Characterisation of cardiovascular function in intensive care unit survivors of sepsis

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Abstract

There are over 200,000 intensive care unit (ICU) admissions in the UK each year, with sepsis being one of the most common admission diagnoses. Over two thirds of ICU survivors experience physical, cognitive or psychological impairments following discharge, often-termed post-intensive care syndrome (PICS). However, the mechanisms by which these impairments occur is unclear.

Patients admitted to ICU with sepsis often experience acute cardiovascular dysfunction, e.g. myocardial infarction, dysrhythmia, or sepsis induced cardiomyopathy. These patients often have significant haemodynamic instability such that they require infusions of vasoactive medicines to support blood pressure and other physiological targets. It is now increasingly recognised that there are often long-term cardiovascular consequences of sepsis admission. Compared to population or hospitalised controls, the incidence of stroke, heart failure and myocardial infarction are increased following an admission with sepsis in a magnitude comparable to other traditional cardiovascular risk factors, such as hypertension or dyslipidaemia. Sepsis is also known to be associated with persistent activation of inflammatory pathways that are also implicated in the pathogenesis of heart failure and other chronic cardiovascular conditions.

Thus, there are plausible mechanisms by which admission with sepsis may result in an increased risk of cardiovascular disease. There is also significant overlap between symptoms commonly experienced in patients with PICS (e.g. breathlessness and fatigue) and those experienced by patients with heart failure. The work in this thesis aims to characterise the cardiovascular function in ICU survivors of sepsis and explore whether cardiovascular dysfunction may be associated with the functional impairments seen in PICS.

Chapter 1 presents an overview of key concepts in critical illness, PICS, sepsis and heart failure. It outlines definitions of critical illness, the long-term consequences of ICU admission and the manifestations of PICS. It highlights key concepts in sepsis and the associations with chronic inflammation during convalescence. Finally, the chapter discusses cardiovascular dysfunction *during* sepsis and how it may be implicated in the pathogenesis of long term cardiovascular disease.

Chapter 2 presents a scoping review of the literature surrounding cardiovascular dysfunction in survivors of sepsis. It demonstrates that whilst there is an increasing body of literature that recognises the risk of adverse cardiovascular events associated with sepsis admission, there is a paucity of data that seeks to address the underlying mechanisms by which this phenomenon occurs.

Chapter 3 presents the methodology used in a multi-site observational cohort study utilising cardiovascular magnetic resonance (CMR) imaging, biomarker analysis and patient reported outcome measures (PROMs) to characterise the cardiovascular function in a cohort of ICU survivors of sepsis from Scottish ICUs.

Chapter 4 describes the overall demographics of 50 patients recruited to the ICU follow-up study after sepsis admission. Of these patients, 34 were successfully followed up with CMR imaging, biomarker analysis and PROMs.

Chapter 5 describes the CMR findings in the study cohort, 6-10 weeks following hospital discharge. Left ventricular systolic dysfunction (LVSD) was present in 7/34 (20.6%) of the study population and was associated with acute LV dysfunction during ICU admission (OR 7.67 (95%CI 1.26, 54.5) p=0.030). The LVSD was global in nature, with no evidence of late gadolinium enhancement and scar in any participants. LVSD was also associated with N terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity troponin (hs-TnT) at 6-10 weeks post hospital discharge. The cohort as a whole had elevated median values of native T1 and ECV, indicating fibrosis and expansion of the extra-cellular volume.

Chapter 6 describes cardiovascular, renal and inflammatory biomarkers in ICU survivors of sepsis at recruitment (at the time of ICU discharge) and at follow-up (6-10 weeks post hospital discharge). It demonstrates elevated levels of the cardiovascular biomarker NT-proBNP (median 1,446pg/mL) at discharge from ICU. Median values were significantly different at follow-up in participants who had LVSD (208 vs 74pg/mL, p=0.024) and were at levels that (dependent on symptom burden and imaging findings) would be supportive of a diagnosis of heart failure. Participants with LVSD also had values of inflammatory biomarkers elevated above their normal reference range, many of which have been highlighted of pathological significance in heart failure.

Chapter 7 describes patient reported outcome measures of exercise capacity and health related quality of life (HRQoL) in the study population. Median Duke activity status index (DASI) score was 21, indicating reduced exercise capacity. As measured by EuroQol 5-level 5-dimension (EQ-5D-5L), there were widespread levels of impairment across multiple domains. Whilst not statistically significant, participants with LVSD had reduced exercise capacity, increased measures of dyspnoea and reduced HRQoL measures in comparison to those without LVSD. Clinical frailty score prior to ICU admission was significantly associated with reduced log DASI score (β=-0.30 (95%CI -0.48, -0.12) p=0.002) and EQ-5D-5L visual analogue scale (β=-6.24 (95%CI -12.3, -0.18), p=0.044) in the study population, underpinning its importance in determining overall functional trajectory upon recovery.

These findings indicate that follow-up with CMR imaging, biomarkers and PROMs was feasible and well tolerated in this population, with attrition rates in keeping with other long-term outcome literature. LVSD was prevalent and associated with abnormal biomarkers of cardiovascular dysfunction and injury. Measures of exercise capacity and HRQoL were reduced, but not to a degree which was statistically significant. The findings are supportive of the hypothesis that chronic cardiovascular dysfunction is prevalent following ICU admission with sepsis, and may be associated with both the acute cardiovascular dysfunction seen during index illness and ongoing inflammation during convalescence. Furthermore, these data suggest there may be a cohort of patients at increased risk of cardiovascular disease following ICU who could benefit from established therapy to modify recovery trajectory and reduce morbidity following admission.

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Author's declaration

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

Any publications from this thesis have been outlined and explained in the relevant chapters.

The work presented was undertaken during a three-year post as a clinical research fellow at the University of Glasgow. The work continued upon re-entry to clinical training in acute, general, and intensive care medicine.

Publications

- **Garrity K**, Gaw S, Blewitt A, Canon P, McCall P, McPeake J. Cardiac dysfunction in survivors of sepsis: a scoping review. Open Heart. 2023 Dec 7;10(2):e002454.

- **Garrity K**, Docherty C, Mangion K, Woodward R, Shaw M, Roditi G, Shelley B, Quasim T, McCall P, McPeake J. Characterizing Cardiac Function in ICU Survivors of Sepsis: A Pilot Study Protocol. CHEST Crit Care. 2024 Mar;2(1):100050.

- Docherty C, Page C, Wilson J, Ross P, **Garrity K**, Quasim T, Shaw M, McPeake J. Association between inflammation and post-intensive care syndrome: a systematic review. Anaesthesia. 2024 Jul;79(7):748-758.

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- **Garrity K**, Docherty C, Mangion K, McCall P, McPeake J. Characterisation of cardiovascular function in intensive care unit survivors of sepsis (CONDUCT-ICU): early pilot phase results. BSCMR Annual Conference:2023 Glasgow. Heart 2024;110:A16.

- **Garrity K**, Docherty C, Mangion K, McCall P, McPeake J. Characterisation of cardiovascular function in intensive care unit survivors of sepsis (CONDUCT-ICU): early pilot phase results. GWSSA/GARC Annual Meeting :2024 Glasgow.

- **Garrity K**, Docherty C, Mangion K, McCall P, McPeake J. Characterisation of cardiovascular function in intensive care unit survivors of sepsis (CONDUCT-ICU): early pilot phase results. ESICM Annual Congress:2024 Barcelona. Best Abstracts. *ICMx* **12** (Suppl 1), 87 (2024)

- **Garrity K**, Docherty C, Mangion K, McCall P, McPeake J. Characterising cardiovascular function in survivors of sepsis: Interim analysis from (CONDUCT-ICU). Scottish right heart symposium:2025.Glasgow

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List of abbreviations

6-MWT	6-minute walk test
ACC	American college of cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AD	Anderson-Darling
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHA	American heart association
AKI	Acute kidney injury
ALI	Acute lung injury
ANOVA	Analysis of variance
APACHE	Adult physiology and chronic health evaluation
APC	Antigen presenting cell
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
AUROC	Area under the receiver operating curve
BMI	Body mass index

BMJ	British medical journal
BODE Index	Body mass index, Obstruction, Dyspnoea, Exercise Capacity Index
BSA	Body surface area
BSE	British society of echocardiography
CAC	Coronary artery calcification
CANTOS	Anti-inflammatory therapy with canakinumab for atherosclerotic disease
CC-BY	Creative commons attribution
CCI	Charleson comorbidity index
CFS	Clinical frailty scale
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CINAHL	Cumulative index of nursing and allied health literature
CKD	Chronic kidney disease
CMR	Cardiovascular magnetic resonance
CNS	Central nervous system
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease

CRP	C reactive protein
CT	Computed tomography
CTCA	Computed tomography coronary angiogram
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cardiovascular event
CVM	Cramer von missus
DAMP	Danger associated molecular pattern
DASI	Duke activity status index
EACVI	European association of cardiovascular imaging
ECG	Electrocardiogram
ECV	Extra cellular volume
EDTA	Ethylenediaminetetraacetic acid
EF	Ejection fraction
EQ-5D-5L	EuroQol 5 level 5 dimension
ESC	European society of cardiology
ESICM	European society of intensive care medicine
ESRF	End stage renal failure

GDF-15	Growth differentiation factor 15
GDMT	Guideline directed medical therapy
GDP	Gross domestic product
GFR	Glomerular filtration rate
GlasBRU	Glasgow biomarker research unit
GLS	Global longitudinal strain
GRACE	Greater recovery after critical illness
HADS	Hospital anxiety and depression score
HDU	High dependency unit
HF	Heart failure
HFSA	Heart failure society of america
HLA	Horizontal long axis
HRQoL	Health related quality of life
hs-TnT	High sensitivity troponin T
HUS	Health utility score
ICC	Intra-class correlation
ICD	International classification of disease
ICS	Intensive care society

ICU	Intensive care unit
ICUAW	Intensive care unit acquired weakness
IHD	Ischaemic heart disease
IL	Interleukin
IQR	Inter quartile range
ITU	Intensive care unit
JBI	Joanne-Briggs institute
JHFS	Japanese heart failure society
KDIGO	Kidney disease: Improving global outcomes
KS	Kolmogorov-Smirnov
LGE	Late gadolinium enhancement
LOD	Limit of detection
LOS	Length of stay
LV	Left ventricle
LVCO	Left ventricular cardiac output
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume

LVM	Left ventricular mass
LVOT	Left ventricular outflow tract
LVSD	Left ventricular systolic dysfunction
LVSV	Left ventricular stroke volume
MACE	Major adverse cardiovascular events
MEDLINE	Medical literature analysis and retrieval system on-line
MI	Myocardial Infarction
MOCA	Montreal cognitive assessment
MOLLI	Modified look-locker inversion recovery
MR	Magnetic resonance
MRC	Medical research council
MRI	Magnetic resonance imaging
MR-proADM	Mid-regional pro-adrenomedullin
NA	Not applicable
NETS	Neutrophil extracellular traps
NHF	Nasal high flow
NHS	National health service
NICE	National institute of clinical excellence

