshold. KDIGO reference values of <0.3ml/kg urine output per hour were used to define oliguria (16): these values were extrapolated to 24-hour daily urine output values and therefore patients with <7.2ml/kg/day for at least one day during their admission were classified as oliguric. This was felt to limit potential inaccuracies of everyday clinical practice where hourly urine outputs are not always accurately measured and recorded. Oliguria was not assessed on the day of ICU admission or discharge as these days would not have complete urine output measurements for 24 hours. Oliguria was defined using actual body weight (ABW) rather than predicted body weight (PBW) as this increases the sensitivity of our definition at the cost of specificity (196); given that the differences between oliguric and non-oliguric kidney injury are poorly studied, it was felt a definition which was as sensitive as possible was more appropriate in order to aid detection of oliguria. Pertinent analyses were repeated using predicted body weight to compare the impact of our chosen definition. Analyses were then repeated with the subgroup of oliguric patients separated into oliguria lasting one day ("point oliguria") against oliguria lasting more than one day ("persisting oliguria"). These cut-offs were selected as a single 24-hour period of oliguria may be due to additional factors such as initial hypovolaemia and requirement for resuscitation or a blocked urinary catheter whereas a 48-hour period is more likely to be indicative of an underlying acute insult.

Demographic variables were described for oliguric and non-oliguric groups using proportions with 95% confidence intervals (95% CIs) or median values with interquartile range (IQR); difference in median values were compared using the Wilcoxon rank-sum test whereas difference in proportions were compared using the Pearson Chi-squared test. Mortality was assessed to ICU discharge and

hospital discharge; long-term survival and development of MAKEs during the total follow-up period were assessed in patients who survived to day 30 following hospital discharge (referred to as "ICU survivors"). Regression analysis was used to identify factors associated with development of oliguric kidney injury, mortality, or development of MAKEs. MAKES were defined as: eGFR drop of >30% from baseline, eGFR drop of >40% from baseline, doubling of baseline creatinine or initiation of chronic kidney replacement therapy (KRT). Initial analysis was attempted using Cox proportional hazards modelling which were reported as hazard ratio (HR) and 95% CIs should it meet all the statistical assumptions of the test. To ascertain if each variable met the proportionality assumption, Schoenfeld residuals were calculated for each individual variable as well as for the multivariable model. Should data not meet the proportionality assumption, results were reported in terms of odds ratios (ORs) and 95% CIs at a time point for which all patients had a complete follow up period to analyse. Initial univariable analyses were performed on each collected variable; univariable p-values of less than <0.2 were included in the multivariable model. For all adjusted analyses, a statistical significance was set at a two-sided *p*-value of <0.05.

6.4 Results

6.4.1 Urine output in ICU patients with de-novo kidney injury

Of the 5,312 patients admitted to ICU over the total study period, 2,147 developed a de-novo kidney injury (40.4%): of these patients, 1,666 (77.6%) had urine output values and a measured admission weight available for interpretation and were included in this study.

Median 24-hourly urine output from across the study population was found to be 1185 ml/24-hours (IQR = 375-1772 ml/24-hours). These values were then corrected individually for patient weights: the median value across the study population was 15.7 ml/24-hours/kg (IQR = 5.2-25.2 ml/24-hours/kg). Median 24-hour urine output per kilogram values were stratified according to presence of oliguric or non-oliguric injury: the median value in the oliguric group was found to be significantly lower than in the non-oliguric group (4.7 vs 19.4 ml/24-hours/kg respectively; *p*-value <0.001). When comparing KDIGO stage of kidney

injury, stage 3 injury had a significantly lower median value (10.3 ml/24/hours/kg) than stage 1 (18.7 ml/24-hours/kg) or stage 2 injury (17.8 ml/24-hours/kg) (both *p*-values <0.001). A similar pattern was seen when patients were grouped based on progression to AKD: patients in the AKD group had a significantly lower median value than patients in the AKI group (8.5 vs 16.7 ml/24-hours/kg; *p*-value <0.001).

6.4.2 Patient characteristics based on type of kidney injury

Of the 1,666 patients who were assessed for presence of oliguric injury, 528 (31.7%) developed an oliguric kidney injury which lasted at least 24 hours; the remaining 1,138 (68.3%) patients did not meet the criteria and were therefore classified as non-oliguric injury. Key baseline demographics for these patients are represented in Table 6.1.

The median age of all 1,666 patients in the study population was found to be 61.0: the median age was similar when patients were separated into non-oliguric and oliguric injury (61.0 vs 61.5 respectively; *p*-value = 0.337). The proportion of male patients in the oliguric group appeared higher than the non-oliguric group (63.1% vs 58.8%) but this difference was not found to be statistically significant (*p*-value = 0.108). This relationship was similar to one seen in patients admitted from a surgical specialty, with a higher proportion of patients in the oliguric group admitted from surgical specialties (54.5% vs 50.9%), but again this between group difference was not statistically significant (*p*-value = 0.180). Patients with available APACHE II data in each group were compared: the median APACHE II score in the oliguric group was significantly higher than the median score in the non-oliguric group (25.0 vs 20.0 respectively; *p*-value <0.001).

Characteristic	De-novo kidney injury (n = 1666)	Non-oliguric kidney injury (n = 1138)	Oliguric kidney injury (n = 528)
Age – median (IQR)	61.0 (49.0 – 72.0)	61.0 (48.0 – 72.0)	61.5 (50.0 – 71.0)
Male - n (%)	1002 (60.1%)	669 (58.8%)	333 (63.1%)
Admitted from surgical specialty – n (%)	867 (52.0%)	579 (50.9%)	288 (54.5%)
Baseline eGFR - median (IQR)	83.1 (60.3 – 99.2)	85.1 (63.7 – 100.7)	78.9 (51.8 – 96.9)
APACHE II score - median[9] (IQR)	22.0 (16.0 – 29.0)	21.0 (15.0 – 27.0)	25.0 (20.0 – 30.0)
Admission due to sepsis – n (%)	531 (31.9%)	341 (30.0%)	190 (36.0%)
Comorbidities – n (%)			
Cardiovascular disease	742 (44.5%)	492 (43.2%)	250 (47.3%)
Respiratory disease	356 (21.4%)	257 (22.6%)	99 (18.8%)
Liver disease	187 (11.2%)	124 (10.9%)	63 (11.9%)
Diabetes	304 (18.2%)	189 (16.6%)	115 (21.8%)
Malignancy	119 (7.1%)	85 (7.5%)	34 (6.5%)

Table 6.1: Baseline demographics in patients with kidney injury during ICU admission based on presence or absence of oliguric injury

Median baseline eGFR was significantly lower in patients who developed an oliguric kidney injury, with a lower median of 78.9 ml/min/1.73m^2 compared with 85.1 ml/min/1.73m^2 in the non-oliguric group (p-value <0.001). The most common precipitating illness requiring admission to ICU across the total study population was sepsis, which was the precipitating diagnosis in 531 of the 1,666

[9] Data unavailable for 79 patients – only 1587 patients used in these calculations (Non-oliguric kidney injury = 1084; Oliguric kidney injury = 503)

patients (31.9%). A significantly higher proportion of patients with oliguric kidney injury were admitted due to sepsis (36.0%) when compared with patients who suffered from non-oliguric kidney injury (30.0%) during their ICU admission (*p*-value = 0.017). Of all the pre-existing comorbidities which were assessed, similar rates were found when comparing the oliguric and non-oliguric groups with the exception of pre-existing diabetes mellitus; a significantly higher proportion of oliguric patients were found to have diagnosis of diabetes prior to admission (21.8% vs 16.6%; *p*-value = 0.013).

Receipt of organ support across the total study population is detailed in Table 6.2. The most common organ support delivered was invasive mechanical ventilation (IMV), which was received by 1,270 out of the total 1,666 patients (76.2%). Similar proportions of patients in the oliguric and non-oliguric group received this intervention (77.5% vs 75.7% respectively; *p*-value = 0.476). However, a far higher proportion of patients in the oliguric group (79.7%) received cardiovascular support (CVS) than patients in the non-oliguric group (67.8%) (*p*-value <0.001). Similarly, a significantly higher proportion of oliguric patients received kidney replacement therapy (KRT) when compared with non-oliguric patients (54.7% vs 9.0% respectively; *p*-value <0.001). When comparing degree of organ support received, a significantly higher proportion of oliguric patients (77.1%) received multi-organ support when compared to patients with non-oliguric injury (58.3%) (*p*-value <0.001). Conversely, there was a significantly higher proportion of patients in the non-oliguric group who required no organ support when compared to patients with oliguric injury (11.1% vs 6.4% respectively; *p*-value = 0.002).

Intervention	De-novo kidney injury (n = 1666)	Non-oliguric kidney injury (n = 1138)	Oliguric kidney injury (n = 528)
Modalities – n (%)			
Invasive mechanical ventilation	1270 (76.2%)	861 (75.7%)	409 (77.5%)
Cardiovascular support	1192 (71.5%)	771 (67.8%)	421 (79.7%)
Kidney replacement therapy	391 (23.5%)	102 (9.0%)	289 (54.7%)
Degree of organ support - n (%)			
None	161 (9.6%)	127 (11.1%)	34 (6.4%)
Single	435 (26.1%)	348 (30.6%)	87 (16.5%)
Multi	1070 (64.3%)	663 (58.3%)	407 (77.1%)

Table 6.2: Recipients of modalities of organ support depending on presence of oliguria during ICU admission

6.4.3 Features associated with developing oliguric injury

Initial univariable analyses of demographic features which may be involved in the development of oliguric injury compared with non-oliguric injury can be found in Table 6.3. Increasing age was found to have a statistically significant effect in development of an oliguric kidney injury compared to a non-oliguric injury (OR = 1.47 for 40-65 year olds and OR = 1.48 for >65 year olds); this was also the case for patients with a pre-ICU baseline eGFR of <30 ml/min/1.73m^2 (OR = 2.36; *p*-value <0.001). Other statistically significant variables included admission due to sepsis (OR = 1.31) and pre-existing diagnosis of diabetes mellitus prior to admission to ICU (OR = 1.40). Whilst other variables did not meet significance on univariable analyses, all were found to have *p*-values <0.2 and were included in the multivariable model with the exception of pre-existing liver disease and pre-existing malignancy.

The results of the multivariable analysis demonstrated that increasing age remained a statistically significant factor in the development of oliguria during kidney injury in ICU, with 40-65 year olds having approximately 50% increased odds compared with patients under 40 years old (*p*-value = 0.034). Similarly, a pre-ICU baseline eGFR of <30 ml/min/1.73m^2 (OR = 2.33; *p*-value <0.001) was a statistically significant factor in the development of oliguric injury. Admission to ICU due to a diagnosis of sepsis also remained significantly associated with development of oliguric injury (OR = 1.37; p-value = 0.006). This was also the case for male sex, which gained significance during the adjusted analysis (OR = 1.25; p-value = 0.048). Whilst admitting specialty was not found to be a significant factor on univariable analysis, admission from surgical specialties was found to confer 30% increased odds of developing oliguric injury once other variables were corrected for (OR = 1.30; *p*-value = 0.017). Conversely, despite statistical significance on univariable analysis, a pre-existing diagnosis of diabetes was no longer found to be a significant factor in development of oliguric injury (OR = 1.28; *p*-value = 0.071). Pre-existing cardiovascular comorbidities, and pre-existing respiratory comorbidities remained non-statistically significant variables.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Age				
<40 years	Ref	-	Ref	-
40-65 years	1.47 (1.04 – 2.12)	0.032	1.48 (1.04 – 2.15)	0.034
>65 years	1.48 (1.04 – 2.12)	0.032	1.40 (0.96 – 2.07)	0.089
Sex				
Female	Ref	-	Ref	-
Male	1.19 (0.97 – 1.48)	0.101	1.25 (1.00 – 1.56)	0.048
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	1.16 (0.94 – 1.43)	0.159	1.30 (1.05 – 1.61)	0.017
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	1.25 (0.96 – 1.63)	0.098	1.23 (0.93 – 1.62)	0.142
<30 ml/min/1.73m^2	2.36 (1.60 – 3.47)	<0.001	2.33 (1.57 – 3.46)	<0.001
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	1.31 (1.05 – 1.63)	0.015	1.37 (1.10 – 1.72)	0.006
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.18 (0.96 – 1.46)	0.112	1.02 (0.81 – 1.28)	0.861
Respiratory comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	0.79 (0.61 – 1.03)	0.081	0.79 (0.60 – 1.03)	0.084
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.40 (1.08 – 1.81)	0.011	1.28 (0.98 – 1.68)	0.071
Liver disease			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.11 (0.80 – 1.52)	0.537		
Malignancy			-	-
Nil	Ref	-		
Pre-existing diagnosis	0.85 (0.56 – 1.27)	0.445		

Table 6.3: Analysis of factors associated with oliguric kidney injury

6.4.4 Patients with oliguric and non-oliguric kidney injury during ICU admission based on severity of injury and progression to AKD

Comparison of the number of patients with oliguric and non-oliguric injury stratified by KDIGO stage of kidney injury is available in Table 6.4: these results demonstrated that patients with oliguric are significantly more likely to suffer from stage 3 injury than patients with non-oliguric injury (73.1% vs 32.2% respectively; *p*-value <0.001). Conversely, patients with non-oliguric injury were significantly more likely to suffer from both a stage 1 and stage 2 injury than patients with oliguric kidney injury (both *p*-values <0.001). The majority of patients who develop a stage 3 injury were found to develop oliguria at some point during their ICU admission (51.3%); this differed from patients with stage 1 and stage 2 injury, who most commonly suffered from non-oliguric injury (85.5% and 82.3% respectively).

Comparison of patients with oliguric and non-oliguric injury separated by progression to AKD is also represented in Table 6.4. Patients with oliguric injury are significantly more likely to develop AKD than patients with non-oliguric injury (43.4% vs 10.7%; *p*-value <0.001). The majority of AKD patients suffer from an oliguric injury (65.2%) whereas the majority of AKI patients suffer from a non-oliguric injury (77.3%).

Characteristic	De-novo kidney injury (n = 1666)	Non-oliguric kidney injury (n = 1138)	Oliguric kidney injury (n = 528)	*p*-value
Severity of kidney injury – n (%)				
Stage 1	602 (36.1%)	515 (45.3%)	87 (16.5%)	<0.001
Stage 2	311 (18.7%)	256 (22.5%)	55 (10.4%)	<0.001
Stage 3	753 (45.2%)	367 (32.2%)	386 (73.1%)	<0.001
Length of kidney injury – n (%)				
AKI	1315 (78.9%)	1016 (89.3%)	299 (56.6%)	<0.001
AKD	351 (21.1%)	122 (10.7%)	229 (43.4%)	<0.001

Table 6.4: Progression to oliguric injury based on severity of initial kidney injury and progression to AKD

6.4.5 In-ICU and in-hospital mortality based on presence of oliguric kidney injury during ICU admission

Raw mortality rates comparing death in ICU and death in hospital are demonstrated in Table 6.5. The total number of deaths in-ICU during the study period was 480 with a corresponding mortality rate of 28.8%. The raw mortality figures amongst groups demonstrated that the oliguric kidney injury group had a significantly higher mortality rate compared to the patient group who suffered from non-oliguric kidney injury (34.5% vs 26.2% respectively; *p*-value <0.001). The total number of deaths during hospital admission for all patients in the study population was 579 which represented an in-hospital mortality rate of 34.8%. The raw in-hospital mortality figures demonstrated a similar pattern to in-ICU mortality rates with a significantly higher in-hospital mortality rate seen in the oliguric kidney injury group (41.9%) when compared with patients who suffered from a non-oliguric kidney injury during their ICU admission (31.5%) (*p*-value <0.001).

Event	De-novo kidney injury (n = 1666)	Non-oliguric kidney injury (n = 1138)	Oliguric kidney injury (n = 528)	*p*-value
Death during ICU admission				
Number of deaths – n (%)	480 (28.8%)	298 (26.2%)	182 (34.5%)	<0.001
95% Confidence Intervals	26.7% - 31.0%	23.7% - 28.8%	30.5% - 38.6%	
Death during hospital admission				
Number of deaths – n (%)	579 (34.8%)	358 (31.5%)	221 (41.9%)	<0.001
95% Confidence Intervals	32.5% - 37.1%	28.8% - 34.2%	37.7% - 46.1%	

Table 6.5: In-patient mortality rates based on development of oliguric kidney injury

6.4.6 Long-term survival in patients with oliguric injury compared with non-oliguric injury

Of the 1,666 patients included in the total study population, 1,068 (64.1%) survived to day 30 following hospital discharge and were classified as ICU survivors; 771 (72.2%) of these patients suffered from non-oliguric injury during their ICU admission and 297 (27.8%) suffered from oliguric injury. The minimum follow-up period for patients in this analysis was 565 days whilst the maximum follow-up period was 1,634 days.

A total of 249 deaths occurred during the follow-up period, with 174 found to be in the non-oliguric group (22.6%) compared with 75 in the oliguric group (25.3%). Kaplan Meier analysis of long-term survival over the total follow-up period is detailed in Figure 6.1: this is stratified by presence of oliguric injury during admission to ICU. This analysis demonstrated similar rates of survival between the oliguric and non-oliguric group with no statistically significant difference found between the two survival curves on log-rank testing (*p*-value = 0.362).

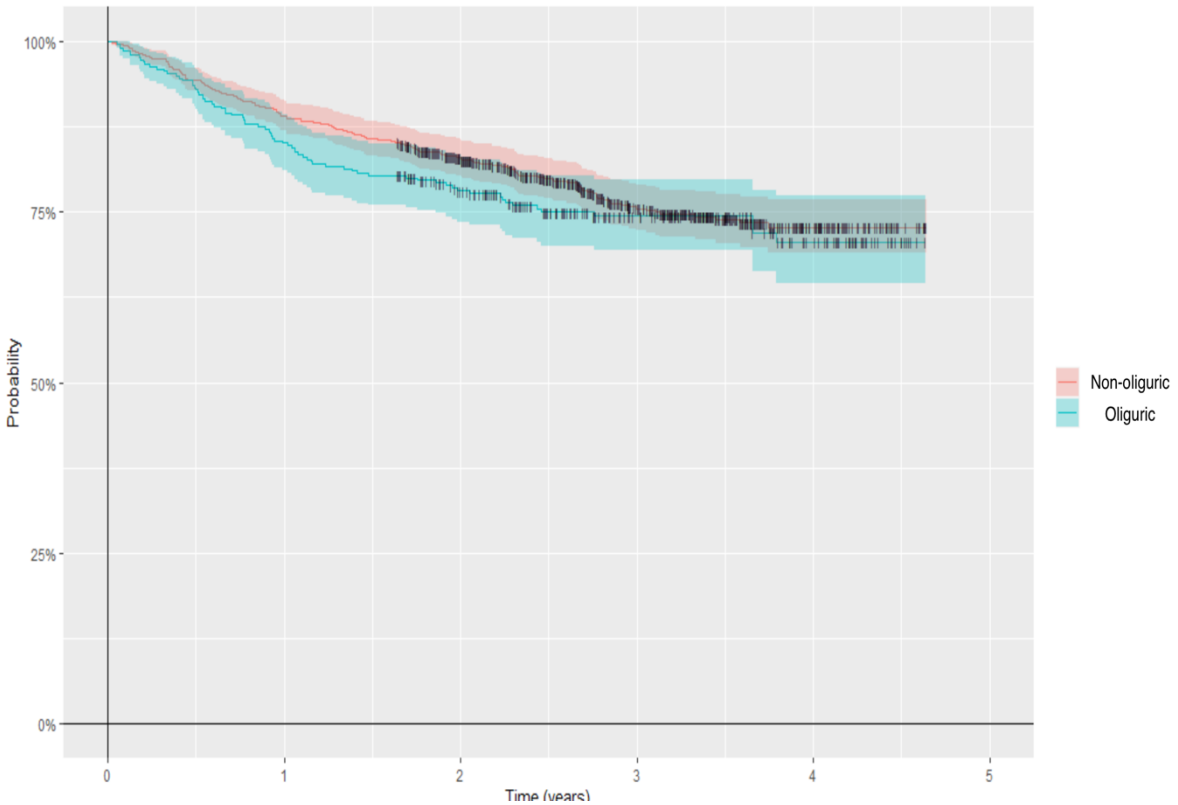


Figure 6.1: Kaplan Meier analysis of long-term survival stratified by presence or absence of oliguric kidney injury during ICU admission. Time 0 represents day 30 following date of discharge from hospital (*p*-value = 0.362)

Further analyses were conducted to assess if oliguric injury was a significant factor with regards to long-term survival. When our data were analysed with the Cox proportional hazards model, it violated the proportional hazards assumption (as most events occurred early in our follow up period) and was therefore deemed inappropriate to analyse using this method. Instead, ORs and 95% CIs at 18 months were used to analyse mortality in ICU survivors as this encompassed the minimum follow up time for all patients in the cohort.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Kidney injury				
Non-oliguric	Ref	-	Ref	-
Oliguric	1.50 (1.04 – 2.13)	0.026	1.49 (1.03 – 2.13)	0.032
Age				
<40 years	Ref	-	Ref	-
40-65 years	1.53 (0.89 – 2.81)	0.144	1.46 (0.83 – 2.68)	0.206
>65 years	1.81 (1.04 – 3.32)	0.045	1.78 (0.99 – 3.33)	0.058
Sex				
Female	Ref	-	Ref	-
Male	1.27 (0.90 – 1.82)	0.175	1.38 (0.97 – 1.99)	0.078
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	0.71 (0.51 – 0.99)	0.042	0.65 (0.46 – 0.93)	0.018
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.67 (1.11 – 2.46)	0.011	1.61 (1.07 – 2.40)	0.021
Malignancy				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	1.84 (1.02 – 3.15)	0.033	2.11 (1.15 – 3.71)	0.012
Baseline eGFR			-	-
>60 ml/min/1.73m^2	Ref	-		
30-60 ml/min/1.73m^2	1.14 (0.71 – 1.78)	0.566		
<30 ml/min/1.73m^2	1.10 (0.55 – 2.03)	0.778		
Admission diagnosis			-	-
Non-sepsis diagnosis	Ref	-		
Sepsis	0.95 (0.66 – 1.36)	0.785		
Cardiovascular comorbidities			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.05 (0.75 – 1.47)	0.768		
Respiratory disease			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.09 (0.72 – 1.61)	0.686		
Liver disease			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.08 (0.60 – 1.86)	0.778		

Table 6.6: Features associated with mortality in ICU survivors

Initial univariable analyses examining factors associated with mortality in ICU survivors is demonstrated in Table 6.6: these results disagreed with the log-rank test reported in Figure 6.1 as oliguric injury was found to have a statistically significant effect on long-term mortality when compared with non-oliguric injury at 18 months (OR = 1.50; *p*-value = 0.026). Other features which were found to have a statistically significant effect on mortality over the total follow up period included age >65 (OR = 1.81; *p*-value = 0.045), admitting specialty (OR = 0.71; *p*-value = 0.042) and pre-existing comorbidities including diabetes mellitus (OR = 1.67; *p*-value = 0.011) and malignancy (OR = 1.84; *p*-value = 0.033).

Multivariable analyses included all of the above statistically significant features as well as patient sex as *p*-value was <0.2 (*p*-value = 0.175). After all variables were corrected for, oliguric injury remained a significant factor on survival in the first 18 months of follow up (OR = 1.49; *p*-value = 0.032). Increasing age suggested a continued association with increased mortality in patients who survived to 30 days following hospital discharge, but this was no longer statistically significant. Other factors which remained statistically significant for increased long-term mortality included pre-existing diabetes mellitus (OR = 1.61; *p*-value = 0.021) and pre-existing malignancy (OR = 2.11; *p*-value = 0.012). In keeping with the initial univariable analysis, admission from surgical specialties was found to be statistically significantly associated with reduced odds of death during the follow up period on multivariable analysis (OR = 0.65; *p*-value = 0.018). Male sex again suggested an association with mortality at 18 months, but this remained non-statistically significant (OR = 1.38; *p*-value = 0.078).

6.4.7 Major adverse kidney events based on oliguric vs non-oliguric injury

Of the 1,068 ICU survivors identified from the total study population, 455 (42.6%) suffered a major adverse kidney event during the total follow-up period. Of the 771 ICU survivors who were found to have non-oliguric injury during their ICU admission, 326 (42.3%) suffered from at least one MAKE during the follow-up period. This compared to 129 out of 297 patients (43.4%) who developed a MAKE in the group with oliguric kidney injury. An estimator plotting the development of MAKE across this patient cohort is demonstrated in Figure 6.2: these patients were differentiated depending on whether they developed oliguric or non-

oliguric injury during ICU admission. Log-rank testing comparing these two event curves showed that there was no statistically significant difference of likelihood of MAKEs occurring between the two groups (*p*-value = 0.631).

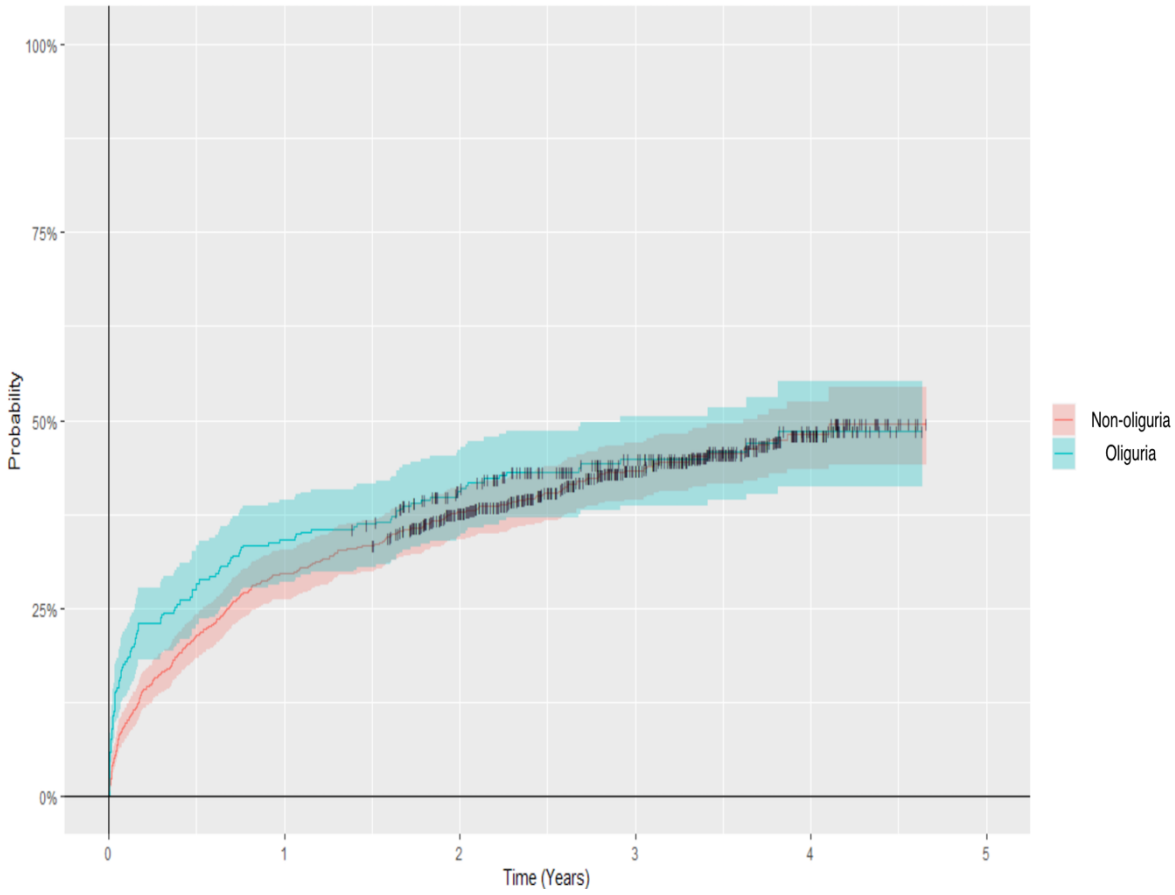


Figure 6.2: Development of major adverse kidney events over the total follow-up period depending on oliguric vs non-oliguric kidney injury during ICU admission. Time 0 represents day 30 following date of discharge from hospital (*p*-value = 0.631)

Prior to further analyses to assess for features associated with the development of MAKEs, tests for proportionality were conducted. As was the case for analyses of long-term survival, our data violated the proportional hazards assumption (as most events occurred early in the follow-up period) and was therefore deemed inappropriate to analyse using the Cox proportional hazards method. Instead, ORs and 95% CIs at 18 months were used to analyse development of MAKEs in ICU survivors as this included the minimum follow up period for all patients in the study.

Univariable analyses examining factors associated with development of major adverse kidney events in ICU survivors can be found detailed in Table 6.7: initial univariable analysis of oliguric vs non-oliguric injury corresponded with the log-rank test results as oliguric injury did not have a statistically significant effect

on long-term development of MAKEs when compared with non-oliguric injury (OR = 1.18; *p*-value = 0.272). Age was found to be strongly associated with development of MAKE over the total follow up period (OR = 3.22 for 40-65 year olds and OR = 4.04 for >65 year olds). Pre-existing comorbidities including cardiovascular disease (OR = 1.58; *p*-value <0.001), and diabetes mellitus (OR = 1.92; *p*-value <0.001) were also significantly associated with development of MAKEs. However, male sex appeared to be statistically significantly associated with reduced odds of long-term adverse kidney events (OR = 0.61; *p*-value <0.001). The effect of pre-ICU baseline eGFR was mixed, as baseline eGFR of 30-60 ml/min/1.73m^2 was associated with significantly increased odds of MAKE (OR = 1.83; *p*-value <0.001) whereas baseline eGFR of <30 ml/min/1.73m^2 was associated with significantly decreased odds of development of MAKE (OR = 0.56; *p*-value = 0.049). However, admitting specialty and pre-existing liver disease and malignancy were not significantly associated with development of MAKE. Whilst admission due to sepsis and pre-existing respiratory disease were also not significant on univariable analysis, it was included in the multivariable analysis as its univariable *p*-value was <0.2.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Kidney injury				
Non-oliguric	Ref	-	Ref	-
Oliguric	1.18 (0.88 – 1.55)	0.272	1.18 (0.87 – 1.59)	0.281
Age				
<40 years	Ref	-	Ref	-
40-65 years	3.22 (2.02 – 5.38)	<0.001	2.67 (1.64 – 4.51)	<0.001
>65 years	4.04 (2.51 – 6.77)	<0.001	2.92 (1.74 – 5.05)	<0.001
Sex				
Female	Ref	-	Ref	-
Male	0.61 (0.47 – 0.80)	<0.001	0.67 (0.51 – 0.88)	0.004
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m	1.83 (1.29 – 2.57)	<0.001	1.45 (1.01 – 2.08)	0.041
<30 ml/min/1.73m^2	0.56 (0.31 – 0.98)	0.049	0.62 (0.35 – 1.01)	0.057
Admission diagnosis				
Non-sepsis diagnosis	Ref	-	Ref	-
Sepsis	1.23 (0.94 – 1.61)	0.135	1.16 (0.87 – 1.53)	0.309
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing	1.58 (1.22 – 2.05)	<0.001	1.23 (0.93 – 1.64)	0.151
Respiratory disease				
Nil	Ref	-	Ref	-
Pre-existing	1.27 (0.93 – 1.73)	0.127	1.08 (0.78 – 1.49)	0.632
Diabetes				
Nil	Ref	-	Ref	-
Pre-existing	1.92 (1.40 – 2.64)	<0.001	1.81 (1.29 – 2.53)	<0.001
Admitting specialty			-	-
Medical	Ref	-		
Surgical	0.86 (0.66 – 1.11)	0.239		
Liver disease			-	-
Nil	Ref	-		
Pre-existing	1.24 (0.80 – 1.89)	0.327		
Malignancy			-	-
Nil	Ref	-		
Pre-existing	1.30 (0.80 – 2.10)	0.281		

Table 6.7: Features associated development of MAKEs in ICU survivors

After all variables were corrected for on multivariable analysis, oliguric injury was still not shown to have a significant effect on development of MAKE (OR = 1.18; *p*-value = 0.281). Increasing age remained strongly associated with increased risk of MAKE in ICU survivors (OR = 2.67 for 40-65 year olds and OR = 2.92 for >65 year olds). Other factors which remained statistically significant for increased long-term mortality included pre-existing diabetes (OR = 1.67; *p*-value <0.001). Male sex also remained significantly associated with decreased odds of developing MAKEs (OR = 0.67; *p*-value = 0.004). Similarly, the previously seen association between pre-ICU baseline eGFR of 30-60 ml/min/1.73m^2 also remained associated with increased odds of MAKEs (OR = 1.45; *p*-value = 0.041). Admission due to sepsis, pre-existing cardiovascular comorbidities and pre-existing respiratory disease were not found to have a significant effect on long-term odds of developing MAKEs on multivariable analysis of all the selected variables.

6.4.8 Point vs persisting oliguria

6.4.8.1 Baseline demographics of oliguric injury based on persisting oliguria compared with point oliguria

The 528 patients with oliguric injury were categorised depending on point vs persisting oliguria: 224 of these patients (42.4%) suffered from point oliguria compared to 304 patients who suffered from persisting oliguria (57.6%). The demographics of these two groups are summarised in Table 6.8. The age of the patients within this group was similar, with a median value of 62.5 years in the point group compared with a median of 61.0 years in the persisting oliguria group (*p*-value = 0.324). No between group differences were found when comparing proportion of male patients, with 141 (62.9%) male patients in the point oliguria group compared with 192 (63.2%) male patients in the persisting group (*p*-value = 0.960). When comparing patients based on admitting specialty, no significant difference in proportion of patients admitted from surgical specialties was seen between the groups (55.8% vs 53.6%; *p*-value = 0.682).

Characteristic	Oliguric kidney injury (n = 528)	Point oliguria (n = 224)	Persisting oliguria (n = 304)
Age – median (IQR)	61.5 (50.0 – 71.0)	62.5 (50.0 – 72.0)	61.0 (50.0 – 71.0)
Male – n (%)	333 (63.1%)	141 (62.9%)	192 (63.2%)
Admitted from surgical specialty – n (%)	288 (54.5%)	125 (55.8%)	163 (53.6%)
Baseline eGFR – median (IQR)	78.9 (51.8 – 96.9)	79.3 (54.5 – 97.3)	78.4 (46.3 – 96.5)
APACHE II score – median[10] (IQR)	25.0 (20.0 – 30.0)	24.0 (18.0 – 30.0)	25.0 (21.0 – 31.0)
Admission due to sepsis – n (%)	190 (36.0%)	70 (31.2%)	120 (39.5%)
Comorbidities – n (%)			
Cardiovascular disease	250 (47.3%)	119 (53.1%)	131 (43.1%)
Respiratory disease	99 (18.8%)	37 (16.5%)	62 (20.4%)
Liver disease	63 (11.9%)	34 (15.2%)	29 (9.5%)
Diabetes	115 (21.8%)	50 (22.3%)	65 (21.4%)
Malignancy	34 (6.5%)	17 (7.6%)	17 (5.6%)

Table 6.8: Demographics of patients with oliguric kidney injury during ICU admission based on presence of point or persisting oliguria

Median baseline eGFR values were calculated for each group: these demonstrated similar median values of 79.3 ml/min/1.73m^2 in the point oliguria group and 78.4 ml/min/1.73m^2 in the persisting oliguria group (p-value = 0.158). As was the case for the total study population and for the subgroup of patients with oliguric kidney injury, sepsis was the most common precipitating reason for

[10] Data unavailable for 25 patients – only 503 patients used in these calculations (Point oliguria = 214; Persisting oliguria = 289)

admission in both the point and persisting oliguria groups; again, no significant differences were seen when comparing proportions of patients admitted due to sepsis (31.2% vs 39.5% respectively; *p*-value = 0.064). This was also the case when comparing median APACHE II scores in the two groups, as values in the two groups were not significantly different (*p*-value = 0.286). Analysis of pre-existing comorbidities showed no significant difference in rates of respiratory disease, liver disease, diabetes, or malignancy between the two groups. However, rates of pre-existing cardiovascular disease were found to be significantly higher in the point oliguria group (53.1%) compared to the persisting oliguria group (43.1%) (*p*-value = 0.028).

Differing modalities of organ support provided to this subgroup of patients throughout their admission to ICU are detailed in Table 6.9. Unlike organ support received by the total study population seen in Table 6.2, the most common organ support in patients with oliguric kidney injury was cardiovascular support (79.7%). This differed between the point oliguria group, where IMV was the most common modality, and the persisting oliguria group, where CVS was most common. Whilst rates of IMV received in the two groups were similar (*p*-value = 0.836), a much higher proportion of patients in the persisting oliguria group received both CVS (*p*-value = 0.002) and KRT (*p*-value <0.001) when compared to the non-oliguria group. Analysis of degree of organ support received in the two groups demonstrated that receipt of multi organ support was significantly higher in the persisting oliguria group when compared to the point oliguria group (*p*-value = 0.001).

Intervention	Oliguric kidney injury (n = 528)	Point oliguria (n = 224)	Persisting oliguria (n = 304)
Modalities – n (%)			
Invasive mechanical ventilation	409 (77.5%)	175 (78.1%)	234 (77.0%)
Cardiovascular support	421 (79.7%)	164 (73.2%)	257 (84.5%)
Kidney replacement therapy	289 (54.7%)	65 (29.0%)	224 (73.7%)
Degree of organ support – n (%)			
None	34 (6.4%)	15 (6.7%)	19 (6.3%)
Single	87 (16.5%)	52 (23.2%)	35 (11.5%)
Multi	407 (77.1%)	157 (70.1%)	250 (82.2%)

Table 6.9: Organ support received in patients with oliguric kidney injury depending on point vs persisting oliguria

6.4.8.2 Features associated with persisting oliguria

For the collected baseline demographic variables, initial univariable analyses were performed: the results of these are detailed in Table 6.10. Patients with a pre-ICU baseline eGFR of <30 ml/min/1.73m^2 were strongly associated with the development of persisting oliguria, with almost three times the odds compared to a "point" oliguric injury (OR = 2.88; *p*-value = 0.002). The only other factor which reached statistical significance on univariable analyses was pre-existing cardiovascular comorbidities: analysis suggested that a pre-existing diagnosis of cardiovascular disease was associated with protection against development of persisting oliguria with an OR of 0.67 (*p*-value = 0.023). Whilst they did not reach statistical significance, other factors which were found to have a *p*-value <0.2 and were therefore included in the multivariable model were admitting specialty and pre-existing liver disease. In addition, as it was considered a clinically important variable, age was included in the multivariable model as well.

Characteristic	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Age				
<40 years	Ref	-	Ref	-
40-65 years	1.30 (0.47 – 3.52)	0.605	1.31 (0.47 – 3.64)	0.599
>65 years	1.15 (0.42 – 3.10)	0.773	1.26 (0.45 – 3.51)	0.656
Baseline eGFR				
>60 ml/min/1.73m^2	Ref	-	Ref	-
30-60 ml/min/1.73m^2	0.75 (0.49 – 1.17)	0.207	0.74 (0.47 – 1.16)	0.184
<30 ml/min/1.73m^2	2.88 (1.52 – 5.87)	0.002	2.67 (1.39 – 5.48)	0.005
Admitting specialty				
Medical	Ref	-	Ref	-
Surgical	1.43 (1.00 – 2.07)	0.052	1.41 (0.97 – 2.06)	0.070
Cardiovascular comorbidities				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	0.67 (0.47 – 0.94)	0.023	0.63 (0.44 – 0.92)	0.016
Liver disease				
Nil	Ref	-	Ref	-
Pre-existing diagnosis	0.59 (0.35 – 1.00)	0.050	0.56 (0.32 – 0.97)	0.037
Sex			-	-
Female	Ref	-		
Male	1.01 (0.70 – 1.44)	0.960		
Admission diagnosis			-	-
Non-sepsis diagnosis	Ref	-		
Sepsis	0.92 (0.65 – 1.29)	0.618		
Respiratory comorbidities			-	-
Nil	Ref	-		
Pre-existing diagnosis	0.95 (0.62 – 1.44)	0.796		
Diabetes			-	-
Nil	Ref	-		
Pre-existing diagnosis	1.29 (0.83 – 2.04)	0.260		
Malignancy			-	-
Nil	Ref	-		
Pre-existing diagnosis	0.72 (0.36 – 1.45)	0.357		

Table 6.10: Regression analyses of features associated with the development of persisting oliguria

Multivariable analysis of factors associated with the development of persistent oliguria during a kidney injury revealed that a baseline eGFR of <30 ml/min/1.73m^2 remained a statistically significant factor with an OR of 2.67 (*p*-value = 0.005). Similarly, a pre-existing diagnosis of cardiovascular disease continued to suggest a significant association with reduced odds of developing persisting oliguria once other variables were factored into the multivariable model (OR = 0.63; *p*-value = 0.016). Although univariable analysis of pre-existing liver disease was not found to be a statistically significant factor in developing persisting oliguria, multivariable analysis suggested that a diagnosis prior to ICU admission also conferred reduced odds of developing persisting oliguria (OR = 0.56; *p*-value = 0.037). Both age and admitting specialty remained non-statistically significant factors when factored into the multivariable model.

6.4.8.3 Short-and long-term mortality rates

Within the 528 patients to experience on oliguric kidney injury during their ICU admission, 182 deaths occurred (34.5%). Raw in-ICU mortality was found to be similar in the point oliguria group when compared to the persisting oliguria group at 36.6% and 32.9% respectively with no significant between group difference found (*p*-value = 0.375). For in-hospital mortality rates, raw mortality rates were also similar, with 45.1% in the point oliguria group compared to 39.5% in the persistent oliguria group; again, no significant difference in raw mortality was observed between the two groups (*p*-value = 0.202).

Event	Oliguric kidney injury (n = 528)	Point oliguria (n = 224)	Persisting oliguria (n = 304)	*p*-value
Death during ICU admission				
Number of deaths – n (%)	182 (34.5%)	82 (36.6%)	100 (32.9%)	0.375
95% Confidence Intervals	30.5% - 38.6%	30.6% - 43.1%	27.9% - 38.4%	
Death during hospital admission				
Number of deaths – n (%)	221 (41.9%)	101 (45.1%)	120 (39.5%)	0.202
95% Confidence Intervals	37.7% - 46.1%	38.7% - 51.6%	34.1% - 45.1%	

Table 6.11: In-ICU and in-hospital mortality rates based on presence of point or persisting oliguria

Of the 297 patients within the oliguric injury group who survived to day 30 following hospital discharge, 122 (41.1%) suffered from a point oliguric injury which lasted just one day of admission and 175 (58.9%) suffered from persisting oliguria which lasted 2 or more days of their ICU admission. The minimum follow-up period for patients in this analysis was 448 days whilst the maximum follow-up period was 1,621 days.

A total of 75 deaths occurred during the follow-up period, with 28 found to be in the point oliguria group (23.0%) compared with 47 in the persisting oliguria group (26.9%). Kaplan Meier estimator of survival over the total follow up period is represented in Figure 6.3 and is stratified based on point vs persisting injury. This analysis demonstrated no statistically significant difference between the two survival curves on log-rank testing (*p*-value = 0.585).

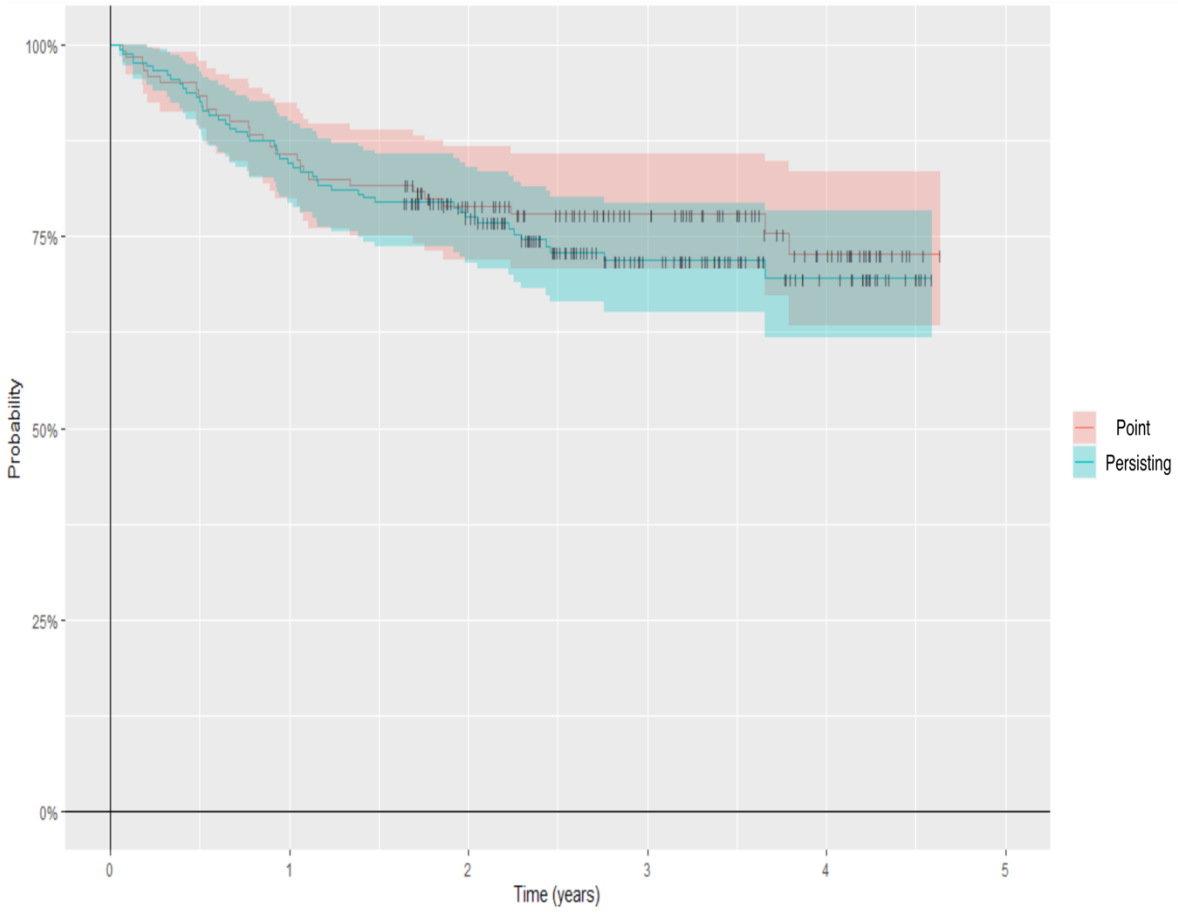


Figure 6.3: Kaplan Meier analysis of long-term survival stratified by presence of point oliguria or persisting oliguria during ICU admission. Time 0 represents day 30 following date of discharge from hospital (*p*-value = 0.585)

Further analyses were conducted to assess if the effect of persisting oliguria had a significant effect on long-term mortality: initial univariable logistic regression at 18 months also suggested no significant difference between the two groups (OR = 1.21; 95% CI = 0.70 – 2.07). When different variables were assessed using univariable logistic regression, none were found to be statistically significant; as a result, multivariable analysis was not conducted in this patient cohort.

6.4.8.4 Major adverse kidney events based on persisting vs point oliguria

A total of 129 patients in the oliguric injury group were found to have at least one major adverse kidney event during the follow-up period: 56 out of the 122 patients (45.9%) in the point oliguria group suffered from a MAKE compared with 73 out of 175 patients who suffered from a MAKE in the persisting oliguria group (41.7%). Figure 6.4 shows development of major adverse kidney events over the total follow-up period and is detailed based on point vs persisting injury. Analysis of the two event curves demonstrated no statistically significant difference between the two groups on log-rank testing (*p*-value = 0.469).

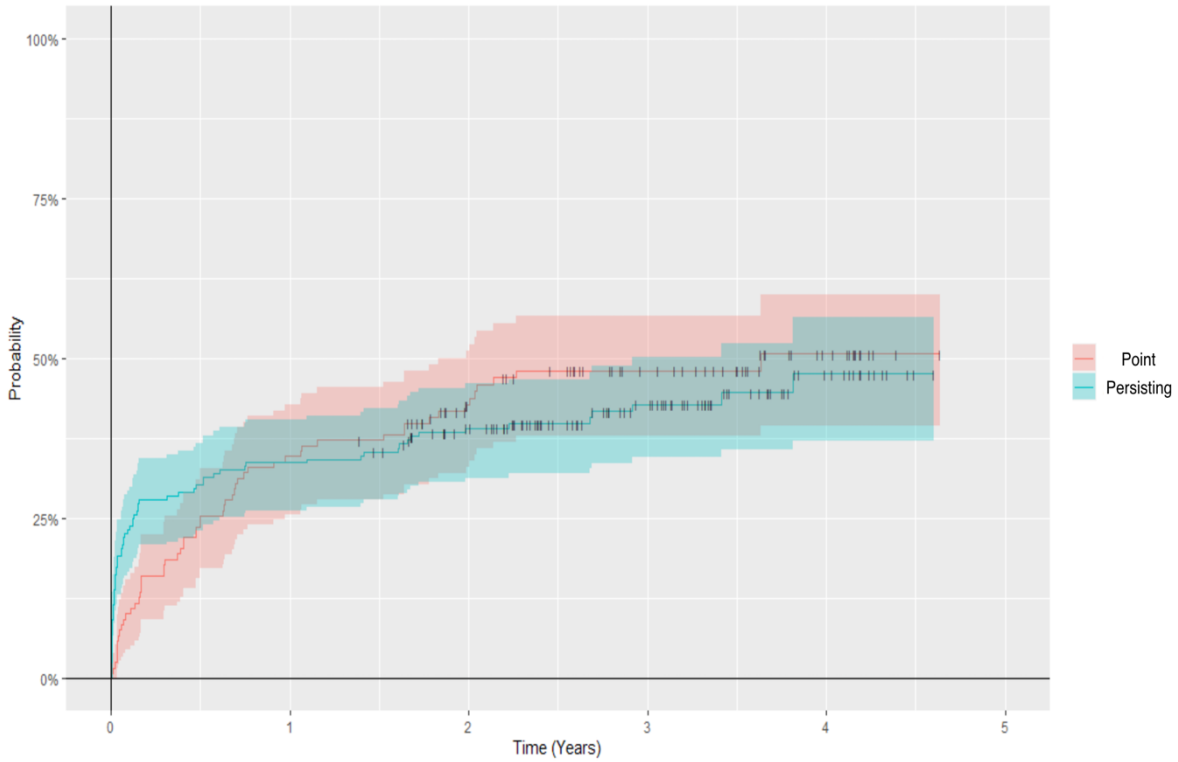


Figure 6.4: Development of major adverse kidney events over the total follow-up period depending on point vs persisting oliguric kidney injury during ICU admission. Time 0 represents day 30 following date of discharge from hospital (*p*-value = 0.469)

Further analyses were carried out to assess if the effect of persisting oliguria had a significant effect on development of future MAKEs. Univariable logistic regression at 18 months also suggested no significant difference between the two groups (OR = 0.82; 95% CI = 0.51 – 1.31). As was the case when assessing long-term survival in this subgroup of patients, when different variables were assessed using univariable logistic regression, none were found to be statistically significant and therefore multivariable analysis was not conducted.

6.5 Discussion

The data generated from this study revealed that approximately one third of patients who were found to have kidney injury in ICU developed oliguria. These patients had at least one full 24-hour period during which their urine output fell below 7.2ml/kg. This cut-off value varied significantly when comparing it to thresholds utilised in previous studies which assessed outcomes following oliguric kidney injury: a study from 2006 by Wald and colleagues defined oliguric injury as patients whose 24-hour urine output fell below 400ml (131) whilst in 2013 a study by Oh et al. (132) defined oliguria as less than 107ml over 6 hours (equating to 428ml over 24 hours). Whilst the cut-off used in this study differs

from these prior data, it correlates more closely with KDIGO clinical guidelines which suggest sustained urine output below 0.3ml/kg/hr is significant oliguria (16). Furthermore, utilising this criterion is more individualised, as the threshold for oliguria is based on individual patient weights rather than one static value: this is more in keeping with the methodology used to define AKI based on urine output values as recommended by KDIGO international guidelines (16). Proportion of oliguric injury in this study was substantially lower than in these previous two studies: 31.7% of patients developed oliguria in this study compared with a previous reported incidence of 50-60% (131, 132). However, it should be noted that only patients who underwent KRT whilst admitted to ICU were included in both of these prior studies.

6.5.1 Characteristics of patients depending on oliguric or non-oliguric kidney injury and features associated with oliguria

When comparing baseline characteristics between patients with non-oliguric injury and patients with oliguric injury, median age was similar across the two groups. However, when assessing for features associated with development of oliguria, patients in older age groups had significantly higher odds. This could be explained by the progressive glomerulosclerosis and loss of functional units within the kidneys as age increases contributing to kidneys which are more vulnerable to an acute insult (197).

Patients with oliguric AKI had statistically significantly higher rates of pre-existing diabetes mellitus when compared with non-oliguric injury. The mechanism underlying this process is likely to be inherently linked with the micro-and macro-vascular damage associated with the pathophysiology of diabetes which contributes to progressive damage to the nephrons within the kidneys; this includes the deposition of advanced glycation end products within the kidneys as well as activation of protein kinase C leading to endothelial dysfunction (198). Whilst diabetes was suggested as being significantly associated with oliguric injury, this was not the case on multivariable analysis.

Patients within the oliguric group also had a significantly lower baseline eGFR prior to admission to ICU. This is likely to reflect this cohort of patients having a greater degree of underlying tubular damage which renders the kidneys more

vulnerable to an acute insult. Kidneys which are already predisposed to reduced ability to filter and concentrate urine are therefore more prone to reduced urine output when exposed to further injury in addition to underlying dysfunction (199). The data from this study demonstrated that baseline eGFR <30 ml/min/1.73m^2 was a significant feature associated with oliguric injury. Given that this baseline value is comparable to chronic kidney disease (CKD) stages 4 and 5, this is in keeping with severe underlying damage to the nephrons predisposing patients to oliguria. Whilst this theoretically explains an increased predisposition to developing oliguria, it is at odds with a commonly reported presentation of patients with CKD in the community. These patients often complain of a "nocturnal polyuria", which has been suggested as a consequence of the kidneys reduced ability to adequately concentrate urine within the nephron (200). Fukuda and colleagues subsequently postulated that this occurs secondary to an osmotic diuresis driven by a natriuresis rather than by high urea concentrations (201). Whilst this impaired concentrating ability highlights underlying nephron damage, it also helps explain why these patients with lower baseline eGFR are associated with increased odds of developing oliguria. The mechanism of oliguria in acute injury is likely secondary to reduced kidney blood flow and reduced tubular flow (202). Given these mechanisms will inherently lead to reduced flow through the nephron, the ability to concentrate tubular fluid will be less important. Combining these factors with an overall reduced number of functioning nephrons can help to explain why these patients may be more prone to developing oliguria following an acute injury despite often complaining of polyuria due to their underlying chronic disease.

As was the case in the prior study assessing features associated with progression to acute kidney disease (AKD), admission due to sepsis was significantly associated with oliguric injury. Sepsis predisposes patients to significant arterial vasodilation which leads to hypoperfusion of the kidneys as well as systemic release of inflammatory mediators which can cause damage to the kidneys at a histological level. Due to a combination of these factors, sepsis has also been shown to cause kidney injuries in approximately one third of patients (147). Whilst previous data has suggested that urine output correlates poorly with severity of kidney injury (199), this association may represent the complex

interplay between oliguria and increasing length and severity of kidney injury in the context of critical illness.

The pathophysiology of oliguria in the context of kidney injury is closely linked to the pathophysiology of sepsis: the reason for a reduced urine output can often be linked to pre-kidney causes as it follows that reduced blood flow reaching the kidneys will result in less glomerular filtration and therefore less tubular fluid and subsequently produced urine. However, other mechanisms linking sepsis to oliguria have been postulated. Animal studies which detailed the response in mice kidneys to the endotoxemia commonly seen in sepsis found that a significant reduction in tubular flow rate was seen due to swelling of the cells in the proximal convoluted tubule which contributed to tubular obstruction (202). Another potential mechanism which has been suggested is the mitochondrial dysfunction which has been observed as part of the septic response and has been previously associated with poorer patient outcomes (203). Specific kidney mitochondrial function was assessed in the context of septic AKI, and the authors reported evidence of significant mitochondrial dysfunction which improved following treatment with a specific mitochondrial antioxidant (204). Whilst these studies have been conducted in animal models, they offer theoretical cellular mechanisms which may contribute to the development of oliguria during kidney injury. As is often the case, it is highly likely that oliguria in the context of sepsis is a combination of reduced kidney blood flow secondary to intravascular depletion and systemic vasodilation, combined with the intra-kidney tubular changes at a cellular level.

Admission from surgical specialties was also associated with significantly increased odds of developing oliguria. Given the limited data available in the literature, it is difficult to fully ascertain the reasons behind this association. However, this may be a representation of deranged pathophysiology due to significant fluid shifts within body compartments which can be corrected over time during an ICU admission but may predispose patients to at least one 24-hour period with reduced urine output.