NIV	Non-invasive ventilation
NLRP3	nucleotide-binding domain, leucine-rich repeat, and pyrin domain containing receptor 3
NPR	Natriuretic peptide receptor
NT-proBNP	N terminal pro-B-type natriuretic peptide
NYHA	New York heart association
OR	Odds ratio
OSF	Open science framework
PACS	Picture archiving and communication system
PAMP	Pathogen associated molecular pattern
PICS	Post intensive care syndrome
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROM	Patient reported outcome measure
PROMS	Patient reported outcome measure
QEUH	Queen Elizabeth University Hospital
Q-Q plot	Quantile-quantile plot
RAAS	Renin angiotensin aldosterone system
RCT	Randomised controlled trial

Rf	Radiofrequency
RIFLE	Risk, injury, failure, loss and end-stage
ROI	Region of interest
RRT	Renal replacement therapy
RV	Right ventricle
RVCO	Right ventricular cardiac output
RVD	Right ventricular dysfunction
RVEDV	Right ventricular end-diastolic volume
RVEF	Right ventricular ejection fraction
RVESV	Right ventricular end-systolic volume
RVM	Right ventricular mass
RVSD	Right ventricular systolic dysfunction
RVSV	Right ventricular stroke volume
SA	Short axis
SCCM	Society of critical care medicine
SCMR	Society of cardiovascular magnetic resonance
SF-36	Short form - 36
SGLT2	Sodium glucose cotransporter 2

SIMD	Scottish index of multiple deprivation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SSFP	Steady-state free precession
SST	Serum separator tube
STROBE	Strengthening the reporting of observational studies in epidemiology
TLR	Toll like receptor
TNF-α	Tumour necrosis factor alpha
TOE	Trans-oesophageal echocardiography
TTE	Trans-thoracic echocardiography
UK	United Kingdom
US	United States
USA	United States of America
VAS	Visual analogue scale

Chapter 1 Introduction

The Intensive Care Unit (ICU) is the designated area within a hospital dedicated to managing the sickest patients. These patients are often admitted on account of conditions which pose an immediate threat to life, have potential for reversibility and require support of vital organs such as the lungs, heart or kidneys without which they may not survive.[1] The care required is often complex and resource intensive, requiring input by dedicated multi-disciplinary teams including medical, nursing, pharmacy and other allied professionals whose main focus is managing these serious conditions in specialised units.

Whilst often lifesaving, ICU treatment and its consequences can be burdensome for patients. Over two thirds of ICU survivors will have physical, psychological, or cognitive impairments often collectively termed post-intensive care syndrome (PICS).[2 3] These impairments are associated with a significant impact on quality of life. Approximately half of ICU survivors are unable to return to work following admission and often experience a decline in functional trajectory and ability to undertake activities of daily living.[4-6] Furthermore, ICU survivors have increased risk of adverse outcomes such as re-hospitalisation following admission or cardiovascular events such as myocardial infarction or heart failure.[7-9]

The study discussed in the following chapters pertains to the long-term cardiovascular consequences of an ICU admission with sepsis, the most common presenting condition to ICU. As such, it is important to understand the nature of the care provided in the ICU, the diagnosis and pathophysiology of sepsis and its impact on the cardiovascular system and finally, the diagnosis of chronic heart failure and how these methods could be applied in ICU survivors of sepsis.

The following section will consider the origin and configuration of the modern ICU, the treatments that might potentially be offered to patients, the nature of ‘critical illness’ and the long-term impact of critical illness and associated treatments.

1.1 The Intensive care unit and critical illness

1.1.1 A brief history of intensive care units

The configuration of the modern ICU is commonly regarded as originating in the mid-20th century, although the concept of centrally locating sick patients was documented as early as the Crimean War, where in the 1850s Florence Nightingale ensured that the sickest patients were closest to ward nursing stations to ensure adequate monitoring.

Nearly a century later, in 1952, a devastating polio epidemic in Copenhagen led to the admission of hundreds of patients with respiratory and bulbar failure, all of whom required invasive mechanical ventilation within a short space of time. This far outstripped the capacity of the health services at the time and required an innovative approach, leading Dr Henry Lassen[1] and colleagues to develop the first documented example of modern critical care using invasive mechanical ventilation via tracheostomy for multiple patients at once, facilitated by a high ratio of trained medical and nursing staff.[10] The approach saved hundreds of lives and served as the foundation for modern ICUs as we know them today.

This approach of providing targeted organ support gained traction. Over the latter half of the 20th century, the subsequent dogma in intensive care was an organ-level physiological approach towards critical illness, that focused on maintaining homeostasis of organ systems (e.g. respiratory, cardiovascular or renal) augmented by provision of supportive therapies such as mechanical ventilation, infusions of vasoactive medications to support the cardiovascular system, or dialysis. Furthermore, the creation of units with dedicated care staff responsible for overall care of the patient became more commonplace and evidence of improved outcomes soon followed.[11]

Whilst this broad approach became ubiquitous, differences in configuration of ICUs have emerged over the last century. There are few recent data comparing the configuration of ICUs and provision worldwide. However, a 2010 review

[1] Prof Henry Lassen, MD. Professor of communicable disease and chief physician, Blegdams Hospital, Copenhagen.

highlighted differences in international provision, with countries like Belgium, Germany and the United States of America estimated to have 21.9, 24.6 and 20.0 ICU beds per 100,000 population.[12] In comparison, the United Kingdom was estimated to have 3.5 beds per 100,000 population, although this number may be as high as 7.3 in recent years.[13] This apparent disparity in resource, even between countries with comparative GDP, gives rise to intrinsic differences in how care is provided within different healthcare systems despite similarities in patient presentation. As such, it is important to consider the configuration of ICU in the United Kingdom and the nature of care received whilst admitted in order to understand the patient population in the study that follows.

1.1.2 Intensive care in the United Kingdom

The Department of Health and Social Care released their comprehensive review of critical care in 2000, outlining standards for critical care and recommending the classification of patients by individual needs regardless of location in the hospital. They classified patients into four levels depending on the level of support required, ranging from those who can be looked after on a standard hospital ward through to those requiring support of multiple organs requiring constant monitoring (Table 1-1).[14]

These ‘levels’ of care have been echoed and expanded upon in more recent guidelines for the provision of intensive care, but ultimately remain similar.[15]

In the UK, patients requiring level 3 care and often patients with level 2 care requirements are the responsibility of the ICU team. Patients requiring level 1 or some patients with level 2 will often be managed within a ‘High Dependency Unit’ (HDU) setting. This is exemplified in national audit data. For example, in a relatively recent national audit of critical care units in Scotland, 46% of ICU patients during 2022 underwent invasive mechanical ventilation, an example of level 3 care, and over 52% required cardiovascular support during their ICU stay. It indicates the complexity and acuity in this patient cohort, and the need for specialist ‘intensivists’ to facilitate their care. In comparison, only 11% of patients admitted to HDUs required any form of organ support.[16]

Table 1-1 Levels of care as outlined by Dept of Health in 'Comprehensive Critical Care'

Level of care	Description
0	Patients whose needs can be met through normal ward care in an acute hospital
1	Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team.
2	Patients requiring more detailed observation or intervention including support for a single failing organ system or post-operative care and those 'stepping down' from higher levels of care
3	Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure.

As perhaps might be expected, staffing levels and ratios are higher in an intensive care setting due to the complexity and the burden of care. Consultant physicians are expected to care for patients between ratios of 1:8 - 1:12. Similarly, nursing ratios are much higher than that expected in a ward. Level 3 patients should expect to be looked after by nurses on a 1:1 basis as a minimum standard and Level 2 patients looked after by a nurse on a minimum of a 1:2 patient ratio.[15] This further demonstrates the complexity of patients requiring ICU care and reflects the increased workload in looking after these patients safely. For example, a nurse looking after a 'Level 3' patient during a 12.5-hour day might be expected, with support of medical staff, to escalate or wean invasive ventilatory support via an endotracheal tube, titrate vasoactive drugs according to prespecified haemodynamic targets and manage a dialysis circuit ensuring it doesn't clot or remove too much fluid. Furthermore, this occurs often simultaneously with day-to-day care such as washing, toileting and skin care all the while ensuring the patient is comfortable and not distressed. Whist

rewarding, it is laborious, burdensome and requires meticulous attention to detail, through routine collection of hourly observations of physiological data.[15]

This illustrates the complexity of care required to manage critical illness and gives insight into the burden.

1.2 Critical Illness

1.2.1 Defining critical illness

Similar to intensive care, critical illness is defined by conditions that are associated with a high risk of imminent death, vital organ dysfunction, are potentially reversible and require intensive care support to avoid death (Figure 1-1).[1]

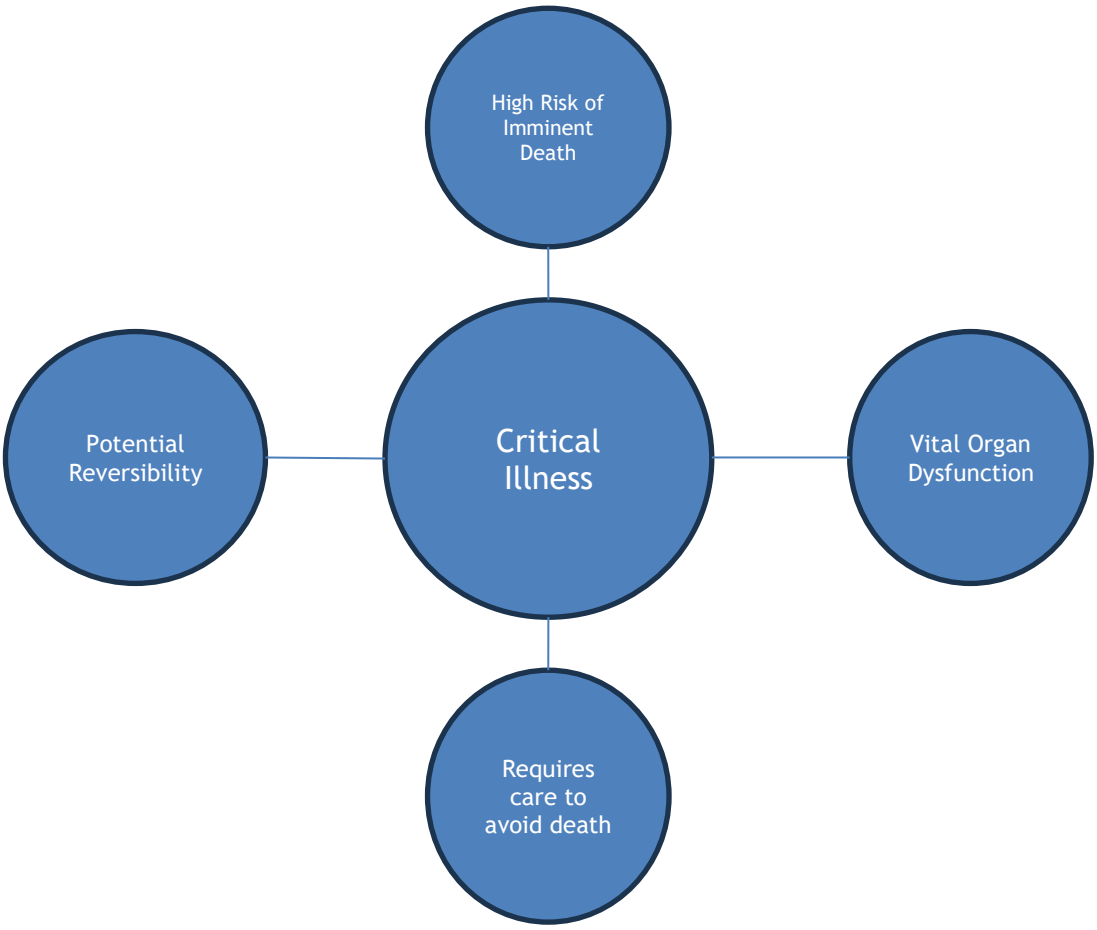

Figure 1-1 Defining Attributes of Critical Illness
Adapted from Kazidule et al (2022)[1] Reproduced with permission from BMJ group.