Significantly higher rates of multi-organ support were seen within the oliguric group when compared with the non-oliguric group. Similarly, significantly higher rates of KRT and CVS were received by patients within the oliguric group. All of

this is likely a surrogate marker of illness severity: more severe illness during ICU admission is more likely to predispose to oliguric injury due to the higher degree of physiological dysfunction rendering the kidneys more susceptible to injury (132). Conversely, this may represent that oliguric injury is an independent marker of illness severity which means that patients are more likely to receive certain modalities of organ support or multi-organ support; this is especially true for receipt of KRT, as oliguria in the context of fluid overload leading to respiratory distress or impaired gas exchange is an indication for implementation of KRT.

Development of greater severity of kidney injury (KDIGO stage 3) was also significantly higher in patients with oliguric kidney injury; this was supported by the majority of patients with stage 3 injury developing an oliguric injury. Furthermore, progression to AKD was also significantly higher in oliguric patients when compared with the non-oliguric group. This is a further representation of the data generated from the preceding study: there is significant interplay between more severe stages of kidney injury and progression to AKD and the high rates seen in the oliguric group is a representation of oliguria as a marker of injury severity.

6.5.2 Oliguric vs non-oliguric in-ICU and in-hospital mortality

The group of patients with oliguric injury were found to have significantly higher rates of in-ICU and in-hospital mortality when compared to patients with non-oliguric injury (both *p*-values <0.001). Previous studies looking specifically at oliguric kidney injury in the context of patients requiring KRT found that in-patient mortality within the first 30 days were specifically high in patient groups with oliguric injury (131): in the 2013 study by Oh and colleagues, they described a significantly reduced multivariable hazard ratio of 0.85 in patients with non-oliguric injury after age, sex and APACHE II scores were adjusted for (132). This result is consistent with the data produced by this study: oliguric kidney injury confers a significantly higher risk of mortality during both ICU admission and hospital admission.

6.5.3 Long-term survival in oliguric and non-oliguric patients

Patients who survived to 30-days following discharge from hospital and were classified as ICU survivors were stratified based on the presence of oliguric vs non-oliguric kidney injury during ICU admission: raw mortality rates over the total follow-up period were slightly higher in the oliguric group however the Kaplan Meier estimator revealed no statistically significant difference between the two survival curves. This was however contradicted by multivariable analysis which revealed oliguria was significantly associated with reduced long-term survival at 18 months. This is likely as a result of the fact that survival declines faster in the oliguric group early in the follow-up period before non-oliguric survival rates catch up later in the follow-up period. Outcomes beyond 28 days for patients with oliguric AKI have not previously been published and these results appear to be novel. As such, the results of this study must be interpreted in isolation: the data suggest that increased mortality risk conferred by oliguric injury significantly impacts long-term survival, at least in the initial 18 months. This may imply that oliguric injury is, a reasonable marker of the severity of kidney injury, as it has previously proven that greater severity of kidney injury does translate to a higher mortality risk over the long-term (26). Since no analyses were performed looking at differences between stage 3 injury according to creatinine compared with stage 3 injury according to oliguria, it is more difficult to quantify whether oliguria was the significant factor in this regard or simply the effect seen in patients with more severe AKI. However, given the understandable overlap between these two features due to the underlying definitions, the detailed associations of oliguric injury are likely to be comparable to those seen in stage 3 kidney injury. While the sample size for this study included over 1000 patients with AKI, the confidence intervals around the survival estimates were wide. Given there was a statistically significant increased raw mortality rate within the oliguric group at 18 months, further study using a larger study population may help identify if this association is maintained over a longer follow up period.

Features associated with mortality in this group included multiple groups of pre-existing comorbidities such as diabetes mellitus and malignancy. These associations are easily explained, as patients with a higher burden of underlying disease prior to ICU admission are more likely to die sooner than non-comorbid

patients. However, the significant association identified between admission from surgical specialties and decreased odds of death during the follow-up period needs to be more thoroughly explored. Admission from medical specialties has been previously documented as an independent risk factor for both sustained reduction in kidney function and reduced long-term survival (51). This may represent the more complex and comorbid patient population who are admitted from medical specialties; it may also suggest that ICU patients admitted directly following an operative procedure may have undergone definitive treatment to fix a specific pathology which renders them more likely to survive over the longer term. This is not a concept specific to patients with kidney injury in ICU, but for all patients with critical illness: a study of patients >65 years old who were admitted to ICU and survived to day 28 showed that the adjusted risk for 1 year mortality was significantly lower in surgical ICU patients when compared to medical ICU patients (HR = 0.88; *p*-value = 0.020) (205).

6.5.4 Long-term major adverse kidney events in oliguric and non-oliguric patients

When the group defined as ICU survivors were assessed for presence of MAKEs over the total follow-up period, patients within the oliguric group had comparable rates of adverse kidney events compared with patients with non-oliguric injury. When event curves were plotted, no significant difference was observed between the two curves: again, this was supported by multivariable logistic regression which found that oliguria was not a statistically significant factor in development of future MAKEs. Of note, on analysis of Figure 6.2, rates of MAKEs developed at a faster rate over the first 12-month period before the lines between the two groups converged towards the end of the follow up period. The wide confidence intervals demonstrated on this graph highlight the small numbers found within this study population, and particularly in the oliguria group. It may be that reduced numbers within this group masked a potentially significant difference between the two groups, but this is conjecture without further evidence on a larger study population. As was the case of data involving long-term mortality, no previous data exist for comparison, but this suggests that oliguric kidney injury does not translate to a significant difference in development of MAKEs over the longer term. However, given the above observations on the difference in MAKEs over the follow up period and the wide

confidence intervals seen in the data from this study, future work analysing major adverse kidney events in the context of oliguric kidney injury would benefit from further study utilising a larger study cohort.

Other features associated with development of MAKEs included increasing age: >65 year olds were at almost three times the odds of adverse kidney events than patients <40 years old. Using MAKE as a surrogate for CKD, this relationship has been described before, with increasing age placing patients at higher risk of developing CKD (168, 169). Other significant features such as reduced baseline eGFR and pre-existing diabetes mellitus are indicative of the underlying cellular damage caused within the kidneys as a result of these disease processes.

6.5.5 Point vs persisting oliguria

The majority of patients to suffer from oliguric kidney injury during their admission had oliguria that persisted beyond a single 24-hour period (57.6%). Baseline demographics between the point oliguria group and persisting oliguria group were similar, but patients with lower baseline eGFR values from prior to admission to ICU were at significantly increased odds of developing persisting oliguria. This was the case for a baseline eGFR of <30 ml/min/1.73m^2, as these patients had greater than two and half times the odds of suffering from a persisting oliguric injury compared to patients with a baseline eGFR >60 ml/min/1.73m^2. Again, these patients can be considered analogous to patients with CKD stages 4 and 5 and are therefore predisposed to reduced physiological reserve within their kidneys: this renders patients more prone to oliguria when vulnerable kidneys are exposed to an acute on chronic insult.

Other features associated with development of an oliguric injury which persisted beyond 24 hours included pre-existing cardiovascular disease and pre-existing liver disease. However, multivariable analysis suggested that both of these comorbidities had a statistically significantly reduced association with the development of prolonged oliguria. With minimal prior data available to compare this to, it is unclear if this is a true association, but it is unlikely that pre-existing comorbidities protect against a prolonged period of oliguria. A more likely explanation is that patients with these comorbidities are at higher

risk of dying soon after development of AKI and multi-organ failure, and death then prevents them from progressing to a persisting oliguria.

Specific analysis of oliguric kidney patients stratified by point vs persisting oliguria revealed no significant difference in raw mortality rates between the two groups for either in-ICU or in-hospital mortality. No previous studies have explored any difference in outcomes based on length of oliguria within the context of kidney injury, so no data exist for comparison; the analyses were pre-specified as it was hypothesised that short-term disturbances in physiology such as hypovolaemia requiring fluid replacement or aberrant factor such as a blocked urinary catheter may dilute the cohort of patients with longer-term oliguria which was more likely to represent more severe pathological processes. However, the data from this study would suggest that presence of oliguria confers a significantly increased risk of in-hospital mortality regardless of whether the oliguria persists beyond 24 hours or not; this must be interpreted cautiously, as it may be that the sample size of the two groups is too small to identify any significant difference in short-term mortality.

Analysis of long-term survival in patients with oliguric injury separated based on point vs persisting oliguria revealed no significant difference between survival curves and this was supported by univariable logistic regression. These analyses would support the results produced from in-ICU and in-hospital mortality, which suggest that persisting oliguria does not affect the risk of survival.

Subgroup analysis involving only patients with oliguric kidney injury was performed to assess for potential effect of persisting oliguria. A time to event curve was produced for each group: no statistically significant difference was seen between these two curves. The lack of a between group difference was also observed on univariable logistic regression. In conjunction with all previous results analysing point vs persisting injury, this data further suggests that persisting oliguria does not increase the risk of either short- or long-term outcomes. However, further data from a larger patient cohort is required to confirm the results of this study.

6.5.6 Strengths and weaknesses

Studies to date comparing oliguric and non-oliguric AKI have had small sample sizes, assessed short-term outcomes, and have had varying definitions of oliguria. The major strength of this study is that it has assessed oliguric outcomes using an internationally accepted definition of oliguria. Furthermore, oliguria was assessed using specific weight data on admission to ICU for each patient to identify an individualised oliguria cut-off and improve sensitivity. In addition, this study compares outcomes based on point and persisting oliguria to assess if a single one-off episode of oliguria is as important as a prolonged period. The relatively large sample size with broad inclusion criteria allows our results to be more easily generalisable to the ICU population within the UK. Compared to existing work, this study also has a long follow-up period (up to 18 months vs 28 days after hospital discharge).

A significant limitation of this study is the inability to utilise Cox proportional hazard modelling to analyse outcomes over a long follow-up period as it did not meet the proportional hazards assumption due to most deaths and MAKEs occurring early in the follow-up timeframe. Odds ratios at 18 months were reported for all long-term analyses as the proportionality assumption failed: this was done to select a time-point at which all patients had an entire follow-up rather than assuming no event occurred in the intervening period between their individual loss to follow up and the maximum follow up time. However, it will have resulted in a loss of data for events which occurred over the longer term. In addition, to limit the potential inaccuracies in hourly urine output data, only total urine output over 24 hours were used. This may mean that oliguric injury was under-represented as patients may have had 24 hours of oliguria straddled across two separate days. Finally, because of incomplete values on day of admission and day of discharge, these values were excluded when calculating presence of oliguria: this reduction in data points may have further reduced the sensitivity for detecting oliguria and caused under-representation within this group of patients.

6.6 Conclusions

Although previous work has been conducted into a comparison of outcomes between oliguric and non-oliguric kidney injury over the short-term, these studies were performed specifically on patients undergoing KRT and none of them have examined the effect of oliguric injury on longer-term outcomes. This study has demonstrated that oliguric kidney injury is common amongst patients with kidney injury whilst in ICU. Older patients, patients admitted from surgical specialties, patients with a lower baseline eGFR and patients admitted due to sepsis all had significantly increased odds of developing oliguric kidney injury. KDIGO stage 3 injury and progression to AKD were also significantly associated with development of oliguria. These patients within the oliguric group had a significantly increased risk of mortality both in-ICU and in-hospital, and this was also seen in rates of mortality at 18 months following hospital discharge. However, oliguria did not increase the risk of future MAKEs. Persisting oliguria did not have any significant effect on either short- or long-term outcomes. Further studies utilising a larger patient population are required to further assess the relationship between oliguric injury and long-term outcomes.

Chapter 7 Discussion

As advances in modern medicine continue to develop therapies which increase average life expectancies and allow treatment of advanced organ failure, the requirement for critical care and survival following admission to the intensive care unit (ICU) is likely to increase in the coming years. Follow-up after ICU is a burgeoning area for research which recognises that the discharge from ICU is the first aspect of recovery following critical illness (206). To help patients in this recovery period, recognition of factors during ICU admission which can predict poorer long-term outcomes and increased burden of disease can be vital in intervening in the process. If clinicians were able to identify individuals at high risk of poor prognosis during their acute admission, then follow-up care and referrals to specialist services could be arranged sooner and prompt interventions may then help arrest future progression of disease and improve both patient survival and quality of life. This not only improves care by tailoring it to the individuals at higher risk of future adverse events, but it improves healthcare delivery by utilising potentially limited resources to patients who will benefit from it the most and limiting unnecessary cost in patients who will not require the additional care.

The aim of the thesis is to identify aspects of care relevant to kidney injury within intensive care which may influence patient outcomes, as well as describing factors associated with the development of adverse short- and long-term outcomes. Furthermore, it will explore whether a novel definition of acute kidney disease (AKD) confers any additional risk of developing these outcomes and whether this is a useful definition for helping to identify patients at higher risk of future death or chronic disease.

7.1 Summary of findings

This thesis describes the literature pertaining to short and long-term outcomes following AKI in ICU followed by a detailed description of a cohort of ICU patients depending on the development of kidney injury and various aspects of injury which may influence outcomes.

7.1.1 Characterisation of kidney injury in intensive care and short-term outcomes

Whilst the reported incidence of new kidney injury in intensive care has varied widely in the literature, this study found that it is a very common problem with two in every five patients affected; within this population, 25% progressed to AKD.

Kidney injury most commonly occurred in older, comorbid, male patients admitted from medical specialties with lower baseline estimated glomerular filtration rate (eGFR) and admitted as a result of sepsis. On specific analysis of these patients, progression to AKD was significantly associated with male sex, admission due to sepsis and a lower baseline eGFR. Patients with de-novo kidney injury were more likely to receive multi-organ support than patient with no injury; AKD patients were also significantly more likely to receive multi-organ support than patients with shorter-term acute kidney injury (AKI).

Short-term mortality across the total study population was high, with more than one in five patients dying prior to discharge from hospital. Crude in-ICU and in-hospital mortality rates were over three times higher in patients who suffered from de-novo kidney injury compared to those with no kidney injury. In addition, patients who progressed to AKD and patients with greater severity of kidney injury had significantly higher short-term mortality rates than short-term injury and less severe injury respectively.

Although little has been published regarding AKD at this point, the results of this study indicate that certain features may be useful in helping to identify patients who are at higher risk of progression to acute disease from an acute injury. Furthermore, given that patients who progress to AKD have significantly increased short-term mortality rates, this may represent a feature which helps in the greater scope of prognostication in patients admitted to intensive care. Whilst the interplay of factors in critical illness is profound, the impact of both de-novo kidney injury and AKD in ICU patients should be further investigated as a possible marker of poor prognosis. In addition, mortality rates in these groups further diverge between ICU discharge and hospital discharge, and this may

represent an opportunity to recognise high risk patients in need of further intervention once they are over the worst of their acute illness.

7.1.2 The effect of kidney injury on long-term survival and major adverse kidney events

In the population of patients who survived to 30 days after hospital discharge, patients who suffered from de-novo kidney injury were more likely to be older, male, admitted from medical specialties, admitted due to sepsis, had a lower pre-ICU baseline eGFR and were more likely to have underlying cardiovascular disease and diabetes mellitus. In this subset of patients, progression to AKD was also more likely to be seen in patients admitted from medical specialties, patients admitted with sepsis, patients with lower pre-ICU baseline eGFR and in patients with pre-existing diabetes mellitus.

Mortality over the four- and half-year follow-up period showed a significant reduction in survival in the de-novo injury group when compared with the group without kidney injury with an independently associated 16% increased risk of dying. Sequential time-period analysis showed that survival rates also declined at a faster rate in the de-novo injury group as time progressed. Despite small numbers in the group of patients admitted with pre-existing established kidney failure (EKF), long-term survival beyond two years was significantly lower compared to both de-novo injury patients and patients with no kidney injury. This difference in survival may be attributed to the increased burden caused by organ damage in the initial acute illness. No significant long-term survival difference was associated with progression to AKD.

Development of de-novo kidney injury and progression to AKD were both significantly associated with a faster decline in eGFR over time as well as development of major adverse kidney events (MAKEs) over the total follow up period. This suggests that both of these conditions accelerate the natural decline in kidney function associated with aging and predispose patients to the development of chronic kidney disease (CKD) following discharge from ICU.

7.1.3 Long-term cardiovascular events following discharge from ICU

Myocardial injury in the study population was assessed by presence of a troponin positive event: patients with at least one troponin value available for analysis were analysed and compared based on presence of myocardial injury. This demonstrated that myocardial injury was significantly more common in older patients admitted from medical specialties with a lower pre-ICU baseline eGFR and in patients with pre-existing cardiovascular, respiratory, and diabetic disease.

When separated based on presence of de-novo kidney injury, myocardial injury was significantly more common in patients with de-novo injury compared to patients with no injury: de-novo injury was independently associated with a 46% increased risk of subsequent myocardial injury. This association represents the close relationship between the cardiovascular and kidney systems and the effect an acute insult to the kidneys can have on cardiovascular risk profile over the long-term. When progression to AKD was assessed as a potential factor, no significant differences in rates of myocardial injury were seen between the AKD group and the shorter-term AKI group.

Absolute events of coronary artery intervention within the study population were small, but there was a significantly higher rate of interventions within the de-novo kidney injury group compared with the no injury group on initial analysis. However, the adjusted analysis revealed that kidney injury in-ICU was not a statistically significant factor for receiving future coronary artery interventions. Similarly, progression to AKD was not found to be a statistically significant factor for future intervention.

Rates of cerebrovascular events were also found to be small during the follow-up period, and no significant difference in events was observed on either unadjusted or adjusted analyses between the de-novo injury group and the no injury group. However, on subgroup analysis of the de-novo injury group, multiple sensitivity analyses revealed that progression to AKD was significantly associated with rates of future cerebrovascular events. This association may be due to the small number of events, but it highlights a potentially important

relationship between a prolonged kidney injury and possible underlying dysfunction to the endothelium and vasculature.

7.1.4 The effect of oliguria during kidney injury on short- and long-term outcomes

Development of oliguria during de-novo kidney injury was more commonly seen in older patients, patients admitted from medical specialties, patients with a lower baseline eGFR and patients admitted because of sepsis. Significantly higher rates of KRT and multi-organ support were observed in the oliguric group, and this may be contributing to more severe underlying acute illness or a marker of more severe illness. Moreover, rates of KDIGO stage 3 injury and progression to AKD were also significantly higher in the oliguric injury group. Crude in-ICU and in-hospital mortality rates were observed to be significantly higher in the oliguric injury group when compared to patients with non-oliguric kidney injury. Again, this is likely a marker that development of oliguria is indicative of greater underlying illness than non-oliguric injury.

Long-term survival was compared between the two groups, and the effect of oliguric injury on short-term mortality was observed over the longer-term when rates of mortality at 18 months were compared: this was the case for both univariable and multivariable analyses. Furthermore, the risk of MAKEs occurring following discharge from hospital was not significantly influenced by the presence of oliguria during initial kidney injury whilst admitted to ICU. This suggests that presence of oliguria may cause significant underlying pathological changes in the kidneys which expose patients to increased risk of death. However, this increased risk was not represented in future progression to CKD.

Point vs persisting oliguria was assessed for characteristics and the above outcomes: patients who went on to develop a persisting injury were more likely to have lower baseline eGFR, but less likely to have underlying cardiovascular or liver disease. This is very unusual but is likely to be due to a mortality effect, with comorbid patients likely to die quickly after the development of oliguria rather than progressing to persisting oliguria. No significant differences in either short- or long-term outcomes were found between the point and persisting oliguria groups. The data from this study would suggest that presence of oliguria

confers a significantly increased risk of in-hospital mortality regardless of whether the oliguria persists beyond 24 hours or not.

7.2 Reflection on the strengths and weaknesses of this thesis

The work towards this thesis has been conducted on a sizable patient population across two hospitals which serve a large population of over one million patients, including one of the most deprived and comorbid regions in the entire country. The 5,312 patients included in this study represent every patient admitted to these two large teaching hospitals over a three-year period and are therefore very representative of the critically unwell population in the West of Scotland in recent times. However, given the study population is comprised from a single region of the country, the generalisability of the reported results must be interpreted with caution.

As data were retrieved and merged from a multitude of different sources, the created dataset contained information which was not readily available prior to the beginning of this work. This enabled the detailed quantification of baseline kidney function for every individual patient utilising validated methodology. Considering that previous studies have often estimated individual patient's serum creatinine and eGFR using a standardised formula, the ability to calculate individualised baseline eGFR for every patient to subsequently apply Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (16) for the diagnosis of kidney injury is a key strength of this study. Still, it should be recognised that due to limitations relating to potential inaccuracies in the collection of hourly urine output values, diagnosis of AKI using urine output as recommended by KDIGO was not considered feasible. As such, this study may have under-represented the incidence of kidney injury within the ICU.

As a result of access to data routinely collected in primary care, long-term outcomes including survival, adverse kidney events and secondary cardiovascular events could be recorded up to four and a half years following discharge from hospital. This work also makes use of clinicians with specialist knowledge in the relevant fields to interpret the results as accurately as possible and determine where events have occurred.

Most prior work has not examined outcomes for such a long period following hospital discharge, and the availability of prolonged follow-up data allowed this study to quantify if events occurring acutely in the context of critical illness carried additional risk for several years following discharge. Whilst this was a significant strength of this study, it must be recognised that certain analyses were unable to make full use of the data available. Certain analyses failed the necessary assumptions required for Cox proportional hazards modelling, and instead multivariable logistic regression was used at a fixed time point during the follow up period. It was considered more accurate to do this at a point which there was available follow-up data for all patients; the alternative was to make the assumption that the outcome of interest did not occur in certain patients for up to three years after their follow-up period ended. With no strong evidence to prove this was the case, it was felt that this was the less appropriate method to use. However, this resulted in a significant loss of data relating to events after the period chosen for these specific analyses which in turn may have altered the interpretation of results.

An additional data source allowed for data on pre-existing comorbidities to be gathered. This improved the validity of the interpretation of the results, as multiple significant underlying disease processes such as cardiovascular disease and diabetes mellitus which have a recognised association with mortality and adverse kidney events could be corrected for. Whilst this was a strength of this study, a limitation was the lack of correction for acute illness severity. Acute Physiology and Chronic Health Evaluation (APACHE) II score was not used as age is incorporated in the calculation and it was thought to introduce a collinear effect. Receipt of organ support was not used as this involves a degree of clinician discretion which was deemed to introduce bias against patients who the treating physician felt institution of such therapy was not in the best interests of the patient. This meant that a potential confounding effect caused by increased illness severity was not accounted for in the adjusted analyses.

A significant strength of this study is that it details the demographics and outcomes of AKD patients: this represents a very new definition and to date very few studies have described this cohort of patients before. Furthermore, any studies which have reported on outcomes on patients with AKD have specifically

looked at outcomes within 12 months as opposed to the significantly longer follow-up period utilised in this work. Despite this, limitations exist regarding the ability to diagnose patients with AKD. There is no universally accepted definition for recovery following kidney injury. The definition most widely used in the literature references recovery as being the point at which a patient no longer meets AKI criteria; and thus was selected as the most appropriate for this study. Additionally, falls in serum creatinine observed in critically unwell patients can occur because of other factors such as reduction in lean body mass commonly seen in ICU or due to initiation of KRT. The effect of KRT was accounted for by discounting creatinine values within 24 hours of discontinuing the therapy, but residual effects of KRT artificially lowering serum creatinine may have persisted beyond this point. Finally, only length of the first injury for each patient was registered: this may mean an initial recovery followed by a prolonged relapse was missed, thus under-representing the number of patients with AKD by categorising them as shorter-term AKI based on the initial recovery.

As with any study which involves collection and merging of large volumes of data, this work was limited by missing data. Data on missing baseline kidney function rendered it impossible to detect de-novo kidney injury during ICU admission. That said, this was only the case for 22 patients and therefore involved minimal data loss. In a similar vein, patients who originated from outside the health boards where long-term data was available could not be included in long-term analyses: again, this represented only 10 patients and therefore minimal data was lost. Lastly, there was a large amount of missing data for APACHE II scores, but considering this variable was not used in any adjusted analyses, it did not have a significant effect on the conclusions drawn during this thesis.

7.3 Considerations for future work and clinical practice

This thesis has detailed the significant influence that a diagnosis of kidney injury and AKD during ICU admission can have on both short- and long-term patient-centred outcomes. However, there are a number of questions which require further research.

AKD represents a new area for research which currently has a very small evidence base on which conclusions can be drawn. The increased rates of mortality in-hospital are likely due to consequences of the acute illness and are unlikely to offer opportunities for intervention beyond current practice and therapy. Conversely, the significantly increased rates of adverse kidney events and cerebrovascular events over the total follow-up period are likely to offer more scope for intervention. Regardless, further work should be conducted to determine if this association is maintained with a greater number of events, as the number identified during this study was very small. One possible solution would be to carry out further data collection at a later point to ensure that all patients had a minimum follow-up time at 3-5 years. Alternatively, re-analysis using a time-varying Cox proportional hazards model may allow for further interpretation of events occurring over differing length of follow-up in analyses which failed the proportionality assumption.

The study population selected for this study was confined to one region of a single country, and as such was limited in its generalisability. Future work could make use of the national Wardwatcher database utilised in this study and the generation of the Scottish Renal Registry to analyse a similar cohort of patients on a national basis. This thesis has provided a significant body of evidence which highlights that kidney injury whilst admitted to ICU has significant long-term effects on patients' health. This data could provide sufficient justification for future funding to aid implementation of data-linkage between these two databases and examine more patient centred outcomes; in addition, it may be possible to further this data linkage to include population data from NHS Research Scotland national data repository *Safe Haven*. Whilst this would still include a study population from a single country, it would be more representative of a general ICU population not selected from an area containing a high proportion of deprivation. This larger study population could be implemented in an interventional randomised controlled trial (RCT) looking at different treatment options to improve outcomes in AKD survivors.

This study also helped to identify features independently associated with progression to AKD in a cohort of patients with kidney injury during ICU admission. Given these features were stratified by how much they influenced

odds of progression to AKD, it is possible that a risk calculator could be constructed to stratify the change of developing AKD. Beyond this, recognition of AKD at an early stage during ICU admission could be considered analogous with identifying patients at higher risk of long-term adverse kidney events. This may represent a good opportunity to refer these high-risk patients to nephrology experts in order to receive high quality follow up care and prevent progression to adverse events.

Whilst patients who progress to AKD may signify a higher risk group based on the data from this study, the significant overlap found between stage 3 injury, requirement for kidney replacement therapy (KRT), progression to AKD and development of oliguria may in fact demonstrate that there is too much interplay between these various factors to simply limit risk stratification to length of injury. Given that some of these factors are involved in the classification of others, and that AKD itself remains a relatively new definition, it is likely that the concept of AKD as a whole warrants further refinement to ensure its validity as a marker of increased risk for progression to long-term adverse outcomes.

Routine follow up of ICU patients occurs in clinics across the West of Scotland to aid in long-term recovery following discharge from hospital. These clinics may represent an opportunity to carry out future prospective work on patients with AKD; routine blood samples and urinalysis for persistently raised serum creatinine, cystatin C levels or microalbuminuria could help further risk stratify patients susceptible to future events and flag individuals who would most benefit from expert follow up by nephrology specialists.

The significantly increased burden of disease which this work has highlighted may help act as an impetus for improved follow up care following ICU. Whilst this is an exceptionally broad subject which encompasses a wide range of illnesses, simple measures such as ensuring early reinstitution of chronic medications which have been withheld during acute illness to prevent acceleration of chronic disease processes may have a significant effect. Further efforts may be focussed on improved communication with primary care physicians that a patient has suffered a kidney injury during admission; these may flag patients who would benefit from guidelines produced by the Royal

College of General Practitioners on care of patients following kidney injury. Finally, institution of novel agents with a burgeoning evidence base for preventing progression of kidney disease such as SGLT2 inhibitors could be considered in prospective trials looking at slowing the progression of kidney disease in this high-risk population. Although further work may be required to identify the ideal interventions for these patients following ICU discharge, this study has shown that it is a vital area for further research as we seek to improve patient outcomes and global health following AKI, critical illness and the significant overlap that occurs between these two important phenomena.