As outlined above, the conceptual birth of critical illness coincided with the inception of ICUs and the realisation that provision of organ specific means of physiological support (e.g. mechanical ventilation) could facilitate the treatment of life-threatening conditions.[17 18] Critical illness was defined by organ-level pathophysiology and therapies were focused on provision of support and homeostasis for specific organ 'failures' (e.g. respiratory failure or cardiovascular failure).[18]

Across the last quarter of the 20th century, further translational research led to a greater understanding of the pathophysiology of the host response to common conditions causing critical illness. Definitions, criteria and scoring systems were developed to grade the severity of illness, such as Acute physiology and chronic health evaluation (APACHE) scoring for illness severity.[19] Common presentations such as sepsis, acute respiratory distress syndrome (ARDS), or acute kidney injury (AKI) were defined using specific criteria (e.g. Systemic Inflammatory Response Syndrome (SIRS), Berlin criteria for ARDS and RIFLE[2] for AKI).[20-22] Such criteria laid the foundations for seminal trials and research that has led to improvements for critically ill patients across the world.[21 23] For example, the 'ARDSnet' group demonstrated mortality benefits using lower tidal volume strategies in mechanical ventilation of ARDS patients and the 'Surviving Sepsis' campaign led to improved outcomes for sepsis patients by focusing on early administration of antibiotics and ensuring that specific bundles of care were defined and implemented.[24 25]

As we move into the 21st century, the field is increasingly recognising the limitations of these definitions. Common conditions such as sepsis, ARDS and AKI are heterogenous in nature, and not necessarily united by distinct pathophysiological mechanisms or biochemical, pathologic or serological criteria. Rather, they are a collection of clinical syndromes, with individual patients potentially having dramatic differences in their clinical course despite similar precipitating insults or receipt of similar treatments.[18] As such, the critical care field is now recognising this heterogeneity, with the acceptance

[2] RIFLE criteria refers to the widely accepted classification of acute kidney injury stratifying patients into those at Risk, Injury, Failure, Loss and those with End-stage kidney disease.[20]

that evolving fields such as "omics"[3] disciplines may give novel insights into subtypes of common conditions, where patients may share a disposition to a dysregulated response and/or biological 'traits' that may predict responses to specific therapies.[27] This approach recognises whilst there may be discrete differences in initial acute insult (e.g. trauma / pancreatitis / major haemorrhage), the resulting host response to these insults may bear similarities in pathophysiology and potential response to treatment (Figure 1-2)[18]

In summary, critical illness (in high-resource settings) is defined broadly by its life-threatening nature, potential for reversibility and the requirement for intensive care to prevent the risk of death. Despite significant advances in understanding clinical syndromes that often result in critical illness, there remains significant heterogeneity in the patient population, pathophysiology and response to treatment. Whilst this is clearly of significance to understanding the acute illness dealt with in the day-to-day practice of intensive care medicine, it is also important to consider the implications for understanding recovery from critical illness.

1.2.2 The course and trajectory of critical illness

Critical illness syndromes mark a significant turning point in an individual's quality of life and risk of mortality. For example, the mortality rate associated with sepsis for patients admitted to European, North American and Australian ICUs is estimated at approximately 34%.[28]

Critical illness is common. At the time of writing, the most recent data available from the Intensive Care National Audit & Research Centre report approximately 130,000 ICU admissions per year in England and Wales between 2019-2021.[29] Of patients admitted to general ICUs, 29.7%, 37.9% and 40% were admitted with sepsis in 2019/2020/2021 respectively. The crude hospital mortality rate for these admissions ranged between 26.6% and 32.7%.[29]

[3] "Omics" refers to the collective technologies used to characterise and quantify pools of biological molecules and to explore their roles, relationships and actions in the cells of a living creature. The 'omics' suffix has been added to describe the use of these technologies to examine proteins (proteomics), metabolites (metabolomics) and RNA molecules (transcriptomics).[26]

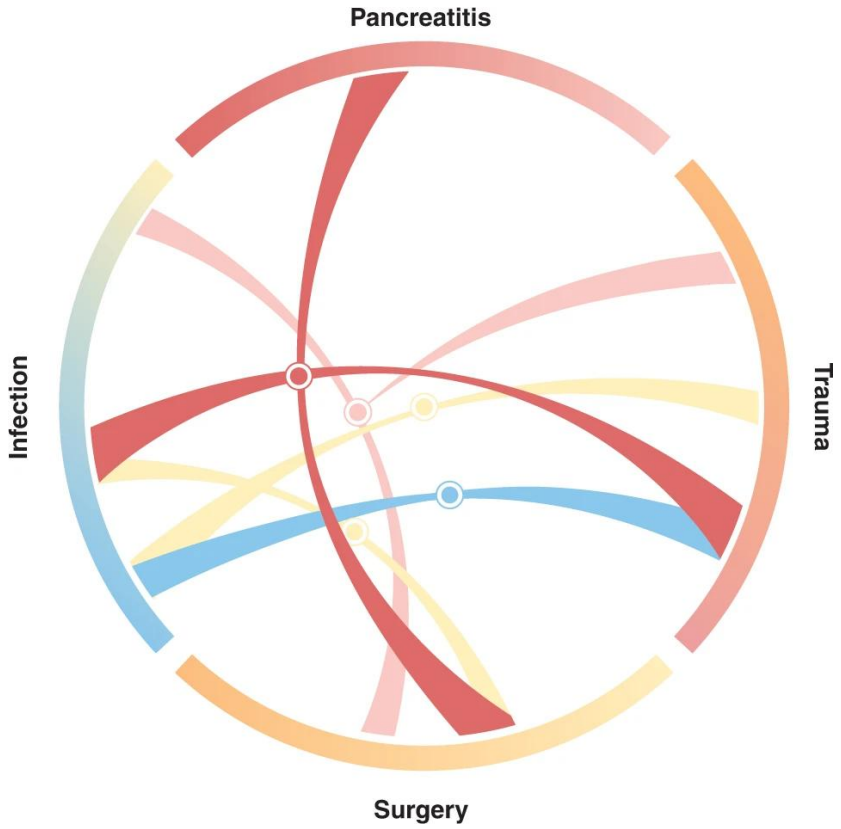

Figure 1-2 Conceptual model of critical illness based on biological features learned from translational research

Individual insults and biological abnormalities are combined in a circular model that recognises that similar abnormalities (represented by interconnecting bands) can arise from multiple discrete insults. For example, similar pathways of inflammation-mediated critical illness may result from either infection or trauma despite differing initial insult. From Maslove et al (2022).[18] Reproduced with permission from Springer Nature.

In Scotland, a country approximately a 10th in population size, there were 16,616 admissions to intensive care and combined HDU/ITU in 2022 with a reported crude mortality rate of 12.3%. Over 50% of patients required some form of organ support.[16] The mean length of an admission to intensive care was approximately 5 days; a significant period of time given the associated burden of intervention required throughout. This is not without impact on patient quality of life.[30 31] Older patients in particular may be predisposed to functional decline following admission, with over 50% of persons over 65 left with disability up to at least year following ICU admission.[6] Other factors associated with persistent impairments include educational attainment and family support.[32]

Whilst severity of illness can help to determine clinical course and trajectory, in some circumstances prior comorbidity aids in prediction of outcomes. For example, the term ‘persistent critical illness’ has been used to define the point

where prior age and comorbidity is better at discriminating mortality risk than reason for admission to ICU. This has been demonstrated in UK settings to occur as early as 5 days and is associated with increased healthcare utilisation and adverse outcomes.[33 34] Given the degree of acute insult required to necessitate a lengthy ICU stay, it might be considered surprising that this insult might bear less prognostic significance than prior comorbidity at such an early stage. It emphasises the complexity of the clinical course of critical illness and its dependence on factors beyond clinical syndromes and diagnoses themselves.

1.2.3 Long-term consequences of critical Illness

Surviving critical illness is associated with an increased risk of mortality. For example, in a Scottish study undertaken in the last decade, the 5-year mortality associated with critical care admission is 32.3% compared to 22.7% in matched hospital control subjects.[35] In addition to this increased risk, it is now recognised that greater than 60% of survivors suffer from long lasting impairments following critical illness. Commonly identified impairments encompass three broad domains: physical, cognitive, and psychological. Collectively, these problems been termed Post Intensive Care Syndrome (PICS).[36] (Figure 1-3)

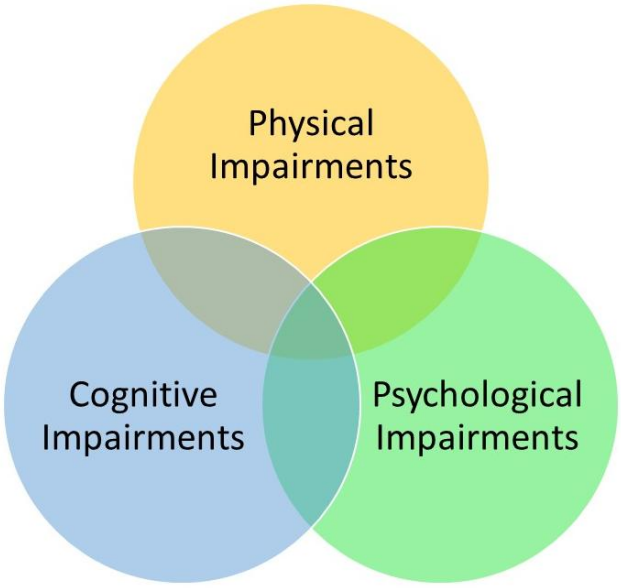

Figure 1-3 Common impairments in survivors of critical illness. A conceptual depiction of the Post-intensive care syndrome (PICS)

PICS can have considerable impact on patients, even 12 months following ICU discharge, the majority of patients will still have persisting symptoms, with a substantial proportion (approximately 20%) having problems in multiple domains.[2] Furthermore, ICU survivorship is associated with increased use of healthcare resources, with up to 30% of ICU survivors readmitted to hospital within 90 days of hospital discharge. Compared to hospitalised controls, ICU survivors also have increased rates of hospital readmission, longer length of stay and a higher costs associated with re-admission. Following ICU discharge, only 50% of patients return to meaningful employment within one year.[4 7 35 37]

Despite this stark association between critical illness and adverse outcomes, the mechanisms by which impairments are mediated are less clear. For example, survivors of ARDS have been shown to have a measurable deterioration in lung function for some time after critical illness and patients with prolonged critical illness often have muscle weakness which persists for some time following discharge.[30 38]

Traditional definitions of PICS are increasingly recognised as limited, and the consequences of intensive care may manifest across a broad spectrum of clinical phenotypes, including problems beyond recognised domains (such as swallowing difficulties or metabolic sequelae).[39 40] Furthermore, critical illness survivors are a heterogenous group by nature and long-term outcomes are likely to be a result of complex interactions between patient factors, illness characteristics and factors related to specific treatments (Figure 1-4).[41] Indeed, the heterogeneity is perhaps exemplified in the literature itself. In trials that focus on long-term outcomes following specific critical illness syndromes (e.g. post-critical care, post-sepsis, post-covid-19, post-ARDS), similar PICS features are identified during recovery despite these data examining distinct cohorts from a pathological perspective.[2 30 36 42]

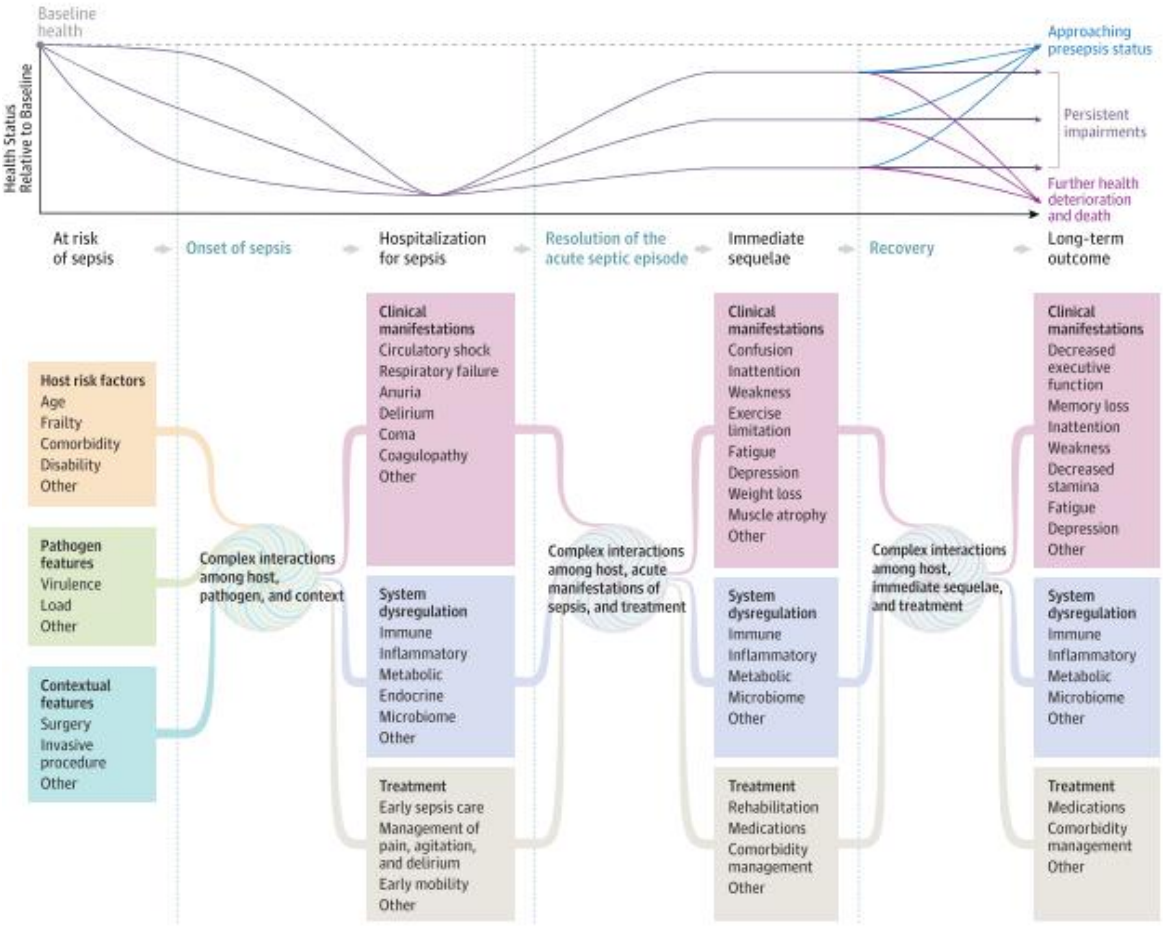

Figure 1-4 Conceptual model of potential network of factors and interactions to determine a patient's clinical course and long-term outcome after sepsis

There a multiple factors that determine prior risk of sepsis, factors related to hospitalization, sequelae of treatment and on recovery which determine and can alter patient trajectory. From Prescott & Angus (2022).[41] Reproduced with permission from JAMA.

Thus, in examining the long-term consequences of critical illness, it is worth considering which specific impairments occur commonly and why they might occur.

1.2.4 Physical impairments following critical illness

A significant proportion of patients experience physical problems following intensive care admission. Commonly documented problems include impairments in pulmonary function, muscle function or neuropathy, reduced exercise capacity and difficulty in resuming activities of daily living.[40]

1.2.4.1 Impaired respiratory function

There have been several studies examining long-term outcomes and the association with objective measures of lung function (e.g. pulmonary function tests) in survivors of ARDS or 'Acute Lung Injury'[4] (ALI).[30 31 43 44] Seminal work by Herridge et al demonstrated that despite long term reductions in global measures of functional capacity such as the 6-minute walk test (6-MWT), there were no corresponding reductions in objective lung function at both 1 and 5 years. In fact, survivors demonstrated parameters of lung function within 80% of that predicted in a normal population, with the exception of a mild reduction in carbon monoxide diffusion capacity in the early stages of convalescence that subsequently resolved with time.[30 31] Furthermore, studies that have assessed diaphragmatic muscle strength following ALI have demonstrated that although there is a trend towards measurable weakness, this is not a statistically significant, and often resolves over time.[45 46]

When comparing different ventilatory strategies *during* critical illness by examining long-term lung function, the literature has also shown similar results. In ICU survivors recovering from ALI or ARDS, there is an absence of a significant reduction in measured pulmonary function, despite often reduced measures global functional capacity, e.g. the 6 minute walk test (6-MWT).[47 48] Thus, despite the acute and profound respiratory dysfunction that define clinical syndromes such as ARDS, objective measures of lung function in the convalescent period do not support the hypothesis that long term respiratory dysfunction is a sole driver of physical impairments seen in PICS.[49]

1.2.4.2 Impaired skeletal muscle function

During the initial stages of critical illness, there is significant loss of skeletal muscle mass. In a systematic review and meta-analysis of observational studies examining muscle wasting during critical illness, it was estimated that participants lost on average -1.75% (95% CI -2.05, -1.45) of thickness and -2.1% (95% CI -3.17, -1.02) of the cross sectional area of the rectus femoris muscle per

[4] Acute Lung Injury has since been superseded by 'mild' ARDS using the latest Berlin criteria for ARDS[22]

day.[50] Quadriceps thickness decreased by -1.82% (95% CI -2.60, -1.80) and biceps brachii by -1.64% (95% CI -3.09, 0.19).[50] Nearly half of the patients in the meta-analysis had so-called ICU-acquired weakness (ICUAW).

ICUAW is a term that encompasses myopathies, polyneuropathies or combinations thereof that occur as a secondary consequence of critical illness and can lead to both acute and long-term consequences.[51] Quantitatively measured reductions in muscle strength have been documented in numerous studies, and are often correlated with the widely documented reductions in more general measures of function such as 6-MWT or SF-36 scores.[45 52]

Often, these impairments in muscle function are correlated with reductions in muscle strength. Poulsen et al assessed ICU survivors one-year following discharge and found significant reductions in maximal quadriceps extension (51%), quadriceps flexion (14%) and handgrip strength (11%) compared to healthy matched controls.[52] When correcting for the associated reduction in muscle mass, any statistically significant difference was negated. The findings suggested the loss in muscle mass may play a causative role in reduced strength in ICU survivors.

Another landmark study of ICUAW published around the same time demonstrated that a significant proportion (36%) of patients with acute lung injury are discharged from ICU with ICUAW, although this gradually resolved such that it was only present in 9% of patients after 2 years.

1.2.4.3 Limitations in overall physical function

In terms of functional limitations, there have been well documented reductions in overall exercise tolerance following ICU admission using measures such as the 6-MWT during convalesence.[44 52-54] The 6-MWT is a global measure of exercise capacity and physical function in which participants are asked to walk back and forward between two cones 30m apart and distance measured and compared with population norms.[55] In a study of 224 participants who were survivors of acute lung injury (of which 154 were followed up until two years beyond discharge), 6-MWT was 60% years beyond discharge from hospital.[45] This too has been demonstrated in other similar studies, with significant reductions in

predicted values persisting at least 5 years following discharge.[30 56] There are also correlations with other PROMs assessing overall physical functioning such as Short Form-36 (SF-36).[45]

1.2.5 Cognitive impairment following critical illness

Iwashyna et al examined US adults over the age of 50 and demonstrated an increased prevalence of moderate to severe cognitive impairment by 11% following an episode of severe sepsis in comparison to persons with non-sepsis hospitalisations.[5] The prevalence of cognitive issues following ICU admission has subsequently been observed in multiple survivor populations; in both 'all-comer' cohorts and discrete critical illness syndromes such as ARDS or post-cardiac arrest.[2 57-60]

The prevalence of cognitive impairment in these studies is often very high. Perhaps the most notable of studies examining this phenomenon was undertaken by Pandharipande et al who followed up adult patients with respiratory failure or shock for 12 months. The group demonstrated that at 4-months post-ICU stay, 40% of survivors had global cognition scores 1.5 standard deviations below the population mean, comparable to those with traumatic brain injury. 24% of survivors had cognition scores with paralleled values seen in patients with Alzheimer's dementia.[57] These changes were independently associated with a longer duration of delirium.[57] Strengths of this particular study included the long duration of follow-up, the careful consideration of key confounders such as delirium and sedative medications and the use of cognitive assessments that can be directly comparable to other patient cohorts.

A similar prevalence has been demonstrated in other prospective cohort studies. Collet et al published data from a cohort study embedded within AID-ICU - an international multi-centre trial of haloperidol in ICU patients with delirium - and demonstrated a 52% prevalence of cognitive impairment in participants from their Danish centres a 6 months.[60 61]

The mechanisms by which cognitive impairment might occur following critical illness are also unclear. It would seem that the association with delirium is important and it has been postulated that systemic inflammation may stimulate

microglial activation in the central nervous system that results in neuronal injury and reduces the threshold for delirium.[62] This model of innate inflammation driving long term impairment and a propensity to chronic disease bears similarities with some of the mechanisms that may underpin physical impairments and offers a mechanistic pathway for future exploration.