Chapter 8 Appendices

Appendix A: Ethical approval, R&D approval and non-substantial amendment approval

NHS
Health Research Authority

London - Surrey Research Ethics Committee
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 1048058

26 November 2018 (Revised 27 November 2018)

Dr Mark Andonovic
University of Glasgow Clinical Academic Department
Level 2, New Lister Building, Glasgow Royal Infirmary
8-16 Alexandra Parade, Glasgow
G31 2ER

Dear Dr Andonovic

Study title:	**An analysis of outcomes for patients with Acute Kidney Injury in Intensive Care**
REC reference:	**18/LO/2060**
Protocol number:	**1**
IRAS project ID:	**254148**

The Proportionate Review Sub-committee of the London - Surrey Research Ethics Committee reviewed the above application on 20 November 2018.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of Glasgow Trials Letter]	1	06 August 2018
IRAS Application Form [IRAS_Form_02112018]		02 November 2018
Research protocol or project proposal [Research Protocol]	7	30 October 2018
Summary CV for Chief Investigator (CI) [M. Andonovic CV]	1	28 September 2018
Summary CV for student [M. Andonovic CV]	1	28 September 2018
Summary CV for supervisor (student research) [K. Puxty CV]	1	02 October 2018
Summary CV for supervisor (student research) [P. Mark CV]	1	27 September 2018

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

18/LO/2060	**Please quote this number on all correspondence**

Yours sincerely

Pp

Mrs Chrissie Lawson
Chair

Email: nrescommittee.secoast-surrey@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Emma Jane Gault*

Figure 8.1: Research and ethics committee ethical approval letter

Senior Research Administrator: Kayleigh McKenna
Telephone Number: 0141 232 1826
E-Mail: Kayleigh.McKenna@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

Clinical Research & Development
West Glasgow ACH
Dalnair Street
Glasgow G3 8SJ
Scotland, UK

27/11/2018

Dr Mark Andonovic
University of Glasgow Clinical Academic Department
Level 2, New Lister Building,
Glasgow Royal Infirmary
8-16 Alexandra Parade,
Glasgow
G31 2ER

NHS GG&C Board Approval

Dear Dr Andonovic,

Study Title:	An analysis of outcomes for patients with Acute Kidney Injury in Intensive Care
Principal Investigator:	Dr Mark Andonovic
GG&C HB site	Glasgow Royal Infirmary and Queen Elizabeth University Hospital
Sponsor	NHS Greater Glasgow & Clyde
R&D reference:	GN18RE531
REC reference:	18/LO/2060
Protocol no: (including version and date)	V7.0 30/10/2018

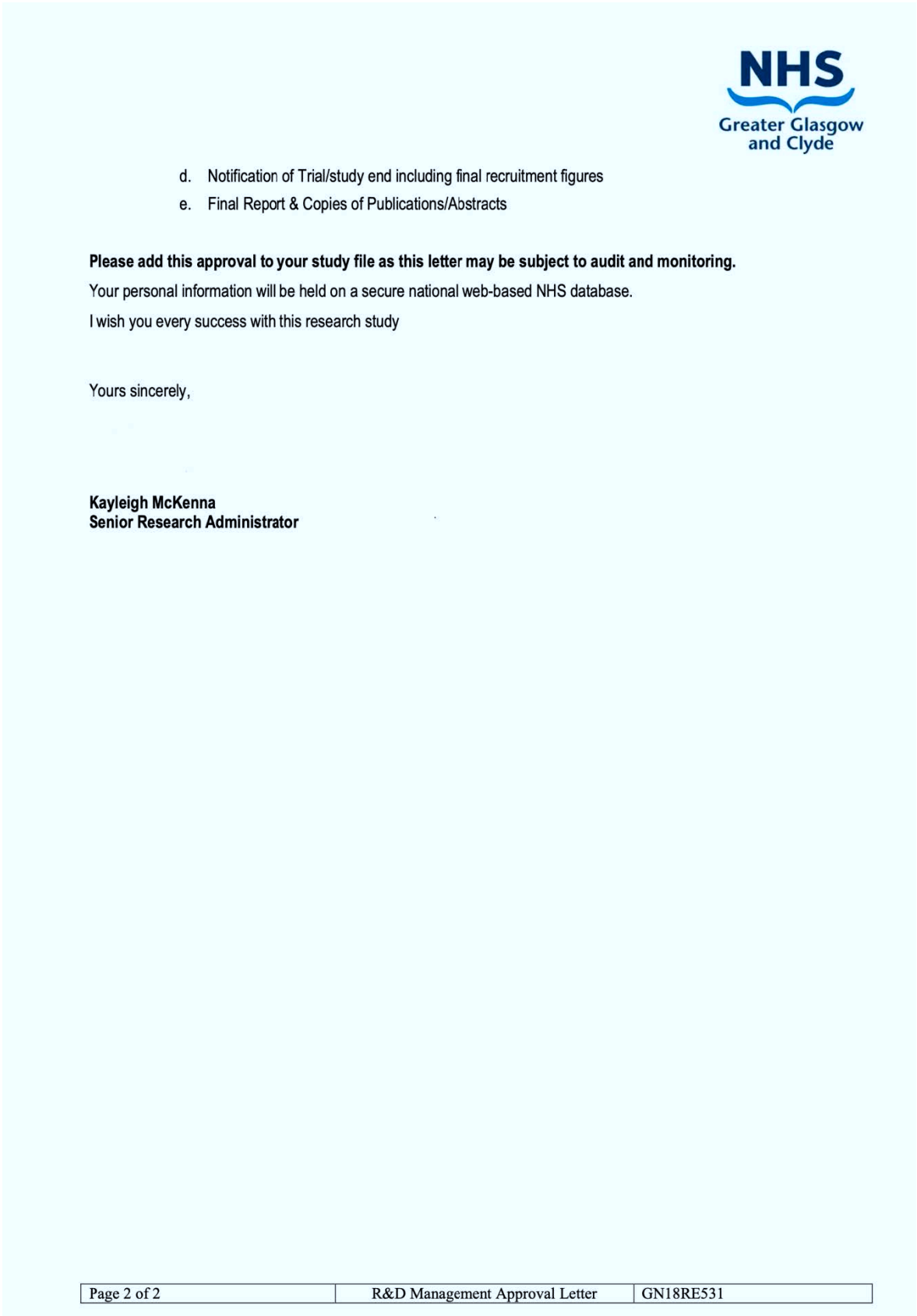
I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a quarterly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial



NHS
Greater Glasgow and Clyde

d. Notification of Trial/study end including final recruitment figures
e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

Kayleigh McKenna
Senior Research Administrator

Page 2 of 2	R&D Management Approval Letter	GN18RE531

Figure 8.2: Research and development department approval letter

Dear Mark,

R&D Ref: GN18RE531 **Ethics Ref**: 18/LO/2060
Investigator and site(s): Dr Mark Andonovic - Queen Elizabeth University Hospital and Glasgow Royal Infirmary
Project Title: An analysis of outcomes for patients with Acute Kidney Injury in Intensive Care
Protocol Number: Version 9.0, 16/03/2020
Amendment: Non-substantial Amendment 1 (17.03.20)
Sponsor: NHS Greater Glasgow & Clyde

I am pleased to inform you that R&D have reviewed the above study's Non-Substantial Amendment 1 and can confirm that Management Approval is still valid for this study.

I wish you every success with this research project.

Yours sincerely,

NHS GG&C R&D
Ward 11 Dykebar Hospital
Grahamston Road
Paisley PA2 7DE

Figure 8.3: Non-substantial amendment approval

Appendix B: Definition of specialty type and diagnostic groupings

Admitting specialty	Specialty type
Cardiology	Medical
Chronic pain	Medical
Dermatology	Medical
Endocrinology	Medical
Gastroenterology	Medical
General medicine	Medical
Geriatric medicine	Medical
Gynaecology	Medical
Haematology	Medical
Infectious diseases	Medical
Neurology	Medical
Oncology	Medical
Psychiatry	Medical
Renal medicine	Medical
Respiratory medicine	Medical
Rheumatology	Medical
Stroke medicine	Medical
Burns surgery	Surgical
Cardiac surgery	Surgical
Cardiothoracic surgery	Surgical
ENT	Surgical
General surgery	Surgical
Maxillo-facial surgery	Surgical
Neurosurgery	Surgical
Obstetrics	Surgical
Orthopaedic surgery	Surgical
Plastic surgery	Surgical
Spinal injuries	Surgical
Transplant surgery	Surgical
Urology	Surgical
Vascular surgery	Surgical

Table 8.1: Admitting specialty dichotomised into medical and surgical types

SICS Diagnosis	Diagnostic Group
Burns	Burns
Smoke inhalation	Burns
Cardiac Arrest (In hospital)	Cardiac Arrest
Cardiac Arrest (Out of hospital)	Cardiac Arrest
Cardiac failure	Cardiac Failure
Cardiogenic shock	Cardiac Failure
Poor left ventricular function	Cardiac Failure
Right ventricular failure	Cardiac Failure
Aortic stenosis	Cardiac (Other)
Atrial fibrillation	Cardiac (Other)
Cardiomyopathy	Cardiac (Other)
Essential hypertension	Cardiac (Other)
Existing prosthetic valve	Cardiac (Other)
Fluid overload	Cardiac (Other)
Heart block	Cardiac (Other)
Mitral stenosis	Cardiac (Other)
Other arrhythmia	Cardiac (Other)
Other cardiac disease	Cardiac (Other)
Other shock	Cardiac (Other)
Secondary hypertension	Cardiac (Other)
Supraventricular tachycardia	Cardiac (Other)
Ventricular tachycardia	Cardiac (Other)
Adverse reaction to therapeutic drug	Drug Related
Alcohol abuse/dependence	Drug Related
Drug abuse/dependence	Drug Related
Drug overdose/misuse	Drug Related
Drug toxicity	Drug Related
Other drug related problem	Drug Related
Self-poisoning	Drug Related
Toxicity of therapeutic drug	Drug Related
Diabetes mellitus (co-existing)	Endocrine/Metabolic
Diabetic ketoacidosis	Endocrine/Metabolic
Disorders of metabolism (other)	Endocrine/Metabolic
Goitre	Endocrine/Metabolic
Hyperthyroidism	Endocrine/Metabolic
Hypoadrenalism	Endocrine/Metabolic
Hypoglycaemia	Endocrine/Metabolic
Hypothermia	Endocrine/Metabolic
Metabolic coma	Endocrine/Metabolic
Non-ketotic diabetic coma	Endocrine/Metabolic
Obesity	Endocrine/Metabolic
Other endocrine disorder	Endocrine/Metabolic
Other metabolic disorder	Endocrine/Metabolic

Acute appendicitis with perforation	Gastrointestinal Perforation
Anastamotic leak	Gastrointestinal Perforation
Diverticular disease with perforation	Gastrointestinal Perforation
Duodenal ulcer (perforated)	Gastrointestinal Perforation
Gastric ulcer (perforated)	Gastrointestinal Perforation
Lower GI perforation	Gastrointestinal Perforation
Oesophageal perforation	Gastrointestinal Perforation
Other upper GI perforation	Gastrointestinal Perforation
Perforated duodenal ulcer	Gastrointestinal Perforation
Perforated gall bladder	Gastrointestinal Perforation
Perforated gastric ulcer	Gastrointestinal Perforation
Acute appendicitis without perforation	Gastrointestinal (Other)
Crohn's disease	Gastrointestinal (Other)
Diverticular disease without perforation	Gastrointestinal (Other)
GI fistula	Gastrointestinal (Other)
GI obstruction (adhesions)	Gastrointestinal (Other)
GI obstruction (any hernia)	Gastrointestinal (Other)
GI obstruction (ileus)	Gastrointestinal (Other)
GI obstruction (other)	Gastrointestinal (Other)
GI obstruction (volvulus)	Gastrointestinal (Other)
Hernia (hiatus or diaphragmatic)	Gastrointestinal (Other)
Hernia (incisional)	Gastrointestinal (Other)
Hernia (inguinal, umbilical, or femoral)	Gastrointestinal (Other)
Large bowel ischaemia/infarction	Gastrointestinal (Other)
Other intestinal disease	Gastrointestinal (Other)
Other retroperitoneal pathology	Gastrointestinal (Other)
Small bowel ischaemia/infarction	Gastrointestinal (Other)
Splenectomy	Gastrointestinal (Other)
Ulcerative colitis	Gastrointestinal (Other)
Anaemia	Haematology/Coagulation
Other acquired coagulation disorder	Haematology/Coagulation
Other coagulation disorder	Haematology/Coagulation
Other haematological disorder	Haematology/Coagulation
Systemic embolism	Haematology/Coagulation
Thrombotic disorders	Haematology/Coagulation
Venous thrombosis (including DVT)	Haematology/Coagulation
Antepartum haemorrhage - Other	Haemorrhage
Antepartum haemorrhage - placenta praevia	Haemorrhage
Duodenal ulcer (bleeding)	Haemorrhage
Gynaecological bleeding	Haemorrhage
Haemorrhage from duodenal ulcer	Haemorrhage
Haemorrhage from gastric erosion / stress ulceration	Haemorrhage
Haemorrhage from gastric ulcer	Haemorrhage
Haemothorax	Haemorrhage

Hypovolaemic/haemorrhagic shock	Haemorrhage
Lower GI haemorrhage	Haemorrhage
Massive blood loss/transfusion without shock	Haemorrhage
Massive blood transfusion	Haemorrhage
Oesophageal variceal haemorrhage	Haemorrhage
Other/unspecified upper GI haemorrhage	Haemorrhage
Peripartum haemorrhage	Haemorrhage
Postpartum haemorrhage	Haemorrhage
Postpartum haemorrhage - atonic uterus	Haemorrhage
Pulmonary haemorrhage	Haemorrhage
Retroperitoneal haematoma/collection/abscess	Haemorrhage
Upper airway haemorrhage	Haemorrhage
Acalculous cholecystitis	Hepatobiliary
Acute cholecystitis	Hepatobiliary
Acute pancreatitis	Hepatobiliary
Biliary obstruction	Hepatobiliary
Cholangitis	Hepatobiliary
Chronic pancreatitis	Hepatobiliary
Non acute gallstone disease	Hepatobiliary
Other gall bladder or bile duct disorder	Hepatobiliary
Other pancreatic disorder	Hepatobiliary
Pancreatic pseudocyst	Hepatobiliary
Primary biliary cirrhosis	Hepatobiliary
Anaphylactic shock	Hypersensitivity/Immune
Anaphylaxis	Hypersensitivity/Immune
Bone marrow transplant	Hypersensitivity/Immune
Immunocompromised (by disease)	Hypersensitivity/Immune
Immunocompromised (by treatment)	Hypersensitivity/Immune
Acute MI	Ischaemic Heart Disease
Acute myocardial ischaemia	Ischaemic Heart Disease
Chronic ischaemic heart disease	Ischaemic Heart Disease
Other ischaemic heart disease	Ischaemic Heart Disease
Acute on chronic kidney injury	Kidney
Acute Tubular Necrosis (ATN)	Kidney
AKI (cause unknown)	Kidney
AKI (circulatory failure)	Kidney
AKI (nephro-toxic agent)	Kidney
AKI (rhabdomyolysis)	Kidney
AKI (sepsis)	Kidney
AKI or rejection in renal transplant	Kidney
Chronic kidney disease (dialysis-dependent)	Kidney
Chronic kidney disease (NOT dialysis-dependent)	Kidney
Functioning renal transplant	Kidney
Glomerulonephritis	Kidney

Obstructive renal failure	Kidney
Other acute kidney injury	Kidney
Other genito-urinary tract disorder	Kidney
Other renal disease	Kidney
Renal/ureteric calculi	Kidney
Acute on chronic hepatic failure (cause unknown)	Liver Disease
Alcoholic liver disease	Liver Disease
Fulminant hepatic failure (other)	Liver Disease
Fulminant hepatic failure (paracetamol induced)	Liver Disease
Hepatitis (other)	Liver Disease
Hepato-renal failure	Liver Disease
Other hepatic disease	Liver Disease
Acute leukaemia	Malignancy
Bladder tumour	Malignancy
Bone tumour	Malignancy
Breast cancer	Malignancy
Carcinoma (bronchus/lung)	Malignancy
Disseminated malignancy	Malignancy
Facial tumour	Malignancy
Gastric carcinoma	Malignancy
GI obstruction (tumour)	Malignancy
Hepato-biliary malignancy	Malignancy
Kidney tumour	Malignancy
Large bowel malignancy	Malignancy
Large/small bowel malignancy	Malignancy
Non-Hodgkin's lymphoma	Malignancy
Oesophageal carcinoma	Malignancy
Oral carcinoma	Malignancy
Other GI malignancy	Malignancy
Other haematological malignancy	Malignancy
Other genito-urinary tract tumour	Malignancy
Ovarian carcinoma	Malignancy
Pancreatic carcinoma	Malignancy
Pancreatic tumour	Malignancy
Primary brain tumour	Malignancy
Prostate tumour	Malignancy
Secondary brain tumour	Malignancy
Skin tumour	Malignancy
Small bowel malignancy	Malignancy
Soft tissue tumour (not skin or breast)	Malignancy
Teratoma	Malignancy
Upper airway carcinoma	Malignancy
Upper airway/oral carcinoma	Malignancy
Uterine/cervical carcinoma	Malignancy

Acute change in mental state	Miscellaneous
Admission for plastic surgery	Miscellaneous
Admitted for tertiary care	Miscellaneous
Epidural care	Miscellaneous
Hanging	Miscellaneous
Non specific abdominal pain	Miscellaneous
Other diagnosis	Miscellaneous
Pain control	Miscellaneous
Palliative care	Miscellaneous
Pre-operative optimisation (includes chronic pathology)	Miscellaneous
Self-inflicted injury	Miscellaneous
Arthritis	Musculoskeletal
Other bone disease	Musculoskeletal
Other chronic physical disorder	Musculoskeletal
Other muscular disorder	Musculoskeletal
Other skin disorder	Musculoskeletal
Pathological fracture	Musculoskeletal
Rhabdomyolysis	Musculoskeletal
Cerebral infarction	Neurological
CNS inflammation	Neurological
Coma (other)	Neurological
Coma (Unknown cause)	Neurological
Diffuse brain injury	Neurological
Diffuse head injury	Neurological
Encephalitis	Neurological
Extradural haematoma	Neurological
Guillain Barre syndrome	Neurological
Hepatic encephalopathy	Neurological
Hypoxic brain damage	Neurological
Intracerebral haemorrhage	Neurological
Other CNS disorder	Neurological
Other neurological vascular disorder	Neurological
Other peripheral nervous system disorder	Neurological
Peripheral nerve injury	Neurological
Quadriplegia (new)	Neurological
Respiratory failure due to neuromuscular disease	Neurological
Subarachnoid haemorrhage (aneurysm)	Neurological
Subarachnoid haemorrhage (other)	Neurological
Subdural haematoma	Neurological
Eclampsia	Obstetrics/Gynaecology
Ectopic pregnancy	Obstetrics/Gynaecology
Hysterectomy	Obstetrics/Gynaecology
Other gynaecological problem	Obstetrics/Gynaecology
Other obstetric problem	Obstetrics/Gynaecology

Ovarian cyst	Obstetrics/Gynaecology
Pre-eclampsia	Obstetrics/Gynaecology
Extended recovery from anaesthesia	Post-operative Complication
Other anaesthetic complication	Post-operative Complication
Post-op respiratory failure	Post-operative Complication
Prolonged surgery	Post-operative Complication
Surgical complication	Post-operative Complication
Acute lung injury	Respiratory/Airway
ARDS	Respiratory/Airway
Asthma (acute)	Respiratory/Airway
Asthma (co-existing)	Respiratory/Airway
Chronic respiratory disease (Restrictive/chest wall/spine)	Respiratory/Airway
COPD-acute exacerbation	Respiratory/Airway
COPD/emphysema (co-existing)	Respiratory/Airway
Other chronic respiratory disease	Respiratory/Airway
Other pulmonary oedema	Respiratory/Airway
Other pulmonary vascular disorder	Respiratory/Airway
Other respiratory disease	Respiratory/Airway
Other upper airway problem	Respiratory/Airway
Pleural effusion	Respiratory/Airway
Pneumothorax	Respiratory/Airway
Pneumothorax (non-traumatic)	Respiratory/Airway
Pulmonary embolism	Respiratory/Airway
Pulmonary fibrosis / alveolitis	Respiratory/Airway
Pulmonary thromboembolism	Respiratory/Airway
Respiratory arrest	Respiratory/Airway
Sleep apnoea	Respiratory/Airway
Sputum retention	Respiratory/Airway
Upper airway obstruction	Respiratory/Airway
Weaning from ventilator	Respiratory/Airway
Epileptic (controlled)	Seizures
Post ictal	Seizures
Seizures (not Status)	Seizures
Status epilepticus	Seizures
Bacteraemia/septicaemia	Sepsis/Infection
Cellulitis	Sepsis/Infection
Chest infection-Aspiration	Sepsis/Infection
Chest infection-Atypical	Sepsis/Infection
Chest infection-Bacterial	Sepsis/Infection
Chest infection-Clinical (culture negative)	Sepsis/Infection
Chest infection-Fungal	Sepsis/Infection
Chest infection-PCP	Sepsis/Infection
Chest infection-TB	Sepsis/Infection

Chest infection-Viral	Sepsis/Infection
Clostridium Difficile	Sepsis/Infection
Empyema	Sepsis/Infection
Empyema of gall bladder	Sepsis/Infection
Epiglottitis	Sepsis/Infection
Gastro-enteritis	Sepsis/Infection
Hepatic abscess	Sepsis/Infection
Infected retained products of conception	Sepsis/Infection
Infective endocarditis	Sepsis/Infection
Intra-amniotic infection	Sepsis/Infection
Joint infection (including prosthesis)	Sepsis/Infection
Lung abscess	Sepsis/Infection
Meningitis	Sepsis/Infection
Meningococcal infection	Sepsis/Infection
Multiple abscess formation	Sepsis/Infection
Necrotising fasciitis	Sepsis/Infection
Osteomyelitis	Sepsis/Infection
Other chest infection	Sepsis/Infection
Other CNS infection	Sepsis/Infection
Other GI infection	Sepsis/Infection
Other infection	Sepsis/Infection
Pelvic infection or abscess	Sepsis/Infection
Pelvic sepsis	Sepsis/Infection
Perioral abscess	Sepsis/Infection
Peritonitis/abscess (no source identified)	Sepsis/Infection
Septic shock (GI tract)	Sepsis/Infection
Septic shock (renal tract)	Sepsis/Infection
Septic shock (respiratory)	Sepsis/Infection
Septic shock (source not specified)	Sepsis/Infection
Spinal abscess	Sepsis/Infection
Superficial abscess	Sepsis/Infection
Systemic fungal infection	Sepsis/Infection
Urinary tract infection	Sepsis/Infection
Wound infection	Sepsis/Infection
Blunt trauma with brain injury	Trauma
Blunt trauma without brain injury	Trauma
Bowel trauma	Trauma
Cardiac/pericardial trauma	Trauma
Cervical spine injury (minus cord damage)	Trauma
Cervical spine injury (plus cord damage)	Trauma
Facial fracture	Trauma
Fractured neck of femur	Trauma
Fractured ribs/sternum	Trauma
Haemothorax (traumatic)	Trauma

Intracerebral contusions/haematoma	Trauma
Kidney/ureteric trauma	Trauma
Large soft tissue injury	Trauma
Liver trauma	Trauma
Lower limb trauma	Trauma
Mediastinal trauma	Trauma
Mesenteric/bowel trauma	Trauma
Other abdominal trauma	Trauma
Other chest/airway trauma	Trauma
Other head trauma	Trauma
Other maxillo-facial trauma	Trauma
Other multiple trauma	Trauma
Other orthopaedic trauma	Trauma
Other soft tissue trauma	Trauma
Other spinal trauma	Trauma
Other trauma	Trauma
Other traumatic brain injury	Trauma
Pelvic trauma	Trauma
Penetrating trauma with brain injury	Trauma
Penetrating trauma without brain injury	Trauma
Pneumothorax (traumatic)	Trauma
Pulmonary contusion	Trauma
Skull fracture	Trauma
Splenic trauma	Trauma
Thoracic/lumbar injury (minus cord damage)	Trauma
Thoracic/lumbar injury (plus cord damage)	Trauma
Upper airway trauma	Trauma
Upper limb trauma	Trauma
Abdominal aortic aneurysm-NOT ruptured/leaking	Vascular
Abdominal aortic aneurysm-ruptured/leaking	Vascular
Aortic dissection	Vascular
Arterial aneurysm-other	Vascular
Carotid artery stenosis	Vascular
Occlusive aortic disease	Vascular
Other vascular disease	Vascular
Peripheral ischaemia	Vascular
Peripheral vascular disease (other than aorta)	Vascular
Thoracic aortic aneurysm	Vascular

Table 8.2: SICS diagnosis and corresponding diagnostic group

Appendix C: Additional code used in defining and classifying AKI

```
# Applying first two baseline to create first rule #

Pauline <- Timothy %>%

  mutate(Baseline_Absent=is.na(`Median Creatinine 1 week to year BEFORE admisison`)) %>%

  mutate(Rule1=if_else(Baseline_Absent == "FALSE", `Median Creatinine 1 week to year BEFORE admisison`,

                       `LOWEST Creat one week up til days of admission to ICU`))

# Creating second rule #

Viki <- Pauline %>%

  mutate(Rule2 = `LOWEST Creat  TWO days up til days of admission to ICU`)

# Separating Yes and nos into date format #

# Identifying first and last yes date #

Jimmy <- Viki %>%

  mutate(`Date admitted to this Unit` = ymd(`Date admitted to this Unit`),

         set_seq = map(str_split(string = `Acute renal replacement therapy`, pattern = ","),~seq_len(length(.x)+1) - 1),

         dates = map2(`Date admitted to this Unit`, set_seq, ~.x + .y),

         last_yes_date = map2(`Acute renal replacement therapy`, dates,

                              ~.y[dplyr::last(which(str_trim(unlist(str_split(string = .x, pattern = "","))) == "Yes"))]),
```

```
      first_yes_date = map2(`Acute renal replacement therapy`, dates,

                            ~.y[dplyr::first(which(str_trim(unlist(str_split(string = .x,
pattern = ","))) == "Yes"))])) %>%

  unnest(c(last_yes_date,first_yes_date))

# Categorise pre-existing ERF #

John <- Jimmy %>%

  mutate(Outcome1 = if_else(`Type RRT for ERF BEFORE Study first admission to
ITU` != 'NA',

                            "Pre-existing_ERF", "0"))

# Determine if creatinine is valid #

# Determine if creatinine is taken after last RRT date or if never on RRT #

Chris <- John %>%

  group_by(`Unique NUmber`) %>%

  mutate(Non_RRT_Creat = if_else

      (`date_creat_from_AdmissionDate_to_31/03/2020`>(last_yes_date +
days(1)) |

          `date_creat_from_AdmissionDate_to_31/03/2020`<first_yes_date, 1,
0)) %>%

  mutate(Creat_Absent=is.na(Non_RRT_Creat)) %>%

  mutate(Valid_Creat = if_else(Non_RRT_Creat == 1 |

                               Creat_Absent == TRUE, 1, 0))
```

```
# Transform rules to numeric #

# Determine if Creatinine taken during ICU stay #

# Determine if Creatinine meets KDIGO Criteria #

# Determine if Creatinine meets all 3 criteria which can be used to diagnose AKI
#

Al <- Chris %>%

  group_by(`Unique NUmber`) %>%

  mutate(Rule1=as.numeric(Rule1)) %>%

  mutate(Rule2=as.numeric(Rule2)) %>%

  mutate(`Creat_from_AdmissionDate_to_31/03/2020`=

           as.numeric(`Creat_from_AdmissionDate_to_31/03/2020`)) %>%


mutate(ICU_Creat=if_else(`date_creat_from_AdmissionDate_to_31/03/2020`>=`
Date admitted to this Unit`

         &`date_creat_from_AdmissionDate_to_31/03/2020`<=`Discharged on
(date)`, 1, 0)) %>%


mutate(AKI_KDIGO=if_else(`Creat_from_AdmissionDate_to_31/03/2020`>=Rule1*
1.5

         | `Creat_from_AdmissionDate_to_31/03/2020`>=Rule2+26.5, 1, 0)) %>%

  mutate(AKI_Yes=if_else(ICU_Creat==1 & AKI_KDIGO ==1 & Valid_Creat == 1, 1,
0))
```

```
# Set variables for CKD-EPI #

Radha <- Al %>%

  group_by(`Unique NUmber`) %>%

  mutate(Var_1=if_else(Sex=="M", 79.6, 61.9)) %>%

  mutate(Var_2=if_else(Sex=="M", -0.411, -0.329)) %>%

  mutate(Var_3=if_else(Sex=="M", 1, 1.018))

# Calculate baseline eGFR #

Kevin <- Radha %>%

  group_by(`Unique NUmber`) %>%

mutate(Baseline_eGFR=(141*min((Rule1/Var_1),1)^Var_2*max((Rule1/Var_1),1)^
-1.209*(0.993^Age)*Var_3))

# Determine if injury based off either Creatinine or RRT #

Rachel <- Kevin %>%

  group_by(`Unique NUmber`) %>%

  mutate(AKI_Diag=as.numeric(any(AKI_Yes==1))) %>%

  mutate(Injury=if_else(AKI_Diag==1

                        | `Renal support days (ACP)`>0, 1, 0))

# Determine first injury date #

# Determine if first yes date or if first injury occurred earlier #

Andy <- Rachel %>%
```

```
  group_by(`Unique NUmber`) %>%

  mutate(injury_date= if_else(AKI_Diag==1,
`date_creat_from_AdmissionDate_to_31/03/2020`,as.Date(NA_real_, origin =
"1900-01-01"))) %>%

  mutate(first_date = dplyr::first(na.omit(injury_date))) %>%

  mutate(first_date = ymd(first_date)) %>%

  mutate(first_date_absent = is.na(first_date)) %>%

  mutate(first_yes_date_absent = is.na(first_yes_date)) %>%

  mutate(first_injury_date = if_else(first_yes_date_absent == FALSE &

                                       first_date_absent == FALSE &

                                       first_yes_date<=first_date, first_yes_date,

                                     if_else(first_yes_date_absent == FALSE &

                                               first_date_absent == FALSE &

                                               first_date<first_yes_date, first_date,

                                             if_else(first_yes_date_absent == FALSE &

                                                       first_date_absent == TRUE, first_yes_date,

                                             if_else(first_yes_date_absent == TRUE &

                                                       first_date_absent == FALSE, first_date,
first_yes_date)))))

# Determine if Creatinine value can be used to diagnose recovery #
```

```
Kathryn <- Andy %>%

  group_by(`Unique NUmber`) %>%

  mutate(Valid_recovery = if_else

         (Valid_Creat ==1 &
`date_creat_from_AdmissionDate_to_31/03/2020`>first_injury_date, 1, 0))

# Determine if Creatinine has recovered to non-AKI value #

# Determine date of recovery #

Roy <- Kathryn %>%

  group_by(`Unique NUmber`) %>%

  mutate(recovery_date = if_else(Valid_recovery==1 &

                                   `Creat_from_AdmissionDate_to_31/03/2020`<Rule1*1.5
&

                                   `Creat_from_AdmissionDate_to_31/03/2020`<Rule2+26,


`date_creat_from_AdmissionDate_to_31/03/2020`,as.Date(NA_real_, origin =
"1900-01-01"))) %>%

                                 mutate(first_recovery_date =
dplyr::first(na.omit(recovery_date)))



# Determine if recovery 7 days or later to diagnose AKI or AKD #

Steve <- Roy %>%
```

```
  group_by(`Unique NUmber`) %>%
  mutate(Outcome2 = if_else(final_recovery_date >= first_injury_date + days(7),
                            "AKD", "AKI"))
# Create rule for stage 3 injury #
# Stage level of injury #
Laura <- Steve %>%
  group_by(`Unique NUmber`) %>%
  mutate(Stage_3 = if_else(`Renal support days (ACP)`>0 |
                           `Creat_from_AdmissionDate_to_31/03/2020` >= 354 |
                           `Creat_from_AdmissionDate_to_31/03/2020` >= Rule1*3, 1,
0)) %>%
  mutate(Stage_Value = if_else(Injury == 1 & Stage_3 ==1, 3,
                       if_else(Injury ==1 &
`Creat_from_AdmissionDate_to_31/03/2020` >= Rule1*2, 2,
                               if_else(Injury == 1, 1, 0)))) %>%
  mutate(Stage = max(Stage_Value))
```

Appendix D: Timing of renal replacement therapy for patients with acute kidney injury: a systematic review and meta-analysis

8.1.1 Introduction

Renal replacement therapy (RRT) is a key strategy in the treatment of severe acute kidney injury (AKI) with life threatening complications such as refractory hyperkalaemia, metabolic acidosis and volume overload unresponsive to medical therapy. Whilst RRT is accepted as an impactful treatment, its implementation remains a matter of debate. In the past, there have been studies which have compared differences between modalities of RRT such as intermittent haemodialysis vs continuous renal replacement therapy (67, 207), haemofiltration vs haemodialysis (68), or dose delivered during RRT (208).