1.2.6 Psychological outcomes following critical illness

Whilst psychological outcomes are not the focus of this thesis, it is important to consider the profound psychological impact that ICU admission has on survivors. The largest study to date conducted by Hatch et al in 2018 analysed survey responses from 4943 survivors of who received level 3 care during three phases: Nov 2006 – May 2008; May 2008 – Oct 2010; and May 2012 and May 2013. Over half of patients reported symptoms of anxiety, depression or post-traumatic stress and 65% of those with one disorder had another present. Depression was associated with a 50% increase in mortality compared to those without when adjusted for confounders.

This magnitude was greater than demonstrated in other studies, but nonetheless is consistent with an increased risk of mortality associated with depression in more general cohorts.[63]

Thus, ICU admission is associated with a wide range of impairments across multiple domains. The mechanisms which underlie these impairments is often unclear. Despite often having distinct critical illness syndromes, patients are often left with similar impairments following ICU discharge.[2] Recovery from sepsis is no exception.[5] The following section will consider the pathophysiology of sepsis and its long-term consequences and implications for survivorship.

1.3 Sepsis

Sepsis is one of the most common reasons for ICU admission, and accounts for approximately one third of ICU admissions in the UK.[64] Like many other critical illness syndromes, it is heterogenous in nature and its defining features have been subject to revision over recent decades.

1.3.1 Definitions of sepsis

Contemporary definitions of sepsis have evolved over time, with a recognition that it has oftentimes been difficult to define what differentiates sepsis from uncomplicated infection, or indeed a significant non-infective inflammatory response.[65] There is also an acknowledgement in the literature that there is no unifying diagnostic test to confirm sepsis. As such, other objective features of organ dysfunction or elements of the host response are required to be identified.[65]

To address some of these issues, a joint task force was convened in 2016 by the European Society of Critical Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) in the US to publish the 'Third International Consensus Definitions for Sepsis and Septic Shock', otherwise known as 'Sepsis-3'. The task-force defines sepsis as '*life-threatening organ dysfunction caused by dysregulated response to infection*'. [65] This was in part due to a recognition that the systemic inflammatory response syndrome or (SIRS) - a key component of previous definitions - may occur in other critical illness syndromes in the absence of infection, is oversensitive and non-specific. In addition, previous definitions offered a lack of means by which to reliably stage severity of sepsis and did not take into account adequate understanding of the pathobiology of sepsis.[66]

Organ dysfunction is defined as a change in 'sepsis-related organ failure assessment (SOFA)' score of greater than or equal to 2 points. The SOFA score was developed in the 1990s as a means of identifying new organ dysfunction and the focus on a *change* in SOFA score allows recognition of chronic organ dysfunction at baseline.[67] Integral to its inclusion in the Sepsis-3 definition was a large validation study utilising SOFA score to identify those at risk of in-hospital mortality. In a large retrospective database comprising 148,907 health records with confirmed infection from 12 hospitals in southwestern Pennsylvania, the SOFA score had an area under the receiver operating characteristic curve (AUROC) = 0.74 (95% CI 0.73, 0.76) for predicting in-hospital mortality vs 0.64 (95%CI 0.62, 0.66) and 0.66 (95%CI 0.64, 0.68) for SIRS and qSOFA respectively. Consequently it became central to the current definition of sepsis.[68]

There are many issues regarding sepsis definitions that remain challenging even with current understanding of the pathobiology. The group responsible for Sepsis 3 recognise that sepsis is a syndrome shaped by a complex interaction between host (e.g. sex, age or comorbidity) and pathogen-related factors that evolve over time, resulting in a *dysregulated* response to infection that leads to life-threatening organ dysfunction. Clinical and biological phenotypes might be modified by pre-existing acute illness, long-standing comorbidity or ongoing treatments.[65]

A further challenge is defining septic shock. Previously, patients with sepsis deemed to have 'septic shock' were identified as being in a state of acute circulatory failure and inability to maintain an adequate systolic (≥90 mmHg) or mean arterial blood pressure (≥60mmHg), despite adequate volume resuscitation.[66] However, there has been much variation in the literature in how these criteria have been applied and interpreted over the years, leading to a wide-ranging set of reported incidence and outcomes. As such, the 2016 Sepsis-3 joint task force conducted a systematic review and meta-analysis, which subsequently informed a Delphi process to move forward and clarify septic shock definitions.[69] The task force recognised that septic shock represents a sub-group of patients in which circulatory, cellular and metabolic abnormalities were associated with a greater mortality and as such identified hypotension, the requirement of vasopressors and abnormal lactate levels as central to the definition. Patients who met all these criteria were recognised to have a greater risk of mortality in comparison to patients who met only some and were recognized to represent a cohort with increased risk of mortality. A lactate of 2mmol/L was identified as the lowest serum lactate level independently associated with an increased risk of in-hospital mortality.[69] As such, septic shock was deemed by the international task force to define adults with sepsis who have *hypotension requiring use of vasopressors to maintain a mean arterial blood pressure ≥65mmHg, and have a lactate >2mmol/L persisting after fluid resuscitation.*[65 70]

Table 1-2 Sepsis-3 definitions as outlined by the 2016 joint ESICM and SCCM task force

Term	Definition[65]
Sepsis	*Life-threatening organ dysfunction caused by dysregulated response to infection*
Septic Shock	Adults with sepsis who have *hypotension requiring use of vasopressors to maintain a mean arterial blood pressure ≥65mmHg, and have a lactate >2mmol/L persisting after fluid resuscitation*

1.3.2 Pathophysiology of sepsis

This dysregulated host response to infection is in sharp contrast to a typical response to contained and localised infection. There is massive upregulation in pro-inflammatory *and* anti-inflammatory mediators, a process of which begins even before a pathogen has induced tissue damage.[71 72] The pathophysiology of sepsis is thought to be a consequence of alterations in normal immune homeostatic mechanisms, in particular, alterations in immune driven hyperinflammation and concurrent relative immunosuppression that lead to the manifestations of critical illness often seen in intensive care.[71 73]

In initial phases of infection, bacteria, viruses and fungi express molecular signals known as pathogen associated molecular patterns (PAMPs), inducing early response signalling from our innate immune system. In addition, local tissue damage may herald production of endogenously produced damage-associated molecular patterns (DAMPs). These molecular signals induce their response by stimulation of toll-like receptors (TLRs) on the surface of antigen presenting cells (APCs) and begin to initiate the upregulation of inflammatory cytokines, chemokines and activation of immature neutrophils from the bone marrow.[71 72] The inflammatory cascade causes activation of various pro-inflammatory interleukins e.g. IL-1, and TNF-alpha, which in turn lead to activation of further inflammatory cascades and alterations in complement and coagulation pathways.[72]

Activation of the complement system leads to production of compounds such as C5a, which promotes chemotaxis of neutrophils into damaged tissues, where upon encountering more PAMPs and DAMPs, the immature neutrophils release neutrophil extracellular traps (NETS). These are physical extracellular structures which help to 'mop up' molecular proteins involved in inflammation. However, the granulytic enzymes and NETS produced by neutrophils also promote initiation of the coagulation cascade and shift homeostasis of coagulation towards prothrombotic activity in damaged tissues, ultimately leading to utilisation of coagulation factors and a consumptive coagulopathy.[71 74] Thus, sepsis results in a dysregulated hyper-inflammatory response, leading to increased vascular permeability, activation of the coagulation cascade and microvascular thrombosis.[71]

These hyper-inflammatory effects are often coupled with relative immunosuppression. This *'hypo-inflammation'* is mediated by the early depletion of T and B Lymphocytes and the apoptosis of APCs. This often manifests as a lymphopaenia which has even been associated with increased risk of mortality in sepsis.[72 75] Furthermore, repeated exposure to PAMPs (e.g. endotoxin) can actually impair monocyte function, a key component of the innate response. Endotoxin exposure results in reduced expression of human leukocyte antigen DR (HLA-DR), a protein which when downregulated leads to impaired monocyte cytokine secretion and loss of subsequent depletion of Th1 and Th2 cell populations, a key part of our adaptive immune response. This reduction in HLA-DR expression has been associated with prediction of sepsis in patients presenting to UK emergency departments, highlighting not only the potential prognostic role of immunosuppression in sepsis, but also the early occurrence during pathogenesis.[76 77] There are numerous cytokines and proteins implicated in either pro-inflammatory or immunosuppressive pathways in sepsis. However, to date there is no randomised controlled trial that demonstrates that isolated blockade of a single cytokine or pathway confers a mortality benefit in 'all-comers' with sepsis.[73]

The degree to which systems of homeostasis are altered or impaired in individual patients is varied and heterogenous, leading to the concept of hyper and hypo-inflammatory phenotypes in sepsis. These subtypes have previously been

identified in ARDS cohorts and had associated differences in molecular signatures.[78] Subsequently, similar subtypes have been found in retrospective analyses of sepsis patients, and share molecular features between similar subtypes in other critical illness syndromes.[79] This has led to a hope that a reframed understanding of the immunobiology of critical illness may lead to targeted therapy, where sub-populations with discrete inflammatory profiles may be more likely respond to specific and targeted treatments based on the underlying immunological mechanisms.[73]

1.3.3 Clinical presentation of sepsis

Despite great advances in the underpinning immunobiology of sepsis, diagnosis remains challenging. The 'life threatening organ dysfunction' defined as a change in SOFA score ≥2 serves as an example to highlight the potential heterogeneity in clinical presentation itself, both in terms of pathogen or 'source' of sepsis and the consequent organ failures.[65] For example, a patient with urinary tract infection that presents with acute kidney injury, thrombocytopaenia, but no other organ failure can meet the equivalent criteria for a sepsis diagnosis as a patient who presents with pneumonia requiring high flow oxygen therapy and infusions of vasoactive drugs to maintain an adequate blood pressure.

Thus, sepsis is a diverse clinical syndrome that is the result of a complex interplay between host factors (frailty, co-morbidity, age), pathogen factors (virulence, load, clinical sequelae) and contextual features. This, in turn, can result in a broad range of manifestations including respiratory dysfunction, cardiovascular dysfunction, acute kidney injury, coma, coagulopathy and delirium.[41]

It is perhaps then understandable why this broad clinical syndrome, which by definition often results in multi-organ failure, represents one of the most common conditions admitted to intensive care and can have such drastic long-term consequences.

1.3.4 Inflammation and recovery from sepsis

Similar long-term complications to those seen in sepsis are also seen in patients who survive severe acute inflammatory responses of other aetiologies, including burns and trauma.[80] It has been proposed that this could be attributed to the development of a persistent inflammatory state in certain subgroups of patients, with ongoing immune dysfunction and catabolic metabolism. [81] [82] However, present research has largely studied factors which initiate the early inflammatory processes associated with sepsis and there are limited data detailing the longitudinal course of inflammation during the recovery phase.[80]

There is a small body of evidence to suggest that patients who survive critical illness may have a persistent inflammatory state during recovery. It has been demonstrated, at ICU discharge, most patients have persistently elevated inflammatory markers including; CRP, TNF-α and procalcitonin. [83] In addition, CRP was persistently elevated until 13 weeks post ICU discharge and IL-6 remained elevated at 26 weeks in a subset of patients with anaemia.[84] However, a detailed longitudinal inflammatory profile in survivors of critical illness specific to sepsis is yet to be conducted.