However, in addition to this, the timing to initiate RRT for AKI remains a matter of significant debate. Many randomised controlled trials (RCTs) have been executed to determine whether "early" implementation of RRT compared to "delayed" initiation is of benefit; two previous studies (209, 210) reported evidence on the subject in 2016. Following these RCTs, which recruited a significant number of patients when compared to previous studies on this subject, several meta-analyses (69, 211, 212) were produced to evaluate how this new data added to previous knowledge. However, within these meta-analyses there was a disparity between conclusions, with reports that no difference is evident between groups (69, 212) whilst others concluded that earlier initiation of RRT conveyed a decrease in mortality (213, 214). A Cochrane review was also published following these trials, but this purposefully excluded studies of patients not admitted to ICU (215). Following all these reviews in 2016, three subsequent RCTs were published in 2018, which added further data within this area (71, 216, 217).

The aim of this chapter was to conduct a systematic review and meta-analysis on all patients suffering from AKI who required RRT. Analysis was carried out on studies comparing timing of the initiation of RRT in two groups of patients: the first group classified as "early" and the second group classified as "late",

"delayed" or "standard treatment". The studies must have reported on all-cause mortality to be included in the analysis.

8.1.2 Study question

Does the timing of initiation of renal replacement therapy for acute kidney injury have any effect on short- and long-term patient outcomes?

8.1.3 Methods

A systematic review is designed to identify, analyse and pool pre-existing information on a subject matter in order to gather all known data for a defined research question. This allows the consolidation of all available prior knowledge rather than certain studies that the authors may have been aware of prior to beginning. The practice is carried out by following a rigorous and structured protocol to allow other people to reproduce the review and arrive at the same results. The Cochrane Collaboration produces detailed information on the process and structure required to conduct a thorough systematic review and their training handbook was consulted prior to beginning this review (218). In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed in 2009 and details an evidence based structure for minimum criteria which must be included in every systematic review (219); a PRISMA checklist was utilised and is available in Appendix E.

A meta-analysis is often conducted following the completion of a systematic review. The aim of this is to incorporate the data of all the individual studies to produce a pooled estimate of the results. This design is used to attempt to increase the precision of the effect size from all the individual studies as well as increase the generalisability of the individual studies. Caution must be used when interpreting these results, as individual studies can often vary both in terms of methodology and primary aims. In addition, individual studies may be open to bias, which would in turn skew the results of the pooled data. To help interpret this, a meta-analysis produces an I^2 statistic: this gives a measure of the heterogeneity of the studies (220). Subgroup analyses should be identified prior to beginning, in order to try and help detect if any specific studies are contributing to potential increased heterogeneity.

8.1.3.1 Registration

In line with accepted guidelines for systematic reviews, this study was prospectively registered with an open-access, online register prior to analysis. The registration information can be found in PROPSERO's Register of Systematic Reviews under the ID Number: CRD42019145074.

8.1.3.2 Eligibility criteria

The inclusion criteria for studies was defined as any RCT reporting on differences between timing of RRT (early vs late, standard vs early, early vs delayed) in adult patients suffering from AKI. The studies must have reported on all-cause mortality to be included. Non-RCTs, the paediatric population and patient population without AKI were excluded. No guidelines as to defining RRT timing exist, therefore the definition of 'early' and 'late' is according to the individual studies' interpretation unless the definition of 'late' was out with that considered a 'standard' RRT initiation which resulted in two 'early' group classifications. Studies that defined the 'late' group as initiation within 12 hours of diagnosis with any stage AKI were also excluded.

8.1.3.3 Search strategy

Three databases (EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL)) were interrogated for the period January 1974 to March 2019. The search strategy was as broad as possible to capture all RCTs conducted on the subject; the only filter applied was to restrict results to English language. MEDLINE and CENTRAL searches used the following MeSH terms: (((((exp Renal Replacement Therapy) OR exp Renal Dialysis) OR exp Dialysis) OR exp Hemofiltration) OR exp Hemodiafiltration) AND (((((((((“time”) OR “timing”) OR “early”) OR “earlier”) OR “late”) OR “later”) OR “delayed”) OR “start”) OR “initiation”) AND ((exp Randomised Controlled Trials) OR exp Controlled Clinical Trial). A near identical search was used to interrogate EMBASE, but with certain terms altered to match Emtree headings. In order to identify ongoing or not published completed trials, the International Trials Registry (https://www.who.int/ictrp/en/) and the National Institutes of Health's registry (https://www.clinicaltrials.gov) were searched.

8.1.3.4 Study selection

For the initial literature search, two reviewers independently compiled a list of citations gathered from the three sources. Obvious duplicate citations were removed by databases when merging; however, if any two citations had discrepancies, they were both retained for title review. Both reviewers then independently conducted a title review and selected eligible studies for abstract review; a thorough abstract review was then conducted to select studies eligible for full text review. A concluding, full text review was then executed and any differences between the two reviewers were referred to a third reviewer to make a final decision on eligibility.

8.1.3.5 Data extraction

The papers were each initially assessed for time-period mortality reported on and then the data were recorded independently using a pre-defined form. The two independent reviewers extracted key data including the number of patients recruited, definition of "early" and "late" RRT groups and measured outcomes. After consolidation, data on the number of events and the total for both 'early' and 'late' groups were collected and outcomes in terms of mean, median, mode and interquartile ranges were extracted as reported.

8.1.3.6 Outcome measures

The selected primary outcome measures were defined as overall mortality rate and period wise mortality rates: in-ICU, in-hospital, 28-day, 60-day and 90-day mortality rates. The secondary outcomes were defined as follows: dialysis dependence at 28 days, 60 days and 90 days; recovery of renal function (return to baseline) at 90 days; adverse events; length of ICU stay; length of hospital stay; number of RRT days; number of RRT free days; number of mechanical ventilation free days;' number of vasopressor free days.

8.1.3.7 Risk of bias

Each study was assessed independently by the two reviewers for potential risk of bias using the 7 domains cited in the Cochrane Collaboration's tool (221). An inverse funnel plot was created to categorise the potential risk of publication

bias across the studies. The quality of evidence for the primary outcomes were assessed independently by the two reviewers using the GRADE tool (222).

8.1.3.8 Data synthesis

The results were expressed in terms of Risk Ratio (RR) and 95% Confidence Intervals (95% CI) for mortality and secondary outcomes. Heterogeneity between studies was determined through the I^2 statistic; a value of >40% was interpreted as a significant degree of heterogeneity. RR for each outcome was estimated using both fixed and random effects to surface high degrees of heterogeneity between studies. Statistical comparison was captured as a p-value for each analysis; a value of <0.05 was considered statistically significant. Any outcome reported in terms of continuous data was expressed in terms of pooled raw differences between the two groups medians (a negative difference favouring early RRT) and 95% CIs. This has been previously described as comparing favourably to methods which transform medians and IQR to mean and standard deviation (223). All data were analysed using the software R (R version 3.5.1, The R Foundation).

The following pre-defined sub-groups were analysed for overall mortality to assess possible sources of heterogeneity including risk of bias, RRT modality, severity of illness and patient population:

- Low risk vs high or unclear risk of bias
- Intermittent haemo-dialysis vs continuous renal replacement therapy vs mixed
- ICU only population vs mixed population
- Medical vs surgical vs mixed patients

8.1.3.9 Contributors

I was involved in reviewing all identified literature, analysing and compiling the results, as well as the production of all tables and figures. Dr Richard Shemilt

acted as second reviewer for all instances previously mentioned. Dr Kathryn Puxty acted as third reviewer when required.

8.1.4 Results

8.1.4.1 Study selection

The literature search returned a total 7008 references after duplicate removal. The PRISMA flow diagram details the number of studies included and removed at each stage of the review and can be found represented in Figure 8.4. The features of the ten studies selected for inclusion in the review are detailed in Table 8.3; the selected studies varied in size from 28 patients (224) to 488 patients (217). Of the ten studies, eight exclusively included patients admitted to intensive care.

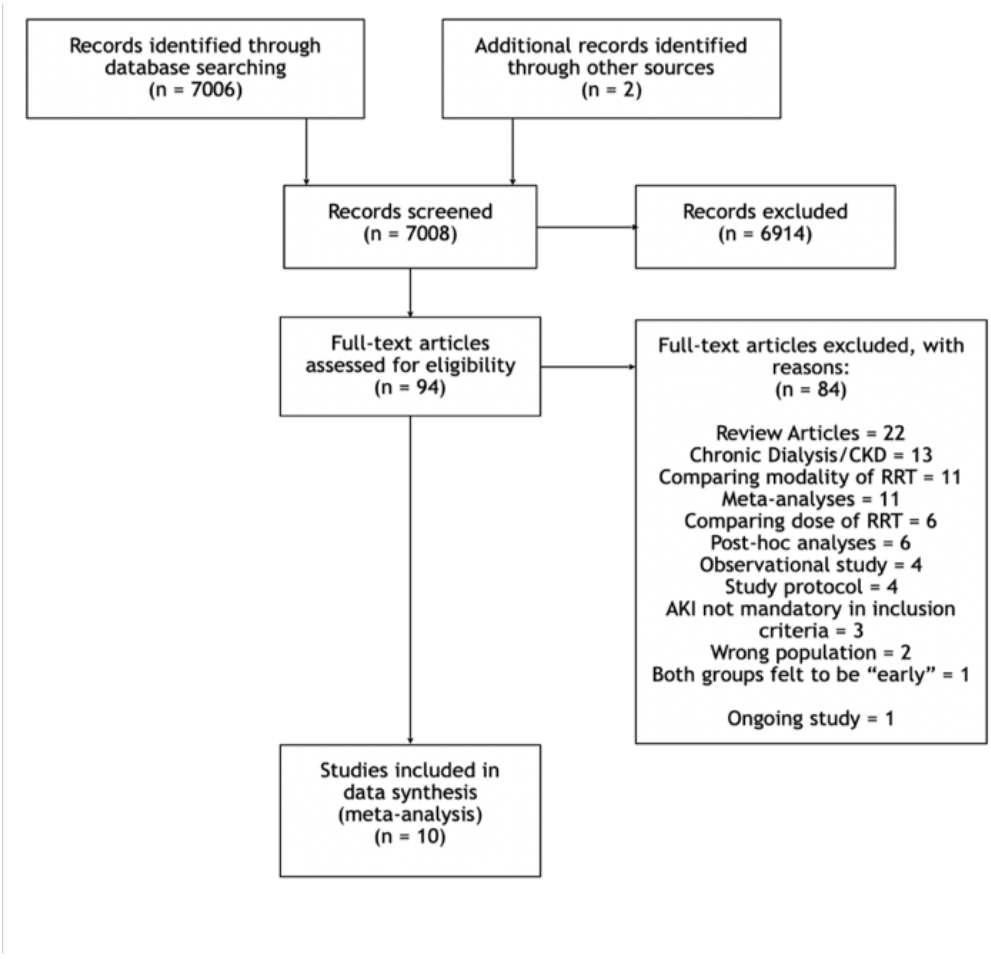


Figure 8.4: PRISMA flow diagram for studies included at each stage of review and exclusion reasons. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

Study	Setting/ Patient Group	Inclusion Criteria	Numbers	RRT Modality	Early Definition for RRT	Late Definition for RRT	Outcomes
Pursnani et al. (225) (1997)	Single centre; all inpatients ; medical only	Diagnosis of Acute Tubular Necrosis with serum creatinine <7mg% and blood Urea <120mg%	Total = 35 Early = 18 Late = 17	IHD	Early haemodialysis (as soon as met eligibility criteria)	Conservative management	Overall mortality Length of hospital stay Adverse events
Bouman et al. (226)[11] (2002)	Two centres, single country; ICU only; mixed patients	Urine output <30ml/hr for >6 hours and creatinine clearance <20ml/min	Total = 106 Early = 70 Late = 36	CRRT	RRT started within 12 hours of inclusion	Plasma Urea level >40mmol/l, potassium >6.5mmol/l or severe pulmonary oedema	ICU, hospital and 28 day mortality Recovery of renal function at 90 days Duration of ICU and hospital stay Adverse events
Sugahara et al. (224) (2004)	Single centre; ICU only; surgical only	Post CABG patients. Hourly urine output <30ml/hr and serum creatinine increased at rate of 0.5mg/dL/day or more	Total = 28 Early = 14 Late = 14	CRRT	Urine Output <30ml/hr for 3 consecutive hours (or daily urinary output 750ml or less)	Urine output <20ml/hr for 2 consecutive hours (or daily urinary output 500ml or less)	14 day mortality Changes in BP, urine output and creatinine
Jamale et al. (227) (2013)	Single centre; all inpatients ; medical only	Severe AKI with increasing serum urea and creatinine levels	Total = 208 Early = 102 Late = 106	IHD	Serum urea >70mg/dL and/or creatinine level >7mg/dL	Treatment refractory hyperkalaemia, volume overload, acidosis. Uremic nausea and anorexia with inability to maintain oral intake	In hospital mortality Dialysis dependence at 90 days Number of RRT days Adverse events

[11] Patients in the early group were split into low-volume (n=35) and high-volume (n=35) haemofiltration

Wald et al. (70) (2015)	Multiple centres, single country; ICU only; mixed patients	Volume replete severe AKI with two criteria from three: creatinine doubled from baseline, urine output <6ml/kg in last 12 hours or whole blood NGAL >400ng/ml. Absence of urgent indications for RRT.	Total = 100 Early = 48 Late = 52	Mixed	RRT started within 12 hours of fulfilling eligibility criteria	Potassium >6.0 mmol/l, serum bicarbonate <10 mmol/l, PaO_2/FiO_2 <200 with infiltrates on chest radiograph suggestive of pulmonary oedema	ICU, hospital and 90 day mortality Dialysis dependence at 90 days Length of ICU and hospital stay Adverse events
Gaudry et al. (209) (2016)	Multiple centres, single country; ICU only; mixed patients	KDIGO stage 3 AKI compatible with a diagnosis of ischaemic or toxic Acute Tubular Necrosis and receiving mechanical ventilation and/or catecholamine infusion.	Total = 619 Early = 311 Late = 308	Mixed	RRT commenced within 6 hours after documentation of KDIGO stage 3 AKI	Urea >40 mmol/l, potassium >6 mmol/l (or >5.5 mmol/l despite medical treatment), pH <7.15, pulmonary oedema due to fluid overload requiring oxygen >5 l/ or FiO_2 >50%, oliguria or anuria >72 hours	28 and 60-day mortality Dialysis dependence at 28 and 60 days Length of ICU and hospital stay Number of RRT, mechanical ventilation and vasopressor free days
Zarbock et al. (210) (2016)	Single centre; ICU only; mixed patients	KDIGO stage 2 AKI (baseline creatinine doubled or urinary output <0.5 ml/kg/hr for >12 hours) despite optimal resuscitation, NGAL >150ng/ml and one of: severe sepsis, use of vasopressors, refractory fluid overload and progression of non-renal organ dysfunction	Total = 231 Early = 112 Late = 119	Mixed	RRT started within 8 hours of diagnosis of KDIGO stage 2 AKI	Commenced within 12 hours of diagnosis of stage 3 AKI, or if urea >100 mg/dL, potassium >6.0 mmol/l and or ECG changes, urine output <200ml in 12 hours or organ oedema resistant to diuretic treatment	28, 60 and 90-day mortality Dialysis dependence at 28, 60 and 90 days Length of ICU and hospital stay Length of mechanical ventilation and RRT Adverse events

Srisawat et al. (216)[12] (2018)	Single centre; ICU only; mixed patients	Patients aged 18 or older diagnosed with AKI by RIFLE criteria	Total = 40 Early = 20 Late = 20	CRRT	RRT started within 12 hours of randomization.	Severe refractory acidosis (pH <7.2 or HCO_3 <15), severe peripheral oedema, pulmonary oedema, no response to diuretics, refractory hyperkalaemia (K >6.2 or ECG changes), anuria or oliguria or high BUN (>60)	28-day mortality Dialysis dependence at 28 days Mechanical ventilation free days ICU free days Renal Recovery at 28 days Balance of input and output fluid
Lumlertgul et al. (71)[13] (2018)	Multiple centres, single country; ICU only; mixed patients	AKI with diagnosis of Acute Tubular Necrosis, clinically resuscitated and euvolaemic, no urgent indication or contraindications for RRT.	Total = 118 Early = 58 Late = 60	CRRT	RRT was started in the early group within 6 hours of randomisation	Urea >100 mg/dL, potassium >6 mmol/l, serum bicarbonate <12 mmol/l, pH <7.15, PaO_2/FiO_2 ratio <200 or chest radiographs compatible with pulmonary oedema	28-day mortality Dialysis dependence and renal recovery at 28 days Length of ICU and hospital stay Number of RRT and mechanical ventilation free days
Barbar et al. (217) (2018)	Multiple centres, single country; ICU only; mixed patients	Early phase of septic shock (within 48 hours of start of vasopressor therapy) developing AKI with at least one criterion of the failure stage of the RIFLE classification system	Total = 488 Early = 246 Late = 242	Mixed	RRT commenced within 12 hours of documentation of "failure" stage AKI	RRT commenced 48 hours after diagnosis of AKI or if prior to this: serum potassium >6.5 mmol/l, pH <7.15 or fluid overload with pulmonary oedema	28, 90 and 180 day mortality Dialysis dependence at 28 and 90 days Length of ICU and hospital stay RRT, mechanical ventilation and vasopressor free days Adverse events

Table 8.3: Characteristics of studies accepted for inclusion in final analysis. Modified from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

[12] Patients were tested for plasma neutrophil gelatinase associated lipocalin (pNGAL) levels after recruitment. Patients with pNGAL level greater than or equal to 400ng/ml were randomized into early or late groups

[13] Patients underwent a furosemide stress test first. If they were non-responsive they were randomised into early or late groups

8.1.4.2 Overall mortality

The ten studies comprising 1956 patients reported on overall all-cause mortality at varying times. 989 patients were assigned into the 'early' groups and 967 patients into the 'late' groups. 918 deaths were reported; 459 in the 'early' groups and 459 in the 'late' groups, corresponding to a crude overall mortality rate of 46.4% for patients receiving early RRT and 47.5% for those receiving conventional/late RRT.

Figure 8.5 illustrates results from the ten studies depicting no significant difference between 'early' or 'late' initiation of RRT for mortality rates: RR=0.98 (95% CI=0.84,1.15 (random effects modelling)). A marked heterogeneity between studies was evident with a calculated I^2 statistic of 46% (p=0.05). The pre-defined subgroup analyses were carried out to further explore the possible cause.

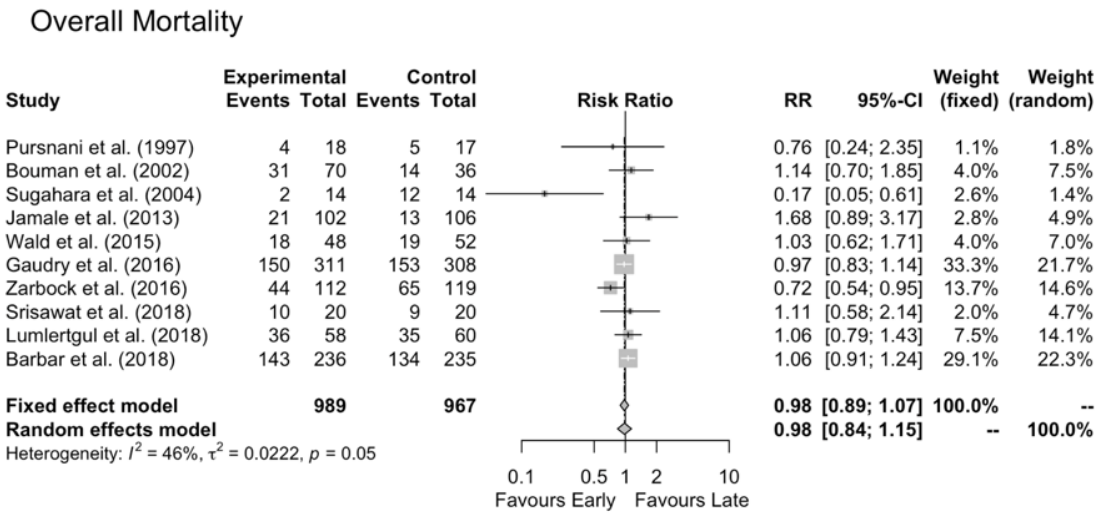


Figure 8.5: Forest plot of the effect of early versus late RRT on overall mortality. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.3 Impact on mortality after accounting for risk of bias

All of the studies were assessed for risk of bias using seven domains and then given an overall rating of low, unclear or high risk of bias. Two of the ten studies were found to have either a high or unclear risk of bias when reviewed

independently by the two researchers. The table detailing the assessed risk of bias in each domain for all ten studies can be found in Appendix E.

The pooled results for these two subgroups can be found in Figure 8.6. The combined results from the two studies with an overall high or unclear risk of bias suggested a mortality benefit for 'early' RRT with a RR = 0.37 (95% CI=0.08,1.65); however, these results were not statistically significant. The remaining eight studies were assessed as having an overall low risk of bias, with pooled results showing no statistically significant difference between the two groups: RR=1.00 (95% CI=0.89,1.13). When the heterogeneity in the low risk of bias group was calculated, the I^2 value was found to have decreased to 23% (from the overall analysis value of 46%).

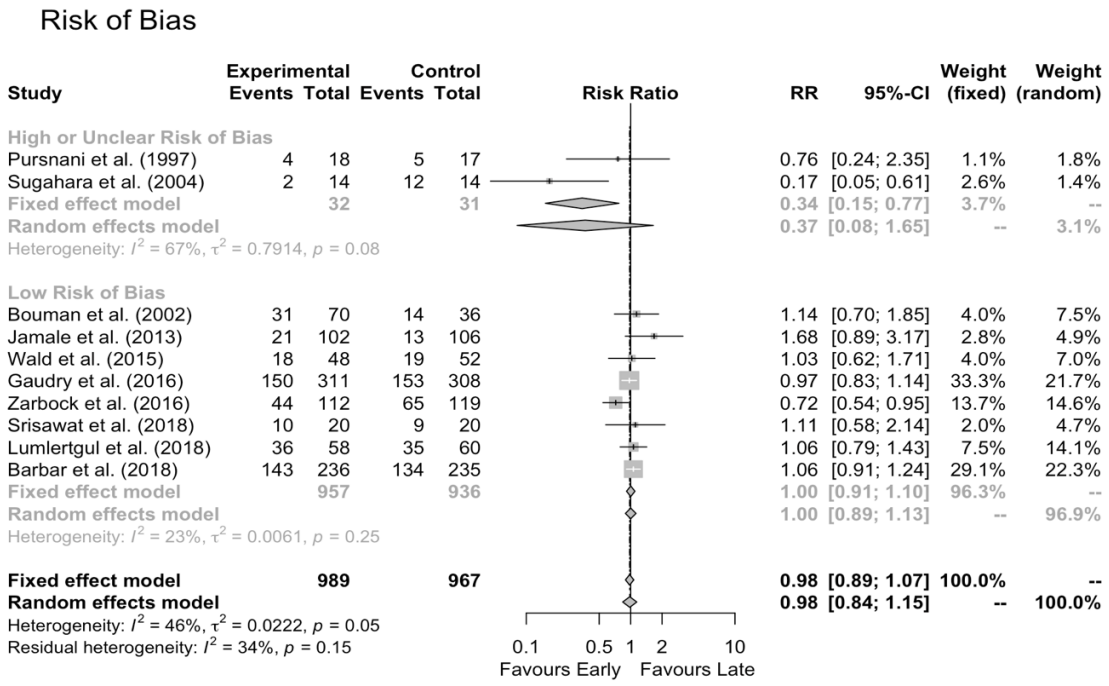


Figure 8.6: Subgroup analysis of low vs high/unclear risk of bias. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.4 Impact on mortality after accounting for RRT modality

The RRT modality used to deliver the intervention and its impact on mortality is presented in Figure 8.7; two studies used intermittent haemodialysis and suggested no significant difference between the 'early' and 'late' arms: RR=1.30 (95% CI=0.63,2.70). Four of the remaining studies used only continuous RRT with

no significant difference between groups: RR=0.91 (95% CI=0.57,1.46). The remaining four studies utilised a mixture of these two modalities and also found no significant difference between groups: RR=0.95 (95% CI=0.81,1.11).