There is growing interest in the association between inflammation and functional outcomes in survivors of critical illness. Higher levels of systemic inflammation early in ICU admission are associated with the subsequent development of ICU acquired weakness.[85] In addition, persistently elevated CRP at 3 months following ICU discharge has been shown to be associated with decreased mobility.[86] Currently there is mixed evidence regarding a possible association between inflammation and cognitive outcomes in survivors of critical illness. A retrospective cohort study demonstrated that higher levels of plasma IL-6 and IL-10 at hospital discharge were associated with long-term cognitive dysfunction [87], however, a subsequent prospective study failed to replicate this association [88].

Indeed, the study which is the focus of this thesis is embedded within a larger biomarker study which aims to establish whether there is an association between chronic inflammation and chronic pain in survivors of critical illness due to sepsis. While the author is not aware of any pre-existing studies in this field,

there is evidence to support an association between systemic inflammation and chronic pain in other populations. For example, concentrations of the pro-inflammatory cytokines IL-1ß, IL-6 and TNF-α have been found to be significantly higher in patients with chronic pain of a variety of aetiologies.[89-91] Moreover, the ratio of pro-inflammatory cytokines to the anti-inflammatory cytokine IL-10 was found to be significantly higher in patients with chronic pain.[90]

1.3.5 Long-term consequences of sepsis

In recent decades there has been increased recognition of the importance of long-term outcomes in survivors of sepsis.[5 92 93] Survivors of sepsis have an increased risk of mortality and hospitalisation and this relative risk may be greater than that of other comparable acute medical conditions. [93-95]

Sepsis survivorship literature has greatly contributed and bears significant overlap to the PICS literature. Much like PICS, patients with sepsis also can acquire multiple impairments spanning cognitive, physical and cognitive domains.[96] Indeed, in a recent survey by the James-Lind alliance of researchers, clinicians, patients and families aimed to set forthcoming research priorities in sepsis. Of those identified, long-term consequences of sepsis and how they are best treated was one of the top priorities according to patients and families, second only to rapid diagnosis and treatment.[97]

As eluded to in the above discussion of long-term outcomes following critical illness, despite long standing recognition of the acquisition of comorbidity and functional impairment following sepsis, there have been little advances in terms of therapeutics which address this burden of acquired comorbidity.

Parallel to PICS, the emergence of the concept of persistent inflammation, immunosuppression and catabolism syndrome (confusingly also termed PICS, but from here-on referred to in unabbreviated form) refers to the chronic low-grade inflammatory state that can occur following the onset of critical illness. It can result in prolonged ICU stay and may be associated with poorer long-term outcomes. [98] This persistent inflammation and catabolism syndrome, although similar, is distinct from PICS as it offers a mechanistic explanation for some of

the adverse outcomes seen in sepsis survivors. For example, in a study examining inflammatory consequences of patients with chronic critical illness (CCI), defined as ICU length of stay > 14 days and organ dysfunction, patients exhibited greater levels of inflammatory cytokines such as IL-6 and IL-8. Other similar increases in cytokines involved in immunosuppression have been identified in these populations over one month beyond the index illness.[99]

Whilst it is unclear what drives this persistent chronic inflammation in some patients following sepsis, it offers a plausible mechanism by which it may be result in some of the clinical features of PICS and other long-term consequences of sepsis.[99]

1.4 Cardiovascular dysfunction in survivors of sepsis

1.4.1 Cardiovascular dysfunction during sepsis and sepsis-induced cardiomyopathy

Cardiovascular dysfunction is common in sepsis. The prevalence of sepsis-induced cardiomyopathy in intensive care patients varies markedly and has been reported to occur in 10-70% of patients depending on the definition used.[100] Definitions vary between echocardiographic parameters of left and right ventricular systolic or diastolic dysfunction (e.g. Left ventricular ejection fraction (LVEF) <50%) or non-echocardiographic definitions such as biomarkers of myocyte injury (e.g. high sensitivity troponin T (hs-TnT)) or myocardial wall stress (e.g. N-Type pro Brain Natriuretic Peptide (NT-proBNP)).[100]

Whilst these definitions confer various advantages and disadvantages in terms of their clinical utility and generalisability, what is clear is that sepsis-induced cardiomyopathy is likely to affect a huge number of patients in the ICU. Whilst the long-term prognostic impact of myocardial dysfunction in sepsis remains unclear,[101 102] the hypothesis that there are long-term consequences resulting from the cardiovascular dysfunction often seen in sepsis, is a compelling narrative.

Much of the conceptualisation of sepsis-induced cardiomyopathy is traditionally framed around the concept that it is reversible.[103 104] However, there are many contemporary data demonstrating there may be long-term cardiovascular consequences of sepsis. Admission to hospital with sepsis has now been associated in multiple observational studies with an increased long-term risk of major adverse cardiovascular events (MACE) such as myocardial infarction, heart failure, or stroke.[105] Indeed, readmission with cardiovascular disease has been estimated to occur in 3.5% of all sepsis patients within 30 days of discharge.[106] Thus, it is possible that the acute cardiovascular dysfunction commonly occurring during index admission may have under-recognised long term consequences. Whilst there is much literature around mechanisms of physical impairments seen in post-intensive care syndrome, there is little prospective work outlining the role by which cardiovascular dysfunction might mediate some of these impairments.

1.4.2 Potential mechanisms of post-sepsis cardiovascular disease following sepsis

There are numerous mechanisms by which cardiovascular disease might occur following critical illness. The initial upregulation in inflammation can trigger a series of events which predispose chronic inflammation and vascular remodelling and bear significant overlap with mechanisms of other chronic cardiovascular conditions.[107]

The response to PAMPs and DAMPs in sepsis leads to activation of TLRs and APCs as described above. This leads to an upregulation in pro-inflammatory pathways via compounds such as the nucleotide-binding domain, leucine-rich repeat, and pyrin domain containing receptor 3 (NLRP3) inflammasome.[108] This molecule upregulates inflammatory pathways, pyroptosis and markers of cell stress via IL-1ß, IL-6 and hs-CRP, the levels of which have been demonstrated to be elevated in ICU survivors months after discharge and are associated with poor outcomes following discharge.[109 110] These pathways have been implicated in other chronic cardiovascular diseases, for example the ‘Anti-inflammatory therapy with canakinumab for atherosclerotic disease (CANTOS)’ trial demonstrated that blocking the IL-1ß pathway could potentially modify cardiovascular disease

activity.[111] However, other attempts to modify inflammation in an attempt to reduce incidence of heart failure or other adverse cardiovascular outcomes have not been as successful.[112 113]

Myocardial injury often occurs in sepsis, and biomarkers such as troponin have been independently associated with mortality.[114] Given sepsis involves significant alterations in inflammation and coagulation, the hypothesis that coronary thrombus and myocardial infarction may be precipitated by sepsis is plausible. However, mechanistic studies have not shown significant differences in functional coagulation in patients with raised troponin values vs those without, suggesting myocardial injury may not be due to formation of thrombus.[115] This is perhaps similar to other populations, for example in the peri-operative setting, where myocardial injury is often not associated with new coronary thrombus.[115] It is also plausible that sepsis induced cardiac dysfunction may be caused by global oxygen supply/demand mismatch, however this is not always consistent with early models and studies demonstrating that rises in troponin often occur in the absence of flow limiting disease.[116 117] Despite the lack of mechanistic clarity regarding why myocardial injury occurs, the narrative that links acute myocardial injury to long-term adverse outcomes remains a plausible hypothesis and can be demonstrated in other populations.[118]

Damage to other organ systems may also contribute to ongoing cardiovascular dysfunction. For example, sepsis is associated with incidence of acute kidney injury, which has been shown to bear considerable association with long-term immune activation and morphological changes that predispose to cardiovascular remodelling and MACE.[119]

In addition to the immune response, there is also considerable metabolic adaptions following critical illness. Critical illness bears similarities to obesity, with considerable macrophage activation in adipose tissue and subsequent insulin resistance.[120] There is a propensity to muscle breakdown and cachexia in part via growth differentiation factor-15 (GDF-15) a cellular stress marker. [121] Deleterious mineralocorticoid signalling, often elevated as part of the primary response during sepsis has also been implicated in pathogenesis of cardiovascular disease. Many T-cell populations and myeloid cells have mineralocorticoid

receptors which when blocked by antagonists can be associated with reductions in cardiac hypertrophy and fibrosis.[122]

Thus, there are numerous immuno-metabolic mechanisms by which critical illness can create conditions similar to that of chronic disease (e.g. hypertension or chronic kidney disease) and predispose survivors to the risk of MACE.

1.5 Evaluation of cardiovascular disease in ICU survivors of sepsis

1.5.1 Heart failure

Heart failure is a major health burden worldwide. Despite marked improvements in treatment, it bears a significant burden of mortality and morbidity that is comparable to other serious health conditions such as cancer.[123] Heart failure is not a single diagnosis, but a clinical syndrome defined by the presence of signs and symptoms of heart failure (e.g. dyspnoea, orthopnoea, oedema) caused by evident abnormalities of cardiac structure or function and either elevated levels of plasma natriuretic peptides or objective evidence of cardiogenic pulmonary or systemic congestion.[124 125]

In recent years, a universal definition of heart failure has been developed by the Heart Failure Society of America (HFSA), the heart failure association of the European Society of Cardiology (ESC) and the Japanese Heart Failure Society (JHFS).[124] The document goes further to recognise and delineate ‘stages’ of heart failure and recognises ‘pre-heart failure’ (Figure 1-5), where patients may not have a burden of symptoms, but are confirmed to have heart failure risk factors or objective evidence of abnormal cardiac function which predisposes them to heart failure in the future. There is a growing evidence base for treatment of these early stages of the syndrome, with a recognition of the heterogeneity of the patient population and the challenges this poses to research and clinical practice. [124]