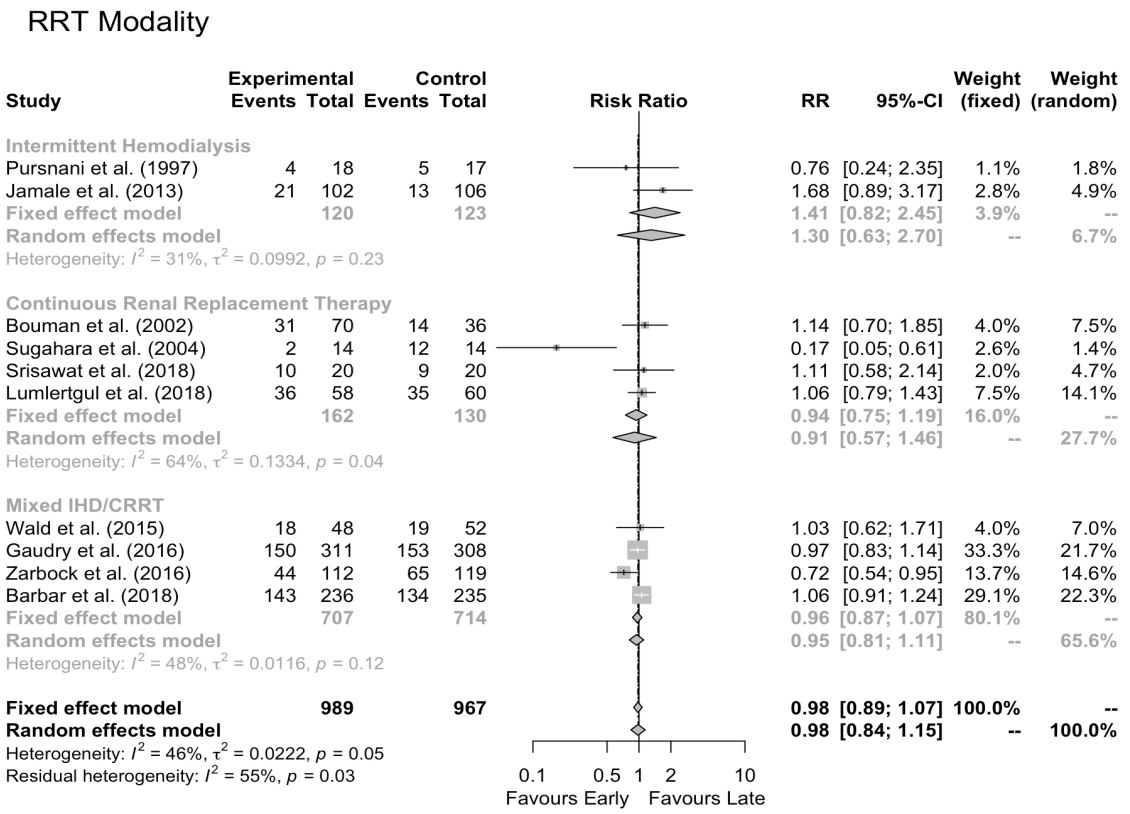


Figure 8.7: Subgroup analysis of RRT modality. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.5 Impact on mortality after consideration of critical illness

Two studies included all inpatients as is demonstrated in both Table 8.3 and Figure 8.8. When pooling the results from just these two studies, the difference between the 'early' and 'late' groups was shown to be not statistically significant; RR=1.30 (95% CI=0.63,2.70). The remaining eight studies included only patients from the intensive care population; similarly, within this subgroup, no observable difference could be found between the two groups: RR=0.95 (95% CI=0.80,1.12).

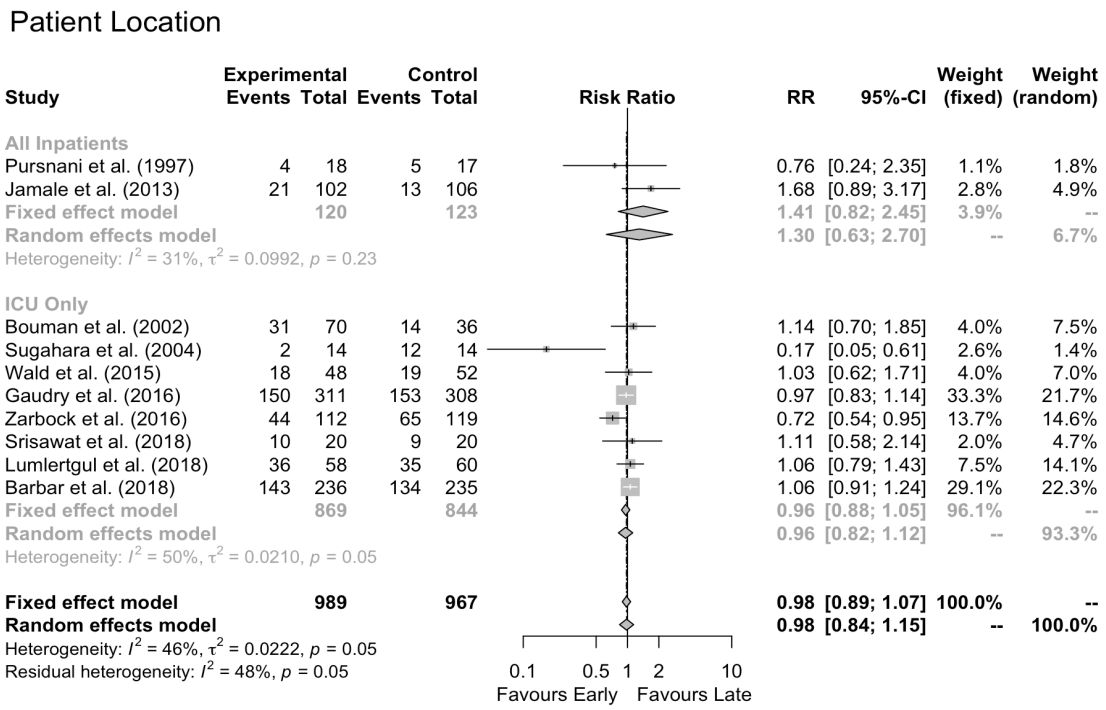


Figure 8.8: Subgroup analysis of inpatients vs ICU only patients. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.6 Impact on mortality by admission type: medical vs surgical vs mixed population

Two studies exclusively included patients from a medical cohort. Within this subgroup, no differences in mortality between the two RRT groups were observed: RR=1.30 (95% CI=0.63,2.70) (Figure 8.9). Only one study of 28 patients used participants from a purely surgical cohort (all of whom underwent cardiothoracic surgery): the result of this study indicated a mortality benefit in the early RRT group with a RR=0.17 (95% CI=0.05,0.61). The remaining seven studies contained a mixed population of patients and no statistical difference existed between the two RRT groups within this subgroup: RR=0.98 (95% CI=0.88,1.10).

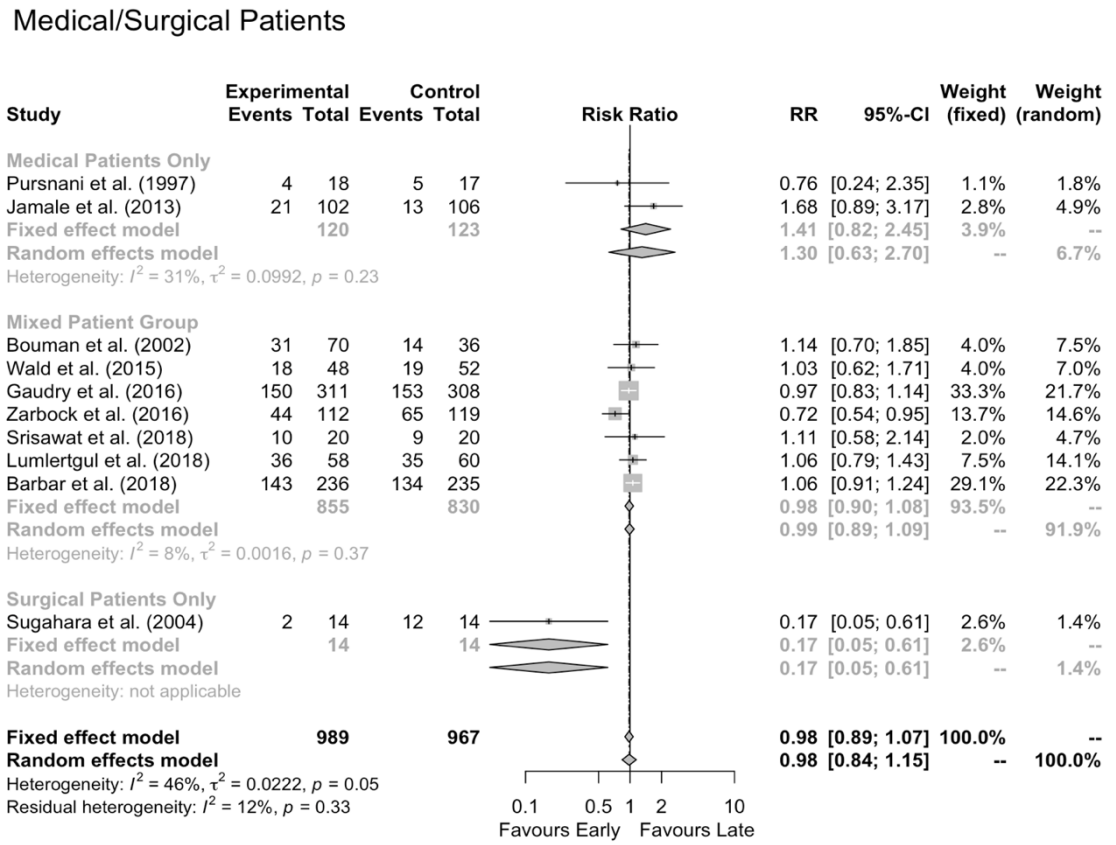


Figure 8.9: Subgroup analysis of medical, surgical and mixed patient populations. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.7 Time-based mortality

All studies reported mortality numbers over differing time periods. These time periods were categorised into in-ICU, in-hospital, 28-day, 60-day and 90-day (Figure 8.10). In-ICU mortality was reported by two studies: their pooled results showed no statistical difference was evident between the two RRT treatment groups: RR=1.02 (95% CI=0.66,1.58). In-hospital mortality was reported by three studies with no significant difference between groups: RR=1.16 (95% CI=0.84,1.60). Six of the studies reported 28-day mortality; with no significant difference found between early and late RRT groups: RR=0.99 (95% CI=0.88,1.11). Two studies reported on 60-day mortality and observed no significant between group difference: RR=0.89, (95% CI=0.71,1.12). Three of the studies reported results for 90-day mortality, with no statistically significant differences found between early and late groups: RR=0.93 (95% CI=0.69,1.23).

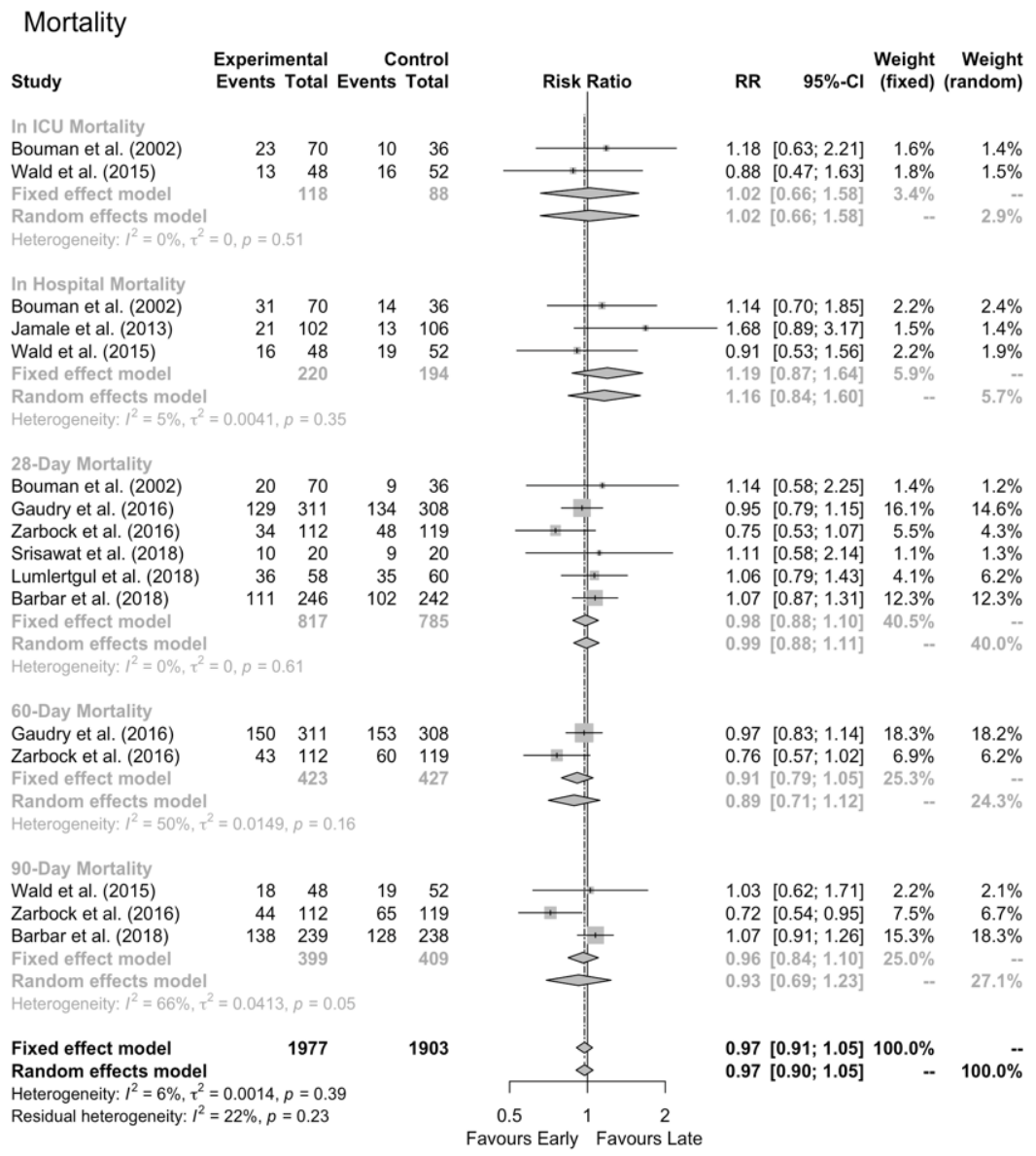


Figure 8.10: Impact of early vs late RRT on mortality rates at various time periods. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.8 Dialysis dependence

Dialysis dependence was reported at 28 days, 60 days and 90 days. Four studies reported on rates of dialysis dependence in surviving patients after 90 days (Figure 8.11). The pooled data demonstrated no significant differences between 'early' and 'late' groups: 16 patients out of 279 survivors vs 18 patients out of 289 survivors (RR=0.87).

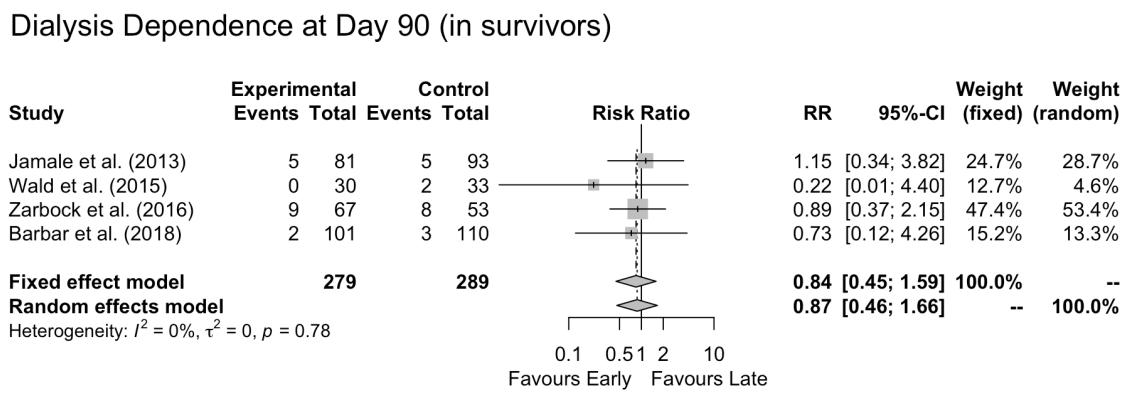


Figure 8.11: Dialysis dependence in survivors at 90 days. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

Four studies reported on rates of dialysis dependence after 28 days with no statistically significant difference (Figure 8.12): 65/423 vs 76/425 patients (RR=0.84). Dialysis dependence at day 60 was reported by two studies with a benefit suggested in the early RRT group (Figure 8.12): 14/226 vs 22/214 patients (RR=0.59). Data on recovery of renal function in survivors (defined as return to pre-morbid baseline) at 90 days was produced by two studies. The pooled results demonstrated no between group differences: RR=1.00 (95% CI=0.94-1.06). This forest plot detailing this can be found in Appendix E.

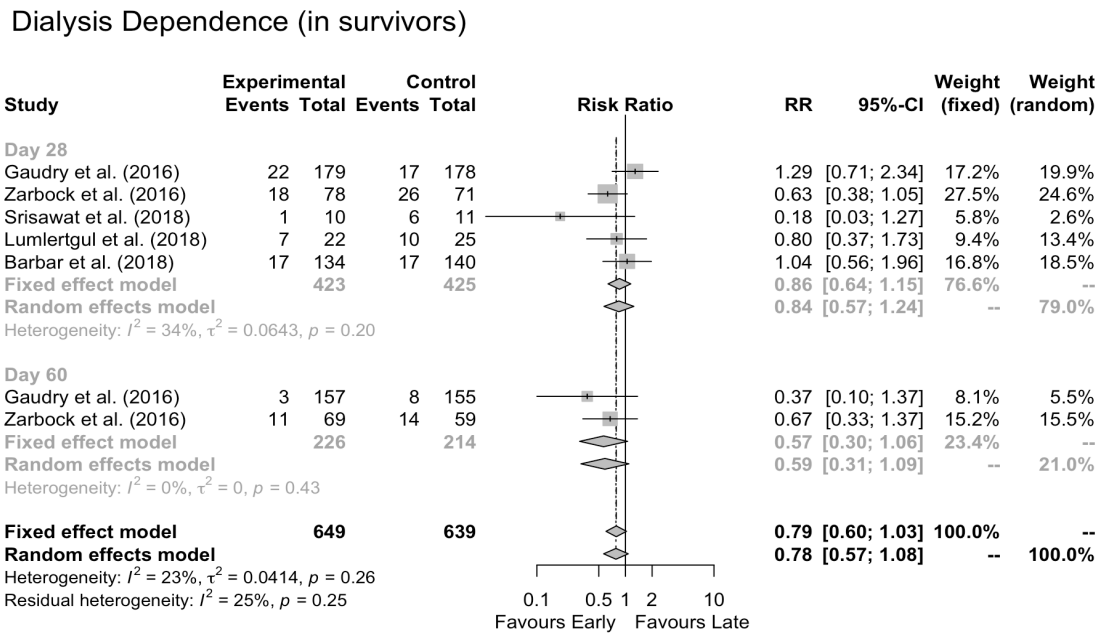


Figure 8.12: Dialysis dependence in survivors at 28 and 60 days. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.9 RRT related adverse events

Potential adverse events associated with the implementation of RRT were reported differently depending on each study. In total, nine different adverse events were reported by at least two studies. Analysis of the six studies reporting catheter related complications (Figure 8.13) suggested an increase in complications within the 'early' group: RR=1.85 (95% CI=1.18,2.88). For the remaining eight adverse events, no statistically significant differences between the 'early' and 'late' groups were observable; the results of these analyses can be found summarised in Table 8.4. Additional forest plots comparing all of these outcomes can be found in Appendix E.

Outcome	Number of participants (studies)	Risk Ratio	95% Confidence Intervals
Catheter related complications	1382 (6 studies)	1.85	1.18 – 2.88
Bleeding events	1905 (8 studies)	0.80	0.56 – 1.15
Arrhythmias	1591 (6 studies)	1.11	0.84 – 1.45
Dialysis related hypotension	1080 (6 studies)	1.14	0.82 – 1.57
Hypokalaemia	737 (2 studies)	1.04	0.77 – 1.40
Thrombocytopenia	725 (2 studies)	1.03	0.89 – 1.19
Hypocalcaemia	449 (3 studies)	1.12	0.92 – 1.36
Hypophosphatemia	737 (2 studies)	2.68	0.62 – 11.58
Hyperkalaemia	1107 (2 studies)	0.27	0.01 – 5.85

Table 8.4: Summary of pooled results for adverse events. Modified from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

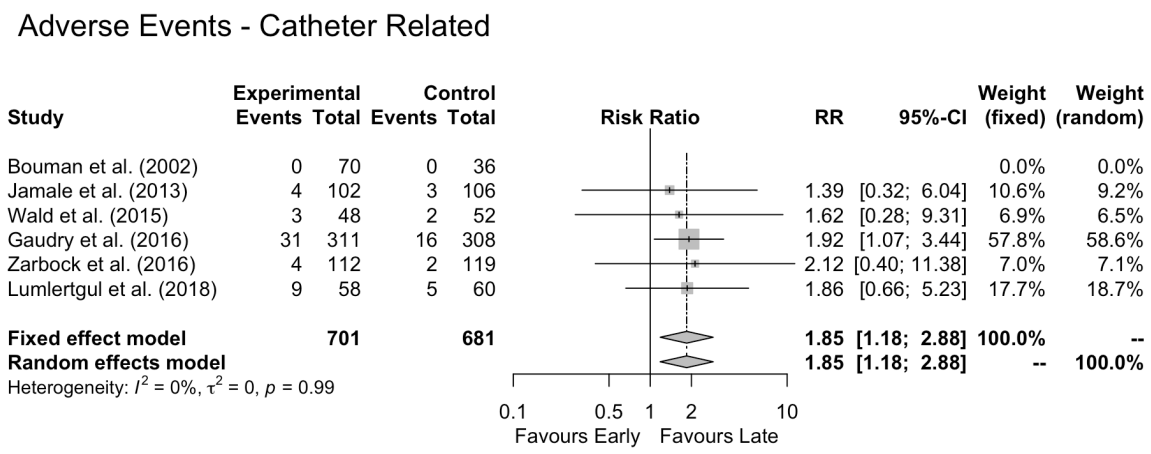


Figure 8.13: Adverse events – catheter related complications. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.4.10 Length of stay

Two studies (209, 226) reported median and interquartile values as two separate classes for early RRT. In the study performed by Bouman et al. (226), the 'early' group was separated into high- and low-volume haemofiltration; in the study by Gaudry et al. (209) values were given for survivors/non-survivors in both 'early' and 'late' groups; these two studies were excluded from the analysis since no composite values were reported. In the remaining four studies (70, 71, 210, 217), medians and interquartile ranges were pooled, showing no statistically significant difference between the 'early' and 'late' groups for either length of ICU stay (estimated difference in length of stay = 0.34 days (95% CI -1.60,2.28, p=0.73)), or length of hospital stay (estimated difference in length of stay = -1.75 days (95% CI -5.84,2.34, p=0.40)).

8.1.4.11 RRT duration

Three studies reported on the impact of the number of RRT days. One study (227) reported in terms of mean, +/- SD and therefore was excluded; the other two reporting in terms of median and interquartile ranges (210, 217). Although a large estimated difference in medians was evident, they were considered statistically insignificant; estimated difference = -5.99 (95% CI -23.52,11.53, p=0.50); this was also the case for the pooled results of the four studies (71, 209, 216, 217) reporting on number of mechanical ventilation free days (estimated difference in length of stay = 6.94 days (95% CI -4.59,18.48, p=0.24)). Three studies reported on the number of RRT free days (71, 209, 217): no clear difference was observable between the two groups (estimated difference in length of stay = -1.33 days (95% CI -3.66,1.01, p=0.27)). The two studies reporting on vasopressor free days (209, 217) also demonstrated no statistically significant difference between the early and late RRT groups (estimated difference in length of stay = -0.45 days (95% CI -3.22,2.32, p=0.75)).

8.1.4.12 Risk of bias across studies

The risk of bias was estimated through a funnel plot using the overall mortality as an outcome. The inverted standard error against the RR is shown in Figure 8.14, where the 'dotted' lines signify the expected distribution of the studies. One study (224) is a significant outlier; otherwise the distribution suggests a reduced risk of bias across the selected studies.

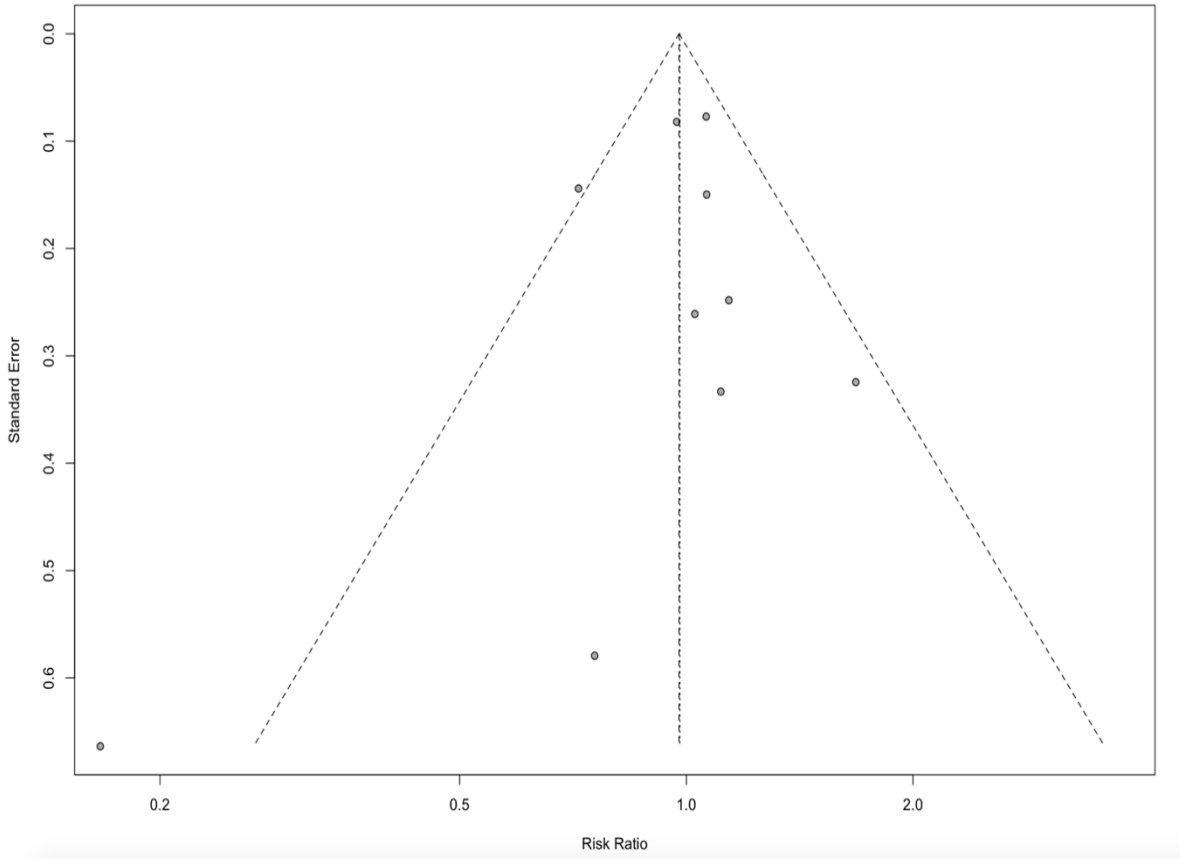


Figure 8.14: Inverted funnel plot utilising overall mortality outcome. Reproduced from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

8.1.5 Discussion

This systematic literature review identified a total of ten studies that describe the impact of early versus conventional/late RRT on mortality. The studies varied widely in the characteristics of study populations, their methodology and in their conclusions drawn. Of note, certain studies only allowed specific modalities of RRT, others drew only from a surgical population of patients and the numbers of patients recruited ranged from 28 to 488. Whilst often sharing similar definitions, the classification of "early" and "late" RRT was almost entirely unique for each individual study. The full description of each of these studies' characteristics is available in Table 8.3. Likely as a result of this, the various authors drew several different conclusions on the subject based on their own data. The majority concluded that timing of RRT in AKI has no effect on overall mortality; others suggested that early initiation of RRT confers a mortality benefit.

Multiple previous meta-analyses have been conducted on this subject over the previous fifteen years but in particular in lieu of the larger AKIKI (209) and ELAIN (210) trials in 2016: these meta-analyses have reached differing conclusions. Two analyses conducted prior to the RCTs performed from 2013 onwards suggested that 'early' RRT may convey a mortality benefit (213, 214). In contrast, more recent analyses performed after the aforementioned RCTs in 2016 concluded that there was no difference in mortality between early and late RRT groups (69, 212). In 2018, three further RCTs of varying sizes were conducted (71, 216, 217). For all three of these studies, the authors concluded that there was no difference in overall mortality between groups. Of note, the largest study included in this meta-analysis, IDEAL-ICU (217), was stopped early due to futility.