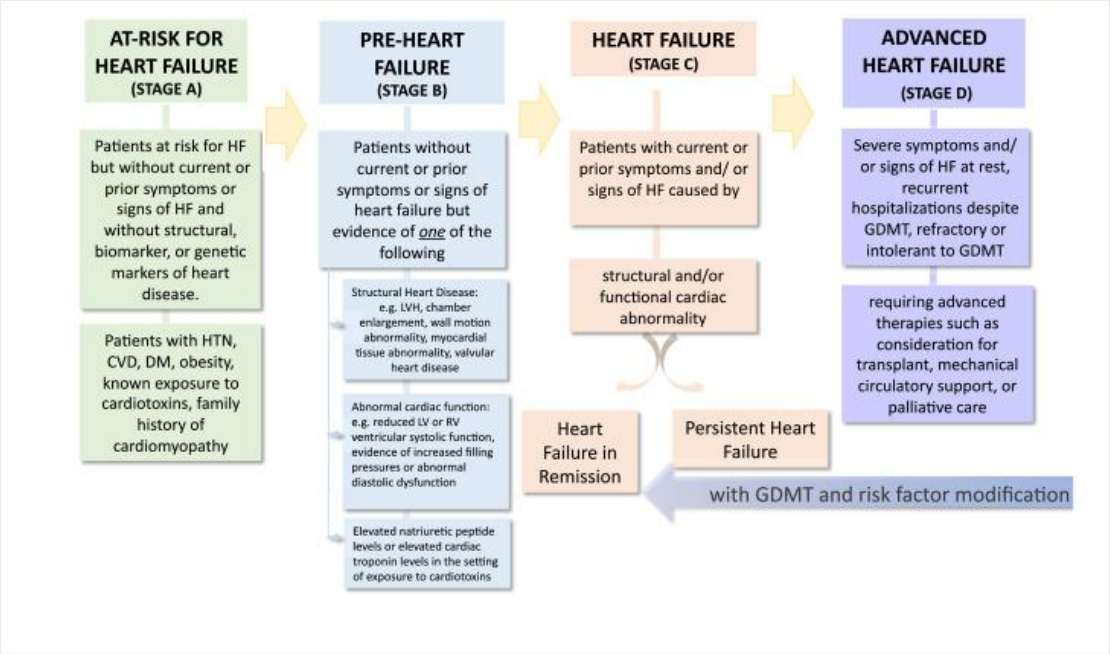

Figure 1-5 Stages in development and progression of heart failure

Outlined in the universal definition of heart failure jointly published by the ESC, HFSA & JHFS.[124] Stage A reflects those at risk of heart failure. Stage B reflects those with 'pre-heart' failure without a prior symptom burden, but evidence of structural or biochemical abnormalities. Stages C and D align with confirmed heart failure and advanced heart failure respectively. Reproduced with permission from the Journal of Cardiac Failure.

In terms of clinical phenotypes, heart failure is commonly stratified by left ventricular ejection fraction (LVEF). Using this parameter, it can be divided into heart failure with reduced ejection fraction (HFrEF), heart failure with moderately reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) (Table 1-3).[125] This is owed to the ability of reduced LVEF to discriminate between patients who are likely to respond to guideline directed medical therapy (GDMT), which has revolutionised management over recent decades. In particular, much of the evidence for GDMT is particularly robust in HFrEF i.e. in patients with an LVEF <40%. In these patients, there an evidence base which has led to the development of robust guidelines and a clear benefit in terms of mortality and burden of symptoms.[125]

On the other hand, the evidence base for HFmrEF and HFpEF is evolving. This is a heterogenous range of symptoms that includes patients with ischaemic heart disease, infiltrative cardiomyopathies and valvular heart disease to name a few. Thus, establishing underlying diagnosis is crucial. Nonetheless, recent well conducted randomized controlled trials have demonstrated reductions in mortality and heart failure admission with SGLT-2 inhibitors in patients with

HFmrEF, showing promise for other therapies in this category.[126 127] In HFpEF, the DELIVER trial also demonstrated reductions in heart failure events, highlighting promise of emerging therapies in this cohort too.

Table 1-3 Phenotypes and definitions of heart failure

Heart Failure Phenotype	HFrEF	HFmrEF	HFpEF
Symptoms and Signs	Yes	Yes	Yes
LVEF	≤40%	41-49%	≥50%
Other	-	-	Evidence of raised LV filling pressures / diastolic dysfunction, including raised natriuretic peptides

HFrEF = Heart failure with reduced ejection fraction, HFmrEF = Heart failure with mildly reduced ejection fraction, HFpEF = Heart Failure with preserved ejection fraction. LVEF = Left ventricular systolic function. LV=Left **ventricl**e. Adapted from ESC guidelines for the diagnosis and treatment of chronic heart failure.[125]

Adjunctive therapies for venous congestion, arrythmia or hypertension, or electrophysiological therapies (e.g. cardiac resynchronizations therapy devices) are beyond the scope of this discussion, as are advanced therapies such as mechanical circulatory support.

However all of the above serves to highlight the vast evidence base for heart failure that has led to marked improvements in mortality over recent decades.[128] Going forward in this thesis, LVEF is an important outcome in both defining participants with left ventricular systolic dysfunction (LVSD) and exploring relationships with other outcomes in the study.

1.5.2 Assessment of cardiovascular function

There is a vast array of modalities and techniques for the assessment and monitoring of cardiovascular function in critical care and beyond. Whilst the study that comprises the majority of this thesis deals with a critical care population, the focus will be on methods of cardiovascular assessment that are applicable both in intensive care and the outpatient setting. These comprise of

imaging modalities, biomarkers of cardiovascular injury and wall stretch, and functional outcomes.

1.5.3 Imaging modalities

1.5.3.1 Echocardiography

Echocardiography has been in use since 1954, when Edler and Hertz demonstrated the use of ultrasound to obtain moving pictures of the structures of the heart.[129] Echocardiographic images can be taken in the form of trans-thoracic echo (TTE) images or transoesophageal (TOE). Whilst TOE confers many advantages in terms of image quality, and diagnostic capability, it is more invasive in nature, can be poorly tolerated and is associated with gastric or oropharyngeal complications.[130]

TTE by comparison is non-invasive, demonstrably safe and similarly aids diagnosis and refinement of management strategies in patients with critical illness syndromes including shock, respiratory failure or post-cardiac arrest and [131] as such, its use has become widespread in critical care. The British Society of Echocardiography (BSE) outline the minimum dataset required for transthoracic echocardiography in adults,[132] allowing comprehensive assessment of left and right ventricular structure, systolic and diastolic function, valvular lesions and significant vascular pathology such as aortic root dilation or dissection.

In recent years, these guidelines have been adapted by the BSE and the Intensive Care Society (ICS) to provide a focus on critical care pathology and decision making.[133] [134] Both aim to address the increase in point-of-care echocardiography and its demonstration as a safe and effective tool that often changes clinical management at the bedside.[135] [136] Similarly, there is an emerging recognition of the potential utility of point-of-care echocardiography for future research.[135]

In the outpatient setting, echocardiography is a pillar of heart failure investigation and management, enabling detailed assessment of cardiac structures that can help refine diagnosis and management strategies. Its low-risk profile and favourable tolerability ensure its place as an ideal tool for

assessment of key measures such as LVEF and other measures in cardiac dysfunction.[137]

1.5.3.2 Cardiovascular magnetic resonance imaging (CMR)

Cardiovascular magnetic resonance (CMR) imaging is the gold-standard method for assessing cardiac function and structure, with superior ability to assess left ventricular volumes, function, wall motion abnormalities and myocardial tissue.[138] It is also the reference diagnostic method for determining myocardial injury, including myocarditis and acute cardiomyopathy by using parametric mapping techniques such as T1, T2 and extra cellular volume (ECV) which enable assessment for myocarditis and other causes of cardiomyopathy.[139] [140]

In terms of myocardial tissue characterisation, T1 mapping measures the longitudinal relaxation time of myocardial protons when a radio-frequency pulse is applied, giving a numeric value in terms of milliseconds. The most important determinants of increased T1 are oedema and an increase in interstitial space due to fibrosis or scar.[141] Through use of gadolinium based contrast, a significantly shortened T1 value can be observed and from this a measurement of the extracellular volume (ECV) derived, often a surrogate marker and differentiator for tissue fibrosis.[141] These T1 maps can be used to aid in differentiation between acute or chronic myocardial infarction and other non-ischaemic cardiomyopathies.

T2 mapping refers to the measurement of decay in overall transverse magnetization and is sensitive to changes in myocardial water content or oedema.[142] In combination with T1 and ECV, these can be utilised to determine the presence of active myocarditis and help to further characterize myocardial disease, enriching the gold-standard functional information as part of a standard CMR study. These features make CMR an attractive approach for research.

1.5.4 Biomarkers of cardiovascular dysfunction

1.5.4.1 Troponin

The utility of biomarkers in assessing risk of cardiovascular disease is long established in ICU, hospital and outpatient settings. High-sensitivity Troponin T (hs-TnT) is a biomarker of cardiomyocyte injury most frequently used in the diagnosis of myocardial infarction. However, values are often abnormal in other settings such as pulmonary embolism, arrhythmia and sepsis.[143] [144] Troponin values have been shown to be associated with mortality in ICU settings and are associated with measures of disease severity including acute physiology scoring systems such as the acute physiology and chronic health evaluation (APACHE) II score.[114] [145] [146] Troponin has also been shown to be associated with objective markers of cardiac dysfunction such as need for vasoactive drugs and wall motion abnormalities on echocardiography.[147] High-sensitivity troponin I (hs-TnI) has also been shown to be associated with an increased risk of adverse CVD events in a community setting.[148]

1.5.4.2 B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide

BNP and NT-proBNP are sensitive biomarkers for ventricular wall stretch and dysfunction and are widely used in diagnosis of heart failure in international guidelines and diagnostic pathways.[125] [149] [150] In a critical care setting, NT-pro-BNP values have been identified, along with other cardiac biomarkers, as predicting risk of death on discharge from ICU.[151] In addition, elevated BNP values have been associated with post-operative impairments in ventricular function.[152] These biomarkers are described in more detail in Chapter 6.

1.5.4.3 Ca-125 and Cystatin-C

CA-125 is a membrane associated glycoprotein, which is most commonly known as a biomarker of ovarian and other cancers.[153] However, more recently CA-125 has been investigated as a novel marker of congestion in heart failure[154] and has been shown to be associated with clinical outcomes including mortality and hospital admission.[155]

Similarly, Cystatin-C - a biomarker traditionally associated with renal dysfunction[156] - has also shown promise as a biomarker for cardiac dysfunction, especially when used in combination with NT-proBNP.[157] It has also been shown to be a predictor of mortality and cardiac events in patients with heart failure.[158 159]

1.6 Summary and aims of thesis

Critical illness is defined as life-threatening but potentially reversible illness associated with organ dysfunction requiring intensive care. It accounts for hundreds of thousands of admissions to intensive care in the UK annually.

The consequences of critical illness are often significant. Two thirds of ICU survivors are burdened with physical, cognitive or psychological issues often collectively termed PICS.[2] Intensive care survivorship and PICS often has a significant impact on quality of life, with a third of patients readmitted to hospital within 90 days and only half returning to meaningful employment within a year.[4 160] Although there are numerous data outlining the existence of PICS, few exist regarding underlying mechanisms. Although there are areas of the literature that explore specific impairments such as respiratory impairment, muscle weakness or overall deficits in physical function, there are few underlying mechanistic data. One area for which there is a paucity of data is cardiovascular dysfunction, despite a growing body of evidence that patients admitted to hospital with sepsis and other critical illness syndromes are at an increased risk of adverse cardiovascular outcomes following admission.[105 161]

Sepsis is of particular interest on account of its ubiquity in intensive care, its clear association with acute cardiovascular dysfunction and an increasingly robust literature around long-term risk of adverse cardiovascular events.[65 105 162] Defined as a life-threatening and dysregulated host response to infection, it is one of the most common reasons for ICU admission.