Since the completion of this systematic review, the STARRT-AKI trial has concluded with results published in the New England Journal of Medicine in 2020 (228). This study was the largest study to date to assess the question of early versus standard initiation of RRT and enrolled 2,927 patients compared to the 488 enrolled in IDEAL-ICU. The conclusions of this large international RCT found that there was no difference in 90-day mortality between an "accelerated" and "standard" strategy for initiating RRT in critically unwell patients. The authors

also observed a higher rate of adverse events in the "accelerated" group. Both of these conclusions agreed with the results found in this study, and it is likely that it would not change the outcome if incorporated into the above meta-analysis. STARRT-AKI was not included in this study as the analysis and initial online publication of this work was concluded in February 2020 prior to the point at which STARRT-AKI's results were made available.

8.1.5.1 Factors affecting mortality

When the overall results of all ten studies were pooled, the meta-analysis demonstrated no statistically significant difference in terms of overall mortality. To try an account for the risk of error, only the random effect modelling results were interpreted; for overall mortality, the risk ratio for this was found to be 0.98 (95% CI = 0.84,1.15). Furthermore, whilst the time period for follow-up varied throughout the individual studies, the analyses for in-ICU, in-hospital, 28-day, 60-day and 90-day mortality all showed no differences between the early and late RRT groups.

The subgroup analyses were pre-defined prior to beginning the analyses to try and surface any potential sources of significant heterogeneity. Due to the varying study populations, 4 were chosen to identify if risk of bias, illness severity, type of patient population or modality of RRT affected the results of the overall analysis. When a meta-analysis was conducted on subgroups differentiated by type of RRT, no significant differences were detected; this was also the case when subgroups were defined based on studies containing general hospital inpatients compared to ICU patients only.

Each individual study was assessed for bias: a table detailing this assessment can be found in Appendix E. Two of the ten studies were found to have an overall unclear or high risk of bias (224, 225), potentially making the data produced from them less reliable. To assess if they were contributing to the significant degree of heterogeneity found in the initial analysis, it was performed again without these two studies. This analysis also showed that there was no impact on the effect of mortality between the two groups, however the heterogeneity reduced significantly (I^2 from 46% to 23%). Based on this analysis, it would

suggest that these two studies are likely to have influenced the consistency of the overall analysis.

The only subgroup analysis that identified a difference in outcome as a function of RRT initiation was performed based on whether patients were from either a surgical, medical or mixed population. Within this, the analysis noted that the early initiation of RRT resulted in an improvement in mortality in patients recruited from a cardiothoracic surgical population. However, it must be noted that the conclusion was based on a single-centre, small study (224) which reported vastly different mortality rates between the 'early' and 'late' groups (14.29% vs 85.71%). The study was the smallest included in the present meta-analysis (n=28) and owing to its limited extent, the impact of a few additional patients will markedly alter the statistical significance between groups. In addition, the study was also assessed to have an overall unclear risk of bias as well as high risk of reporting incomplete outcome data; therefore, as the sole representative study comprising of an exclusively surgical population, it is likely that this study has skewed results significantly. Nonetheless, it should be noted that whilst limited conclusions can be drawn, this may indeed represent a difference based on patient population and that further studies may provide better understanding.

8.1.5.2 Factors affecting secondary outcomes

When the meta-analysis was performed on dialysis dependence it did not identify any association between timing of RRT for AKI and dialysis dependence at 28 or 90 days; however it should be noted that absolute numbers of patients still dependent on RRT at both time points were small owing to both low incidence of the outcome and the small number of studies which chose to measure either of these. Although results from two studies (209, 210) investigating dialysis dependence at day 60 suggested a benefit in the early RRT group, fewer studies reported day 60 compared to day 28 and 90. In both studies, the absolute numbers of dialysis dependent patients at 60 days were relatively small which potentially skew the conclusions drawn. Further to this, the study by Zarbock et al. (210) also reported on dialysis dependence at day 90 with no significant difference between the groups.

Other reported secondary outcomes such as renal recovery at day 90, length of ICU stay, length of hospital stay, number of RRT days, RRT free days, mechanical ventilation free days and vasopressor free days also showed no statistically significant differences between groups. Owing to the wide variety in choices for these reported outcomes between the studies, most of these secondary outcomes were only measured in a small number of studies compared to the total involved in the overall analysis.

The insertion of a catheter to enable RRT and disruption to several physiological and biochemical mechanisms within the body whilst it is taking place gives rise to a number of potential adverse events. Across the ten studies, at least two papers chose to report on nine separate adverse events; these events are listed in Table 8.4, as well as the pooled results for the analyses performed on each one. These analyses demonstrated that the majority of adverse events showed no significant difference between groups with the exception of one: higher rates of catheter related complications were seen in the 'early' group (RR=1.85, 95% CI=1.18,2.88). The most obvious explanation for this difference is intrinsically linked with the fact that more people within the early RRT groups will receive RRT compared to the late groups; this will require an increased number of catheters to be inserted which will in turn increase the likelihood of complications occurring.

8.1.5.3 Assessed quality of evidence

In addition to conducting several quantitative analyses of the pooled data, it has previously been described as good practice to carry out a qualitative review of the evidence to assess the quality. A common tool for this is the GRADE tool, which utilises four domains to determine if the evidence gathered is of very low, low, moderate or high quality (222). The two reviewers conducted an independent review on each primary outcome using the GRADE tool.

Outcomes	Number of participants (studies)	Anticipated absolute effects (95% CI)[14]		Relative effect (95% CI)	Certainty of evidence (GRADE)
		Control group risk (Late)	Intervention group risk (Early)		
Overall mortality	1956 (10 studies)	473 per 1000	464 per 1000 (397 – 544)	RR = 0.98 (0.84 – 1.15)	⊕⊕⊖⊖ LOW[15,16]
In ICU mortality	206 (2 studies)	293 per 1000	299 per 1000 (193 – 463)	RR = 1.02 (0.66 – 1.58)	⊕⊕⊕⊖ LOW[7]
In hospital mortality	414 (3 studies)	365 per 1000	423 per 1000 (307 – 584)	RR = 1.16 (0.84 – 1.60)	⊕⊕⊕⊖ LOW[17]
28-day mortality	1602 (6 studies)	428 per 1000	424 per 1000 (377 – 475)	RR = 0.99 (0.88 – 1.11)	⊕⊕⊕⊖ MODERATE[5]
60-day mortality	850 (2 studies)	500 per 1000	445 per 1000 (355 – 560)	RR = 0.89 (0.71 – 1.12)	⊕⊕⊖⊖ LOW[5,6]
90-day mortality	808 (3 studies)	538 per 1000	500 per 1000 (371 – 662)	RR = 0.93 (0.69 – 1.23)	⊕⊕⊖⊖ LOW[5,6]

Table 8.5: GRADE assessment of evidence for primary outcomes. Modified from *"Timing of renal replacement therapy for patients with acute kidney injury: A systematic review and meta-analysis"* Andonovic et al. JICS (2021) with permission.

The individual outcomes can be found detailed in Table 8.5. Across each primary outcome of overall mortality and period-wise mortality, the overall

[14] The basis for the baseline risk is calculated using the median control group risk across studies. The anticipated absolute effect is expressed as risk difference (and 95% CI) and is based on baseline risk in comparison group and relative effect of intervention

[15] Inconsistency – Moderate/high heterogeneity
[16] Imprecision – CIs cross threshold for clinically meaningful effect
[17] Serious imprecision – CIs significantly wide and crossing threshold for clinically meaningful effect

quality of evidence was found to be low for all outcomes with exception of one: the evidence for 28-day mortality was found to be of moderate quality. The different rationale behind marking each outcome down was due to measures of either inconsistency, imprecision or a combination of the two. Inconsistency was determined if there was a moderate or severe degree of heterogeneity calculated for that specific analysis. Imprecision was determined based on the 95% confidence intervals and if they crossed the threshold for a clinically meaningful effect. If these intervals both crossed this threshold and were significantly wide, this was interpreted as significant imprecision.

8.1.5.4 Strengths and weaknesses

This study details the current literature regarding the implementation of a vital mainstay in the treatment of AKI in ICU and its current best practice. Whilst multiple meta-analyses have been carried out on the subject in the past, the addition of three recent RCTs have added further data into a field with relatively little data to date; these studies contribute 629 of the total 1,956 patients (32.16%).

The strengths of this study include a rigorous methodology to attempt to incorporate all existing data on the subject of timing of RRT for AKI. It utilises a very broad initial search strategy to ensure all of the studies on the subject are captured, as well as pre-defining subgroup analyses to attempt to identify possible sources for heterogeneity which may arise. In addition, a significant attempt is made to account for risk of error by utilising random effect modelling for each analysis.

The principal weakness of this study arises from the lack of data available in this field; this results in a high degree of inconsistency in certain aspects of the methodology between the individual studies. The variability in the classification of the ‘early’ and ‘late’ groups contribute to increasing the difficulty in pooling data for direct comparisons. Recent studies for the early group (70, 71, 209, 210, 216, 217) have adopted a time frame from eligibility whilst others utilised physiological variables to determine the initiation of RRT. Timeframes ranged from commencement within 6-12 hour window from meeting eligibility criteria, whereas physiological criteria ranged from varying urine outputs to serum

creatinine or urea levels. In addition to the difference between timing vs physiological factors, studies utilising international guidelines for either inclusion or to determine commencement of early RRT used varying classifications (4, 10, 16). Whilst a known factor prior to devising the search strategy, it was nevertheless deemed that that a systematic comparison of differing strategies would be informative despite the paucity of available data.

8.1.6 Conclusions

This systematic review and meta-analysis identified 10 studies assessing the impact of timing of RRT on mortality. The pooled results of these studies revealed no significant difference between early and late initiation of RRT for AKI with regards to the primary outcome of overall mortality and multiple secondary outcomes such as length of ICU and hospital stay and dialysis dependence at 90 days. The value of initiating RRT earlier has been subject to extensive debate, and whilst theoretical benefits have been postulated such as limiting fluid overload and organ dysfunction as well as removal of inflammatory mediators (229), the hypothesis has not been supported through an assessment of measured patient outcomes. Initiation of RRT at an earlier stage will also result in a higher proportion of patients receiving RRT which may in turn result in higher rates of complications as well as significant increases to cost. This study's findings agree with recent previous meta-analyses that current evidence does not support the use of early RRT for patients with AKI. Additional data from the large STARRT-AKI study have helped to support the results found in this study (228); however, further data from ongoing and future RCTs are necessary to strengthen the evidence base to help add valuable information in an area where there is still a lack of contextualised data which in turn continues to fuel significant debate.

Appendix E: Additional systematic review and meta-analysis tables and figures

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,22
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,19-21
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Supp
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11, 22-25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11, 22-25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11,25
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8, 9, 23, Supp
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Figure 8.15: PRISMA Checklist for systematic review and meta-analysis

Paper	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other Bias	OVERALL
Pursnani (1997)	Unclear	Unclear	Low	Low	Low	Low	Unclear	**Unclear**
Bouman (2002)	Unclear	Low	Low	Low	Low	Low	Low	**Low**
Sugahara (2004)	Unclear	Unclear	Low	Low	High	Low	Unclear	**Unclear**
Jamale (2013)	Low	Low	Low	Low	Low	Low	Low	**Low**
Wald (2015)	Low	Low	Low	Low	Low	Low	Low	**Low**
Gaudry (2016)	Low	Low	Low	Low	Low	Low	Low	**Low**
Zarbock (2016)	Low	Low	Low	Low	Low	Low	Low	**Low**
Srisawat (2018)	Low	Low	Low	Low	Low	Low	Low	**Low**
Lumlertgul (2018)	Low	Low	Low	Low	Low	Low	Low	**Low**
Barbar (2018)	Low	Low	Low	Low	Low	Low	Low	**Low**

Table 8.6: Assessed risk of bias for studies included in meta-analysis

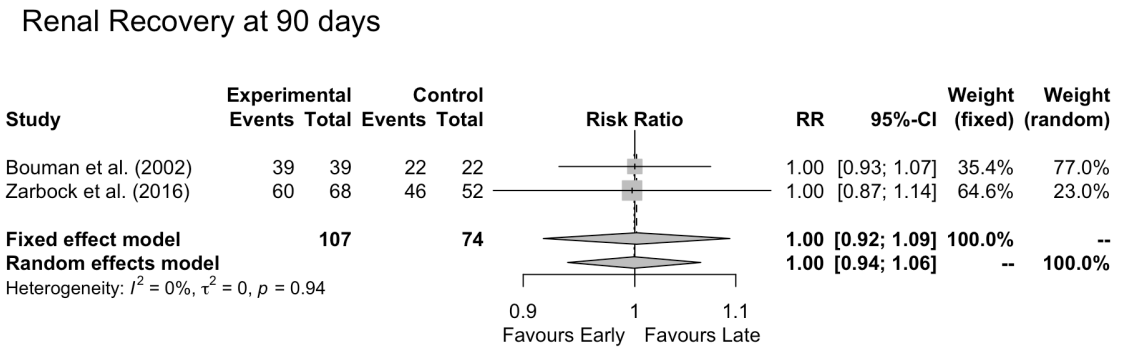


Figure 8.16: Renal recovery in survivors at 90 days

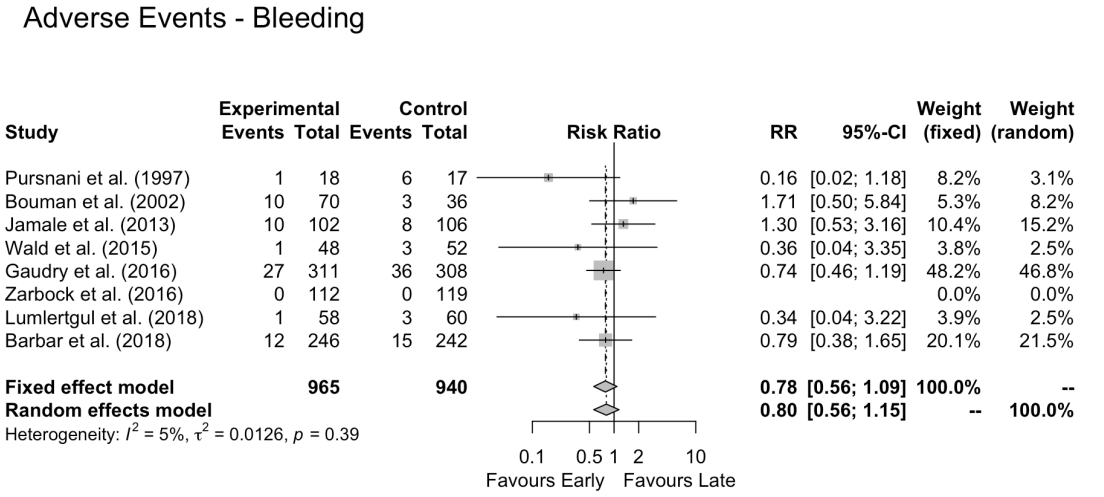


Figure 8.17: Adverse events – bleeding

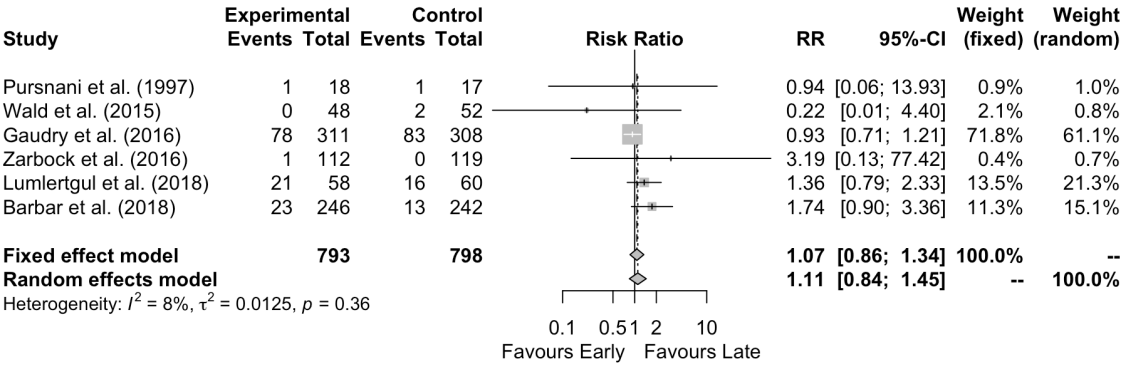


Figure 8.18: Adverse events – arrhythmias

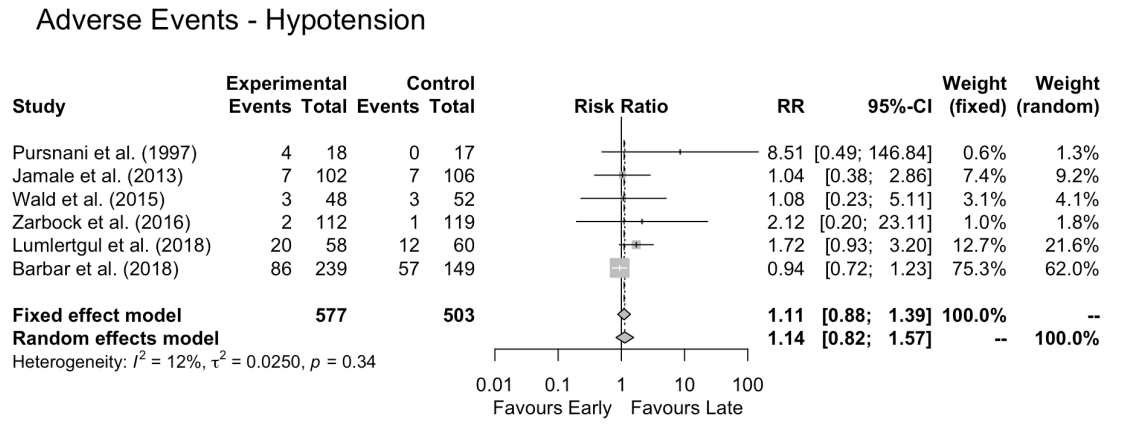


Figure 8.19: Adverse events – hypotension

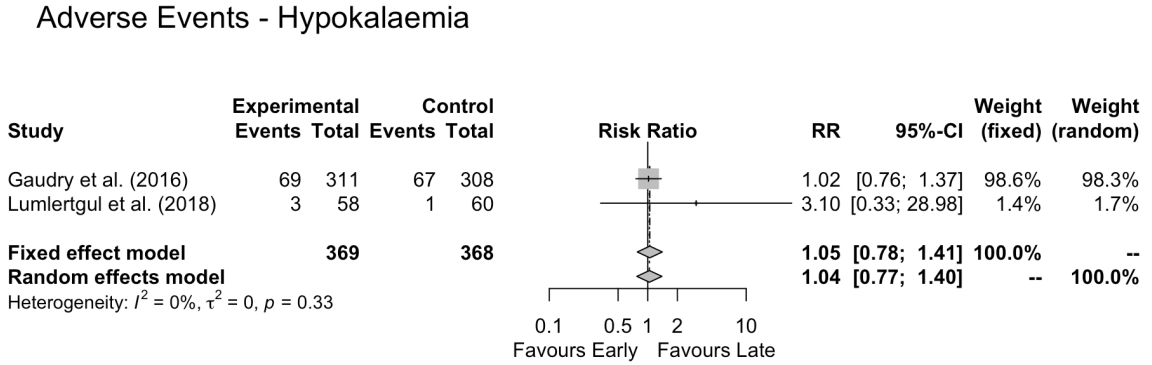


Figure 8.20: Adverse events – hypokalaemia

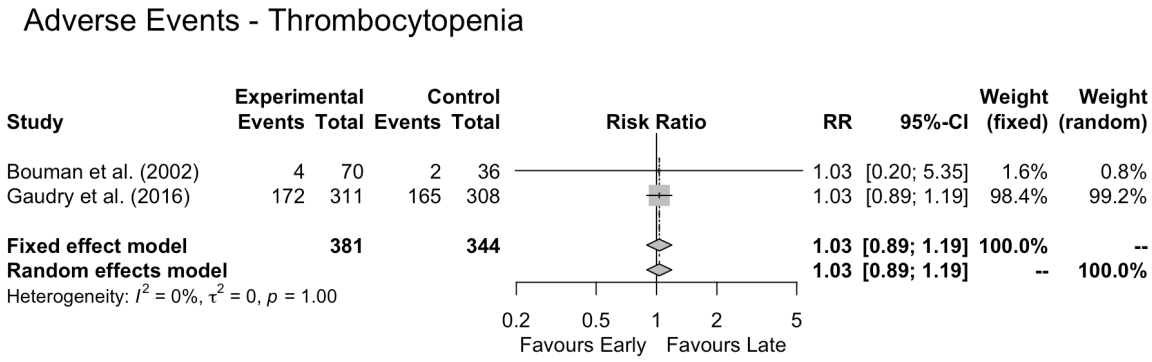


Figure 8.21: Adverse events – thrombocytopenia

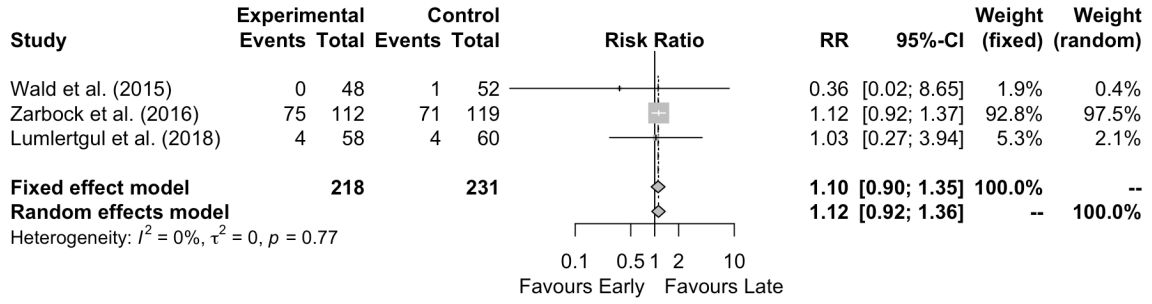


Figure 8.22: Adverse events – hypocalcaemia

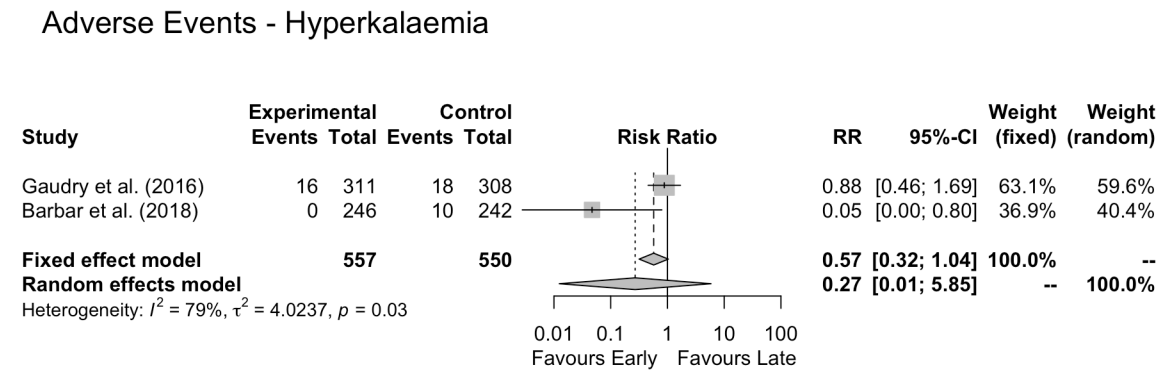


Figure 8.23: Adverse events – hyperkalaemia

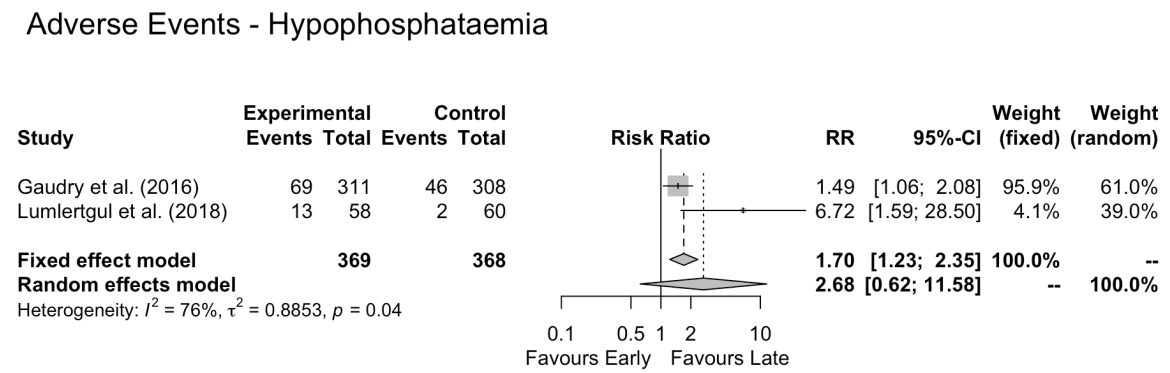
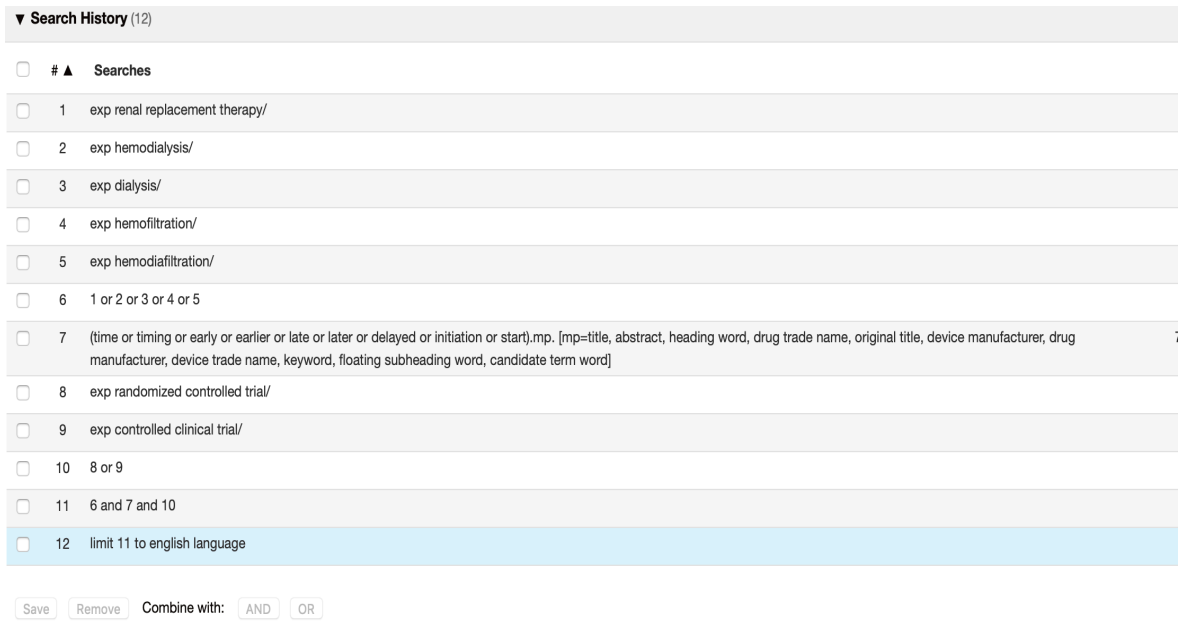


Figure 8.24: Adverse events – hypophosphataemia



▼ **Search History** (12)

# ▲	Searches
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2	exp hemodialysis/
3	exp dialysis/
4	exp hemofiltration/
5	exp hemodiafiltration/
6	1 or 2 or 3 or 4 or 5
7	(time or timing or early or earlier or late or later or delayed or initiation or start).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8	exp randomized controlled trial/
9	exp controlled clinical trial/
10	8 or 9
11	6 and 7 and 10
12	limit 11 to english language

Save Remove Combine with: AND OR

Figure 8.25: EMBASE search strategy

Chapter 9 References

1. ALWALL N. On renal failure complicating surgical diseases (laparotomy etc.), with special regard to conservative treatment, and the need for the artificial kidney (dialyser, ultrafilter) in rational renal therapy; acute tubular nephritis, chronic pyelonephritis and prostatic hypertrophy with urinary retention. Acta Chir Scand. 1954;108(2-3):95-113.
2. LUNDING M, STEINESS I, THAYSEN JH. ACUTE RENAL FAILURE DUE TO TUBULAR NECROSIS, IMMEDIATE PROGNOSIS AND COMPLICATIONS. Acta Med Scand. 1964;176:103-19.
3. Liaño F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int. 1996;50(3):811-8.
4. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, workgroup ADQI. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.
5. Levin A, Warnock DG, Mehta RL, Kellum JA, Shah SV, Molitoris BA, et al. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis. 2007;50(1):1-4.
6. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10(3):R73.
7. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35(8):1837-43; quiz 52.
8. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney Int. 2008;73(5):538-46.
9. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008;23(4):1203-10.
10. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
11. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clin Kidney J. 2013;6(1):8-14.
12. Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN--time for reappraisal. Crit Care. 2009;13(3):211.
13. Cruz DN, Bagshaw SM, Ronco C, Ricci Z. Acute kidney injury: classification and staging. Contrib Nephrol. 2010;164:24-32.
14. Shacham Y, Leshem-Rubinow E, Ziv-Baran T, Gal-Oz A, Steinvil A, Ben Assa E, et al. Incidence and mortality of acute kidney injury in acute myocardial infarction patients: a comparison between AKIN and RIFLE criteria. Int Urol Nephrol. 2014;46(12):2371-7.
15. Bagshaw SM, George C, Bellomo R, Committe ADM. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008;23(5):1569-74.
16. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84.
17. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.

18. Srisawat N, Sileanu FE, Murugan R, Bellomod R, Calzavacca P, Cartin-Ceba R, et al. Variation in risk and mortality of acute kidney injury in critically ill patients: a multicenter study. Am J Nephrol. 2015;41(1):81-8.
19. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med. 2014;40(10):1481-8.
20. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol. 2007;22(11):1839-48.
21. Hsu CY, Bansal N. Measured GFR as "gold standard"--all that glitters is not gold? Clin J Am Soc Nephrol. 2011;6(8):1813-4.
22. Horio M, Imai E, Yasuda Y, Hishida A, Matsuo S, GFR JEfE. Simple sampling strategy for measuring inulin renal clearance. Clin Exp Nephrol. 2009;13(1):50-4.
23. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int. 1985;28(5):830-8.
24. Puthucheary ZA, McPhail MJ, Hart N. Acute muscle wasting among critically ill patients--reply. JAMA. 2014;311(6):622-3.
25. Sawhney S, Fluck N, Marks A, Prescott G, Simpson W, Tomlinson L, et al. Acute kidney injury-how does automated detection perform? Nephrol Dial Transplant. 2015;30(11):1853-61.
26. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21(2):345-52.
27. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249(5):851-8.
28. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;53(6):961-73.
29. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol. 2007;18(4):1292-8.
30. Fuchs L, Lee J, Novack V, Baumfeld Y, Scott D, Celi L, et al. Severity of acute kidney injury and two-year outcomes in critically ill patients. Chest. 2013;144(3):866-75.
31. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76(8):893-9.
32. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79(12):1361-9.
33. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442-8.
34. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223-8.
35. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2(2):1303-53.
36. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011;7(4):189-200.
37. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85-98.

38. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nat Rev Dis Primers. 2021;7(1):52.
39. Hegarty NJ, Young LS, Kirwan CN, O'Neill AJ, Bouchier-Hayes DM, Sweeney P, et al. Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow. Kidney Int. 2001;59(3):1059-65.
40. Liaño F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney Int Suppl. 1998;66:S16-24.
41. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? Nat Rev Nephrol. 2011;7(4):209-17.
42. Bedford M, Stevens PE, Wheeler TW, Farmer CK. What is the real impact of acute kidney injury? BMC Nephrol. 2014;15:95.
43. Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. Crit Care. 2016;20(1):188.
44. Zager RA, Johnson AC, Lund S, Hanson S. Acute renal failure: determinants and characteristics of the injury-induced hyperinflammatory response. Am J Physiol Renal Physiol. 2006;291(3):F546-56.
45. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017;13(4):241-57.
46. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int. 2014;85(1):49-61.
47. Coca SG, King JT, Rosenthal RA, Perkal MF, Parikh CR. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int. 2010;78(9):926-33.
48. Mehta S, Chauhan K, Patel A, Patel S, Pinotti R, Nadkarni GN, et al. The prognostic importance of duration of AKI: a systematic review and meta-analysis. BMC Nephrol. 2018;19(1):91.
49. Han SS, Kim S, Ahn SY, Lee J, Kim DK, Chin HJ, et al. Duration of acute kidney injury and mortality in critically ill patients: a retrospective observational study. BMC Nephrol. 2013;14:133.
50. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516-26.
51. Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after Acute Kidney Injury. Am J Respir Crit Care Med. 2017;195(6):784-91.
52. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7-20.
53. Pannu N, James M, Hemmelgarn B, Klarenbach S, Network AKD. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol. 2013;8(2):194-202.
54. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int. 2012;81(5):477-85.
55. Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. Clin J Am Soc Nephrol. 2014;9(6):1015-23.

56. Liu KD, Thompson BT, Ancukiewicz M, Steingrub JS, Douglas IS, Matthay MA, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med. 2011;39(12):2665-71.
57. Prowle JR, Leitch A, Kirwan CJ, Forni LG. Positive fluid balance and AKI diagnosis: assessing the extent and duration of 'creatinine dilution'. Intensive Care Med. 2015;41(1):160-1.
58. Doi K, Yuen PS, Eisner C, Hu X, Leelahavanichkul A, Schnermann J, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. J Am Soc Nephrol. 2009;20(6):1217-21.
59. Thomas DM, Coles GA, Williams JD. What does the renal reserve mean? Kidney Int. 1994;45(2):411-6.
60. Kelly FE, Fong K, Hirsch N, Nolan JP. Intensive care medicine is 60 years old: the history and future of the intensive care unit. Clin Med (Lond). 2014;14(4):376-9.
61. LASSEN HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet. 1953;1(6749):37-41.
62. McCarthy N. The countries with the most critical care beds per capita 2020 [Available from: https://www.statista.com/chart/21105/number-of-critical-care-beds-per-100000-inhabitants/.
63. Department of H. Comprehensive critical care: a review of adult critical care services. 2000.
64. Group SICS. Audit of Critical Care in Scotland 2020: Reporting on 2019. Public Health Scotland; 2020.
65. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40(12):1795-815.
66. Antonelli M, Levy M, Andrews PJ, Chastre J, Hudson LD, Manthous C, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27-28 April 2006. Intensive Care Med. 2007;33(4):575-90.
67. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. Nephrol Dial Transplant. 2009;24(2):512-8.
68. Wald R, Friedrich JO, Bagshaw SM, Burns KE, Garg AX, Hladunewich MA, et al. Optimal Mode of clearance in critically ill patients with Acute Kidney Injury (OMAKI)--a pilot randomized controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project. Crit Care. 2012;16(5):R205.
69. Bhatt GC, Das RR. Early versus late initiation of renal replacement therapy in patients with acute kidney injury-a systematic review & meta-analysis of randomized controlled trials. BMC Nephrol. 2017;18(1):78.
70. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int. 2015;88(4):897-904.
71. Lumlertgul N, Peerapornratana S, Trakarnvanich T, Pongsittisak W, Surasit K, Chuasuwan A, et al. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). Crit Care. 2018;22(1):101.

72. Le Gall JR. The use of severity scores in the intensive care unit. Intensive Care Med. 2005;31(12):1618-23.
73. Bouch DC, Thompson JP. Severity scoring systems in the critically ill. Continuing Education in Anaesthesia Critical Care & Pain. 2008;8(5):181-5.
74. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med. 1981;9(8):591-7.
75. Le Gall JR, Loirat P, Alperovitch A, Glaser P, Granthil C, Mathieu D, et al. A simplified acute physiology score for ICU patients. Crit Care Med. 1984;12(11):975-7.
76. Lemeshow S, Teres D, Pastides H, Avrunin JS, Steingrub JS. A method for predicting survival and mortality of ICU patients using objectively derived weights. Crit Care Med. 1985;13(7):519-25.
77. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg. 1985;202(6):685-93.
78. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26(11):1793-800.
79. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23(10):1638-52.
80. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
81. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619-36.
82. Knaus WA, Wagner DP, Zimmerman JE, Draper EA. Variations in mortality and length of stay in intensive care units. Ann Intern Med. 1993;118(10):753-61.
83. Falcão ALE, Barros AGA, Bezerra AAM, Ferreira NL, Logato CM, Silva FP, et al. The prognostic accuracy evaluation of SAPS 3, SOFA and APACHE II scores for mortality prediction in the surgical ICU: an external validation study and decision-making analysis. Ann Intensive Care. 2019;9(1):18.
84. Capuzzo M, Valpondi V, Sgarbi A, Bortolazzi S, Pavoni V, Gilli G, et al. Validation of severity scoring systems SAPS II and APACHE II in a single-center population. Intensive Care Med. 2000;26(12):1779-85.
85. Czajka S, Ziębińska K, Marczenko K, Posmyk B, Szczepańska AJ, Krzych Ł. Validation of APACHE II, APACHE III and SAPS II scores in in-hospital and one year mortality prediction in a mixed intensive care unit in Poland: a cohort study. BMC Anesthesiol. 2020;20(1):296.
86. Sakr Y, Krauss C, Amaral AC, Réa-Neto A, Specht M, Reinhart K, et al. Comparison of the performance of SAPS II, SAPS 3, APACHE II, and their customized prognostic models in a surgical intensive care unit. Br J Anaesth. 2008;101(6):798-803.
87. Fuchs L, Chronaki CE, Park S, Novack V, Baumfeld Y, Scott D, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med. 2012;38(10):1654-61.
88. Atramont A, Lindecker-Cournil V, Rudant J, Tajahmady A, Drewniak N, Fouard A, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. JAMA Netw Open. 2019;2(5):e193215.

89. Utzolino S, Kaffarnik M, Keck T, Berlet M, Hopt UT. Unplanned discharges from a surgical intensive care unit: readmissions and mortality. J Crit Care. 2010;25(3):375-81.
90. Bagshaw SM, Webb SA, Delaney A, George C, Pilcher D, Hart GK, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care. 2009;13(2):R45.
91. Guidry CA, Swenson BR, Davies SW, Dossett LA, Popovsky KA, Bonatti H, et al. Sex- and diagnosis-dependent differences in mortality and admission cytokine levels among patients admitted for intensive care. Crit Care Med. 2014;42(5):1110-20.
92. Lipes J, Mardini L, Jayaraman D. Sex and mortality of hospitalized adults after admission to an intensive care unit. Am J Crit Care. 2013;22(4):314-9.
93. Cohen IL, Lambrinos J. Investigating the impact of age on outcome of mechanical ventilation using a population of 41,848 patients from a statewide database. Chest. 1995;107(6):1673-80.
94. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit Care. 2013;17(2):R81.
95. Pittet D, Thiévent B, Wenzel RP, Li N, Gurman G, Suter PM. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med. 1993;19(5):265-72.
96. Zampieri FG, Colombari F. The impact of performance status and comorbidities on the short-term prognosis of very elderly patients admitted to the ICU. BMC Anesthesiol. 2014;14:59.
97. Boumendil A, Maury E, Reinhard I, Luquel L, Offenstadt G, Guidet B. Prognosis of patients aged 80 years and over admitted in medical intensive care unit. Intensive Care Med. 2004;30(4):647-54.
98. Wright JC, Plenderleith L, Ridley SA. Long-term survival following intensive care: subgroup analysis and comparison with the general population. Anaesthesia. 2003;58(7):637-42.
99. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH, et al. Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. Am J Respir Crit Care Med. 2016;194(2):198-208.
100. Organization WH. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res. 1993;2(2):153-9.
101. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. JAMA Intern Med. 2015;175(4):523-9.
102. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787-94.
103. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293-304.
104. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502-9.
105. Cuthbertson BH, Wunsch H. Long-Term Outcomes after Critical Illness. The Best Predictor of the Future Is the Past. Am J Respir Crit Care Med. 2016;194(2):132-4.

106. Garland A, Olafson K, Ramsey CD, Yogendran M, Fransoo R. Distinct determinants of long-term and short-term survival in critical illness. Intensive Care Med. 2014;40(8):1097-105.
107. Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39(3):420-8.
108. Wiersema R, Eck RJ, Haapio M, Koeze J, Poukkanen M, Keus F, et al. Burden of acute kidney injury and 90-day mortality in critically ill patients. BMC Nephrol. 2019;21(1):1.
109. Wang HE, Muntner P, Chertow GM, Warnock DG. Acute kidney injury and mortality in hospitalized patients. Am J Nephrol. 2012;35(4):349-55.
110. Fortrie G, de Geus HRH, Betjes MGH. The aftermath of acute kidney injury: a narrative review of long-term mortality and renal function. Crit Care. 2019;23(1):24.
111. De Corte W, Dhondt A, Vanholder R, De Waele J, Decruyenaere J, Sergoyne V, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. Crit Care. 2016;20(1):256.
112. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. Clin J Am Soc Nephrol. 2014;9(3):448-56.
113. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney Int. 2019;95(1):160-72.
114. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP. Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. Kidney Int. 2002;62(3):986-96.
115. Arulkumaran N, Annear NM, Singer M. Patients with end-stage renal disease admitted to the intensive care unit: systematic review. Br J Anaesth. 2013;110(1):13-20.
116. Bell M, Granath F, Schön S, Ekbom A, Martling CR, SWING. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med. 2007;33(5):773-80.
117. Prescott GJ, Metcalfe W, Baharani J, Khan IH, Simpson K, Smith WC, et al. A prospective national study of acute renal failure treated with RRT: incidence, aetiology and outcomes. Nephrol Dial Transplant. 2007;22(9):2513-9.
118. Harel Z, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. Kidney Int. 2013;83(5):901-8.
119. Silver SA, Goldstein SL, Harel Z, Harvey A, Rompies EJ, Adhikari NK, et al. Ambulatory care after acute kidney injury: an opportunity to improve patient outcomes. Can J Kidney Health Dis. 2015;2:36.
120. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2016;67(3 Suppl 1):Svii, S1-305.
121. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.

122. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and Long-Term Risk for Cardiovascular Events and Mortality. J Am Soc Nephrol. 2017;28(1):377-87.
123. Wu VC, Wu CH, Huang TM, Wang CY, Lai CF, Shiao CC, et al. Long-term risk of coronary events after AKI. J Am Soc Nephrol. 2014;25(3):595-605.
124. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. Am J Respir Crit Care Med. 2014;189(9):1065-74.
125. Ou SM, Chu H, Chao PW, Lee YJ, Kuo SC, Chen TJ, et al. Long-Term Mortality and Major Adverse Cardiovascular Events in Sepsis Survivors. A Nationwide Population-based Study. Am J Respir Crit Care Med. 2016;194(2):209-17.
126. Lee S, Park S, Kang MW, Yoo HW, Han K, Kim Y, et al. Postdischarge long-term cardiovascular outcomes of intensive care unit survivors who developed dialysis-requiring acute kidney injury after cardiac surgery. J Crit Care. 2019;50:92-8.
127. Parikh CR, Puthumana J, Shlipak MG, Koyner JL, Thiessen-Philbrook H, McArthur E, et al. Relationship of Kidney Injury Biomarkers with Long-Term Cardiovascular Outcomes after Cardiac Surgery. J Am Soc Nephrol. 2017;28(12):3699-707.
128. SICSAG. Audit of Critical Care in Scotland 2019: Reporting on 2018.
129. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
130. Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. JAMA. 2019;322(2):113-4.
131. Wald R, Deshpande R, Bell CM, Bargman JM. Survival to discharge among patients treated with continuous renal replacement therapy. Hemodial Int. 2006;10(1):82-7.
132. Oh HJ, Shin DH, Lee MJ, Ko KI, Kim CH, Koo HM, et al. Urine output is associated with prognosis in patients with acute kidney injury requiring continuous renal replacement therapy. J Crit Care. 2013;28(4):379-88.
133. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64(6):821-35.
134. Prischl FC, Rossing P, Bakris G, Mayer G, Wanner C. Major adverse renal events (MARE): A proposal to unifying renal endpoints. Nephrol Dial Transplant. 2019.
135. Wilcoxon F. Individual Comparisons by Ranking Methods. Biometrics Bulletin. 1945;1(6):80-3.
136. Pearson K. X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science. 1900;50(302):157-75.
137. McDonald J. Handbook of biological statistics: Sparky House Publishing; 2014.
138. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958;53(282):457-81.

139. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B (Methodological). 1972;34(2):187-220.
140. Breslow NE. Analysis of Survival Data under the Proportional Hazards Model. International Statistical Review / Revue Internationale de Statistique. 1975;43(1):45-57.
141. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34(7):1913-7.
142. Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med. 2008;36(4 Suppl):S146-51.
143. Neugarten J, Golestaneh L. Female sex reduces the risk of hospital-associated acute kidney injury: a meta-analysis. BMC Nephrol. 2018;19(1):314.
144. Porter CJ, Juurlink I, Bisset LH, Bavakunji R, Mehta RL, Devonald MA. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. Nephrol Dial Transplant. 2014;29(10):1888-93.
145. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 2001;29(7 Suppl):S99-106.
146. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. Am J Emerg Med. 2008;26(6):711-5.
147. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int. 2019;96(5):1083-99.
148. Nie S, Feng Z, Tang L, Wang X, He Y, Fang J, et al. Risk Factor Analysis for AKI Including Laboratory Indicators: a Nationwide Multicenter Study of Hospitalized Patients. Kidney Blood Press Res. 2017;42(5):761-73.
149. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-45.
150. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74(1):101-7.
151. Singh P, Rifkin DE, Blantz RC. Chronic kidney disease: an inherent risk factor for acute kidney injury? Clin J Am Soc Nephrol. 2010;5(9):1690-5.
152. Forni LG, Darmon M, Ostermann M, Oudemans-van Straaten HM, Pettilä V, Prowle JR, et al. Renal recovery after acute kidney injury. Intensive Care Med. 2017;43(6):855-66.
153. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. Am J Kidney Dis. 2015;65(6):860-9.
154. Lai TS, Wang CY, Pan SC, Huang TM, Lin MC, Lai CF, et al. Risk of developing severe sepsis after acute kidney injury: a population-based cohort study. Crit Care. 2013;17(5):R231.
155. James MT, Grams ME, Woodward M, Elley CR, Green JA, Wheeler DC, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. Am J Kidney Dis. 2015;66(4):602-12.
156. He L, Wei Q, Liu J, Yi M, Liu Y, Liu H, et al. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int. 2017;92(5):1071-83.
157. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia

between 2009 and 2019- results from a systematic review and meta-analysis. Crit Care. 2020;24(1):239.
158. Rennie TJ, Patton A, Dreischulte T, Bell S. Incidence and Outcomes of Acute Kidney Injury Requiring Renal Replacement Therapy: A Retrospective Cohort Study. Nephron. 2016;133(4):239-46.
159. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg. 2010;90(4):1142-8.
160. Raghavan S, Vassy JL, Ho YL, Song RJ, Gagnon DR, Cho K, et al. Diabetes Mellitus-Related All-Cause and Cardiovascular Mortality in a National Cohort of Adults. J Am Heart Assoc. 2019;8(4):e011295.
161. Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, et al. Performance of GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Statistical Simulation. J Am Soc Nephrol. 2019;30(9):1756-69.
162. Nojima J, Meguro S, Ohkawa N, Furukoshi M, Kawai T, Itoh H. One-year eGFR decline rate is a good predictor of prognosis of renal failure in patients with type 2 diabetes. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(9):746-54.
163. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, et al. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol. 2007;18(4):1353-61.
164. Imig JD, Ryan MJ. Immune and inflammatory role in renal disease. Compr Physiol. 2013;3(2):957-76.
165. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, et al. Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. J Immunol Res. 2018;2018:2180373.
166. Cribbs SK, Martin GS, Rojas M. Monitoring of endothelial dysfunction in critically ill patients: the role of endothelial progenitor cells. Curr Opin Crit Care. 2008;14(3):354-60.
167. Roumeliotis S, Mallamaci F, Zoccali C. Endothelial Dysfunction in Chronic Kidney Disease, from Biology to Clinical Outcomes: A 2020 Update. J Clin Med. 2020;9(8).
168. Ravani P, Quinn R, Fiocco M, Liu P, Al-Wahsh H, Lam N, et al. Association of Age With Risk of Kidney Failure in Adults With Stage IV Chronic Kidney Disease in Canada. JAMA Netw Open. 2020;3(9):e2017150.
169. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney disease in the elderly: evaluation and management. Clin Pract (Lond). 2014;11(5):525-35.
170. Musso CG, Oreopoulos DG. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol. 2011;119 Suppl 1:p1-5.
171. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA. 2009;302(11):1179-85.
172. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376(9758):2096-103.
173. Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrol Dial Transplant. 2010;25(7):2203-9.

174. Cao Z, Cooper ME. Pathogenesis of diabetic nephropathy. J Diabetes Investig. 2011;2(4):243-7.
175. Markou N, Gregorakos L, Myrianthefs P. Increased blood troponin levels in ICU patients. Curr Opin Crit Care. 2011;17(5):454-63.
176. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol. 2003;41(11):2004-9.
177. Ottani F, Galvani M, Nicolini FA, Ferrini D, Pozzati A, Di Pasquale G, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Heart J. 2000;140(6):917-27.
178. McCarthy CP, Raber I, Chapman AR, Sandoval Y, Apple FS, Mills NL, et al. Myocardial Injury in the Era of High-Sensitivity Cardiac Troponin Assays: A Practical Approach for Clinicians. JAMA Cardiol. 2019;4(10):1034-42.
179. Sandoval Y, Smith SW, Shah AS, Anand A, Chapman AR, Love SA, et al. Rapid Rule-Out of Acute Myocardial Injury Using a Single High-Sensitivity Cardiac Troponin I Measurement. Clin Chem. 2017;63(1):369-76.
180. McManus DD, Nguyen HL, Saczynski JS, Tisminetzky M, Bourell P, Goldberg RJ. Multiple cardiovascular comorbidities and acute myocardial infarction: temporal trends (1990-2007) and impact on death rates at 30 days and 1 year. Clin Epidemiol. 2012;4:115-23.
181. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular Risks Associated with Gender and Aging. J Cardiovasc Dev Dis. 2019;6(2).
182. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Cannon CP, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation. 2010;121(3):357-65.
183. Hansen MK, Gammelager H, Mikkelsen MM, Hjortdal VE, Layton JB, Johnsen SP, et al. Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: a cohort study. Crit Care. 2013;17(6):R292.
184. Doi K. Kidney-Heart Interactions in Acute Kidney Injury. Nephron. 2016;134(3):141-4.
185. Wang Y, Li J, Zheng X, Jiang Z, Hu S, Wadhera RK, et al. Risk Factors Associated With Major Cardiovascular Events 1 Year After Acute Myocardial Infarction. JAMA Netw Open. 2018;1(4):e181079.
186. Rakugi H, Yu H, Kamitani A, Nakamura Y, Ohishi M, Kamide K, et al. Links between hypertension and myocardial infarction. Am Heart J. 1996;132(1 Pt 2 Su):213-21.
187. Holzmann M, Jernberg T, Szummer K, Sartipy U. Long-term cardiovascular outcomes in patients with chronic kidney disease undergoing coronary artery bypass graft surgery for acute coronary syndromes. J Am Heart Assoc. 2014;3(2):e000707.
188. Power A. Stroke in dialysis and chronic kidney disease. Blood Purif. 2013;36(3-4):179-83.
189. Parikh NS, Navi BB, Schneider Y, Jesudian A, Kamel H. Association Between Cirrhosis and Stroke in a Nationally Representative Cohort. JAMA Neurol. 2017;74(8):927-32.
190. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with

acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-75.
191. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci. 2016;351(4):380-6.
192. Wu VC, Wu PC, Wu CH, Huang TM, Chang CH, Tsai PR, et al. The impact of acute kidney injury on the long-term risk of stroke. J Am Heart Assoc. 2014;3(4).
193. Morgan DJ, Ho KM. A comparison of nonoliguric and oliguric severe acute kidney injury according to the risk injury failure loss end-stage (RIFLE) criteria. Nephron Clin Pract. 2010;115(1):c59-65.
194. Anderson RJ, Linas SL, Berns AS, Henrich WL, Miller TR, Gabow PA, et al. Nonoliguric acute renal failure. N Engl J Med. 1977;296(20):1134-8.
195. Mandelbaum T, Lee J, Scott DJ, Mark RG, Malhotra A, Howell MD, et al. Empirical relationships among oliguria, creatinine, mortality, and renal replacement therapy in the critically ill. Intensive Care Med. 2013;39(3):414-9.
196. Thongprayoon C, Cheungpasitporn W, Akhoundi A, Ahmed AH, Kashani KB. Actual versus ideal body weight for acute kidney injury diagnosis and classification in critically ill patients. BMC Nephrol. 2014;15:176.
197. Hodgin JB, Bitzer M, Wickman L, Afshinnia F, Wang SQ, O'Connor C, et al. Glomerular Aging and Focal Global Glomerulosclerosis: A Podometric Perspective. J Am Soc Nephrol. 2015;26(12):3162-78.
198. Sun YM, Su Y, Li J, Wang LF. Recent advances in understanding the biochemical and molecular mechanism of diabetic nephropathy. Biochem Biophys Res Commun. 2013;433(4):359-61.
199. Lehner GF, Forni LG, Joannidis M. Oliguria and Biomarkers of Acute Kidney Injury: Star Struck Lovers or Strangers in the Night? Nephron. 2016;134(3):183-90.
200. Feinfeld DA, Danovitch GM. Factors affecting urine volume in chronic renal failure. Am J Kidney Dis. 1987;10(3):231-5.
201. Fukuda M, Motokawa M, Miyagi S, Sengo K, Muramatsu W, Kato N, et al. Polynocturia in chronic kidney disease is related to natriuresis rather than to water diuresis. Nephrol Dial Transplant. 2006;21(8):2172-7.
202. Nakano D, Doi K, Kitamura H, Kuwabara T, Mori K, Mukoyama M, et al. Reduction of Tubular Flow Rate as a Mechanism of Oliguria in the Early Phase of Endotoxemia Revealed by Intravital Imaging. J Am Soc Nephrol. 2015;26(12):3035-44.
203. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219-23.
204. Patil NK, Parajuli N, MacMillan-Crow LA, Mayeux PR. Inactivation of renal mitochondrial respiratory complexes and manganese superoxide dismutase during sepsis: mitochondria-targeted antioxidant mitigates injury. Am J Physiol Renal Physiol. 2014;306(7):F734-43.
205. Fuchs L, Novack V, McLennan S, Celi LA, Baumfeld Y, Park S, et al. Trends in severity of illness on ICU admission and mortality among the elderly. PLoS One. 2014;9(4):e93234.
206. McPeake J, Iwashyna TJ, Henderson P, Leyland AH, Mackay D, Quasim T, et al. Long term outcomes following critical care hospital admission: A prospective cohort study of UK biobank participants. Lancet Reg Health Eur. 2021;6:100121.
207. Schwenger V, Weigand MA, Hoffmann O, Dikow R, Kihm LP, Seckinger J, et al. Sustained low efficiency dialysis using a single-pass batch system in acute

kidney injury - a randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts. Crit Care. 2012;16(4):R140.
208. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356(9223):26-30.
209. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375(2):122-33.
210. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315(20):2190-9.
211. Xu Y, Gao J, Zheng X, Zhong B, Na Y, Wei J. Timing of initiation of renal replacement therapy for acute kidney injury: a systematic review and meta-analysis of randomized-controlled trials. Clin Exp Nephrol. 2017;21(4):552-62.
212. Wierstra BT, Kadri S, Alomar S, Burbano X, Barrisford GW, Kao RL. The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. Crit Care. 2016;20(1):122.
213. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care. 2011;15(1):R72.
214. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis. 2008;52(2):272-84.
215. Fayad AII, Buamscha DG, Ciapponi A. Timing of renal replacement therapy initiation for acute kidney injury. Cochrane Database Syst Rev. 2018;12:CD010612.
216. Srisawat N, Laoveeravat P, Limphunudom P, Lumlertgul N, Peerapornratana S, Tiranathanagul K, et al. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study. J Crit Care. 2018;43:36-41.
217. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med. 2018;379(15):1431-42.
218. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions* 2019 (version 6.0).
219. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
220. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions* 2019 (version 6.0).
221. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

222. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
223. McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. Biom J. 2020;62(1):69-98.
224. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int. 2004;8(4):320-5.
225. Pursnani ML, Hazra DK, Singh B, Pandey DN. Early haemodialysis in acute tubular necrosis. J Assoc Physicians India. 1997;45(11):850-2.
226. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med. 2002;30(10):2205-11.
227. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62(6):1116-21.
228. Bagshaw SM, Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med. 2020;383(3):240-51.
229. Lameire N, Vanmassenhove J. Timing of Dialysis in Sepsis and Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2018;198(1):4-5.