An initial response to PAMPs and DAMPs initiates a cascade of inflammatory events, resulting in inflammation, increased endothelial permeability, activation of the coagulation cascade and microvascular dysfunction and thrombosis. In

severe cases it can result in septic shock, where the body is unable to meet the metabolic demands of tissues despite institution of vasoactive medications.[65] This state is often associated with significant cardiac dysfunction as evidenced by changes in echocardiographic appearances and biomarkers, many of which are often associated with poor prognosis.[114 151]

This raises the question regarding the long-term implications of cardiovascular dysfunction during acute illness. The literature surrounding heart failure - the final common pathway in many causes of chronic cardiomyopathy - has a robust evidence base and recent decades have demonstrated significant advances in treatment and outcomes.[125 128] The fundamentals of heart failure assessment are well established and involve a combination of symptomatology, biomarkers of myocardial dysfunction and functional appearances on echocardiography or other imaging.[125]

Whilst critical illness, and in particular sepsis, are associated with an increased risk of adverse cardiovascular outcomes, the underlying mechanisms for this are unclear. There is a paucity of prospective mechanistic data characterising the long-term effects of sepsis on the heart and whether structural or biochemical changes may be associated with the functional impairments seen in PICS. Furthermore, given the extensive evidence base in treatment of heart failure, this may represent a treatable comorbidity that may positively alter recovery trajectory and reduce risk of hospital readmission.

As such, this thesis aims to address the following questions:

- What is the existing evidence regarding cardiovascular dysfunction following ICU admission with sepsis and what gaps remain in the literature?

- What is the prevalence of right and left ventricular systolic dysfunction in ICU patients following admission with sepsis?

- Is cardiac magnetic resonance imaging feasible 6-10 weeks following hospital discharge in this patient cohort?

- How do biochemical changes associated with cardiac dysfunction and injury in ICU survivors of sepsis compare with that of the general population?

- What is the relationship between biomarkers of cardiac dysfunction and injury, indices of cardiac function as measured on CMR and patient reported outcomes in ICU survivors of sepsis?

Going forward, this thesis will present a review of the literature examining available evidence regarding cardiac dysfunction following admission with sepsis (Chapter 2). Subsequent chapters (Chapters 3-7) will present methods and results of a prospective, observational cohort study, aiming to characterise cardiovascular function in ICU survivors of sepsis using CMR imaging, biomarker analysis and PROMs.

Chapter 2 Cardiac dysfunction in survivors of sepsis: a scoping review

The work in the following chapter was published in BMJ Open Heart in 2023, and is cited using the following reference:

Garrity K, Gaw S, Blewitt A, Canon P, McCall P, McPeake J. Cardiac dysfunction in survivors of sepsis: a scoping review. Open Heart. 2023 Dec 7;10(2):e002454.

The original idea for the literature review was developed by the author of this thesis. The published study manuscript was drafted in full by the author and modified for integration in this thesis. The search strategy was developed by the author. Dr S Gaw and Dr A Blewitt helped in review of articles identified by the search strategy. Dr P Canon is an experienced librarian and advised on the search strategy. Dr P McCall and Prof J McPeake acted in a supervisory capacity and contributed to revisions of the chapter.

2.1 Introduction

There are multiple plausible mechanisms by which sepsis might result in an increased risk of adverse cardiovascular events.[107] In planning the work presented in subsequent chapters, it became apparent that several large observational cohort studies and at least one systematic review had demonstrated that sepsis admission was associated with increased incidence of adverse events such as myocardial infarction and heart failure admission.[8 105 163] Furthermore, this association is comparable in incidence to other established cardiovascular risk factors such as hypertension or dyslipidaemia.

Thus, it is logical to hypothesise that chronic cardiovascular dysfunction may be common following critical illness and may play a role in some of the functional impairments commonly observed following admission to intensive care. Whilst there is an increasing body of evidence that embellishes the narrative of sepsis

as a non-traditional cardiovascular risk factor, there are few data regarding *mechanisms* of chronic cardiovascular dysfunction following acute illness, the relationship to functional impairments seen in survivors of sepsis and how we might identify and manage at risk patient groups.

It is therefore important to understand existing data on the subject, types of evidence available and clarify key concepts. As such, a scoping review was conducted on the topic of cardiac dysfunction following sepsis.

2.2 Methods

The scoping review aimed to answer the following interrelated questions:

- To what extent does current literature explore cardiovascular function or dysfunction *following* an episode of sepsis?

- What research methodologies have been employed to explore the long-term cardiovascular effects of hospital admission with sepsis?

- To what extent does this literature explore the role cardiovascular function might play in functional impairment following admission with sepsis?

- Does this literature explore any mechanisms by which cardiovascular dysfunction might cause long-term functional impairment (e.g. objective evidence of ischaemia or heart failure).

2.2.1 Protocol and registration

A scoping review strategy was chosen with a view to ensuring inclusion of a broad range of articles and a focus on identification of research gaps. This would complement a recent meta-analysis examining focused incident outcomes and aid in further mapping of the literature.[105] The review was conducted in alignment with the Joanna Briggs Institute (JBI) guidance and reported in accordance with Preferred reporting items for systematic reviews and meta-analyses (PRISMA-ScR) checklist.[164] Ethical approval was not required. The study

protocol and search strategy were registered on Open Science Framework (OSF https://doi.org/10.17605/OSF.IO/QPSY5).

2.2.2 Search strategy, sources and eligibility criteria

Using an initial focused search, key papers in the literature were identified to aid in devising a comprehensive search strategy in conjunction with an experienced librarian. The MEDLINE, Embase and CINAHL databases were searched using the Concept, Context, Population (CoCoPop) framework as outlined by the JBI for use in scoping reviews.[165]

The search strategy (Table 2-1), including text words and subject headings, was adapted for each database. The reference list of all included sources of evidence was also screened for additional eligible articles.

2.2.2.1 Participants

This scoping review focused on *adult* survivors of sepsis and included any literature which considered outcomes for adult patients >18 years old, regardless of comorbidity or frailty.

2.2.2.2 Concept

The search strategy was aimed at identifying literature with the terms 'heart failure' or 'cardiovascular outcomes' in the title or abstract, focusing on the concept of cardiac dysfunction *following* an episode of sepsis. Papers that focused on acute haemodynamic instability during an episode of sepsis (e.g. septic shock or acute arrhythmia) were not included unless they contained data pertaining to long-term cardiovascular outcomes following discharge from hospital.

2.2.2.3 Context

The search focused on sepsis survivorship. The terms 'sepsis', 'bacteraemia' and other related terms were used to identify relevant literature for potential inclusion. The 'Sepsis 3' definitions are widely recognised by the sepsis and critical care research communities and define sepsis as life threatening organ

dysfunction caused by a dysregulated host response to infection. Data in this scoping review utilised this definition for inclusion of articles in this review.[65]

Table 2-1 Search strategy for scoping review

#	Query
1	Cardiovascular Diseases/
2	Heart Failure/
3	heart failure.mp.
4	cardi* failure.mp.
5	cardi* dysfunction.mp.
6	cardiogenic shock.mp.
7	cardiovascular outcomes.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Sepsis/
10	Bacteremia/
11	bacter?emia.mp.
12	endotox?emia.mp.
13	Shock, Septic/
14	(Septic* or Seps*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15	pneumonia.mp.
16	9 or 10 or 11 or 12 or 13 or 14 or 15

17	exp Adult/
18	Cohort Studies/
19	Retrospective Studies/
20	Prospective Studies/
21	Longitudinal Studies/
22	(follow-up or long-term or cohort or longitudinal or prospective or retrospective).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23	18 or 19 or 20 or 21 or 22
24	8 and 16 and 17 and 23
25	limit 24 to English language

2.2.3 Sources and selection of evidence

Prospective and retrospective observational or cohort studies were included. In addition, the review considered both experimental and quasi-experimental designs including randomised controlled trials, non-randomised controlled trials, before and after studies and interrupted time-series studies. The review also considered descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion. Conference proceedings, conference abstracts or book chapters were not reviewed to avoid duplication that may have occurred in published studies.

Following the search, all identified citations were collated and uploaded into the *Rayyan* platform and duplicates removed. A pilot test ensuring reviewer agreement (>75%) was conducted prior to screening results. Subsequently, titles and abstracts were then screened by two or more independent reviewers for assessment against the inclusion criteria for the review using Rayyan software. Any disagreements that arose between reviewers at each stage were resolved

through discussion, or with (an) additional reviewer(s). The results of the search and the study inclusion process were reported using the (PRISMA-ScR) flow diagram.[164]

2.2.4 Data extraction, analysis and presentation

Data was extracted from studies by two or more independent reviewers using a data extraction tool (Appendix 1). The data extracted included specific details about the participants, concept, context, study methods and key findings relevant to the review questions. Reviewers identified patients who had sepsis as defined by Sepsis 3 criteria.[65] Where patients were not explicitly identified has having sepsis by the reviewers, the article was included only if sepsis was present in the majority of participants (>50%).

The data extraction tool was developed a priori and was modified and revised as necessary during the process of extracting data from each included evidence source. Any disagreements that arose between the reviewers was resolved through discussion, or with (an) additional reviewer(s).

The literature was collated and mapped according to the review questions. Literature was tabulated by author, date, population, context, relevant clinical outcomes and by methods that gave mechanistic insights into long-term cardiovascular outcomes (i.e. cardiac biomarkers, electrocardiographic findings, cardiac imaging). In addition, articles were mapped according to whether they documented cardiovascular symptoms or patient reported outcome measures. Research gaps were then identified in the literature with a view to formulating questions for further research.

In keeping with JBI guidance on conducting scoping reviews, there was no meta-analysis conducted. This would have required assessment for bias, leading to exclusion of articles that may compromise the review's ability to map gaps in the literature.[166]

2.3 Results

2.3.1 Summary

The study selection process is outlined in Figure 2-1. In total 11,210 individual articles were identified for review. From these articles, 9533 were eligible for screening after removal of duplicates and subsequently 70 articles were eligible for full text review. 42 articles were removed from the final data set. Of these papers, 26 articles were removed because they did not contain septic cohorts with reported outcomes of interest, 11 articles were removed because they did not report outcomes related to long term cardiac dysfunction, 1 article was removed as it was a prospective study protocol with no results as yet and 3 articles were narrative or systematic reviews. One further article was removed as it was a pathological study with no focus on long-term cardiovascular dysfunction.

2.3.2 Characteristics of studies

Of the 28 articles included (Table 2-2), all examined long-term outcomes related to cardiovascular dysfunction in patients who had sepsis. Articles covered a 17-year period from 2005 until 2023 and studied patient populations in a variety of geographical locations including, North America 19/28 (68%), Europe 4/28 (14%) and Asia 5/28 (17%). Articles focused on a wide range of follow-up periods from 30 days up to 10 years. All included articles studied adult patients, of which two focused on particular sub-groups of patients vulnerable to cardiovascular disease (patients with chronic kidney disease and patients with end-stage renal failure commencing dialysis).[167 168] In total, 23/28 (82%) of articles explicitly described patient cohorts who had sepsis, however, 5/28(18%) were articles in which the primary concept was pneumonia, but explicitly reported outcomes related to cardiovascular dysfunction for septic patients.

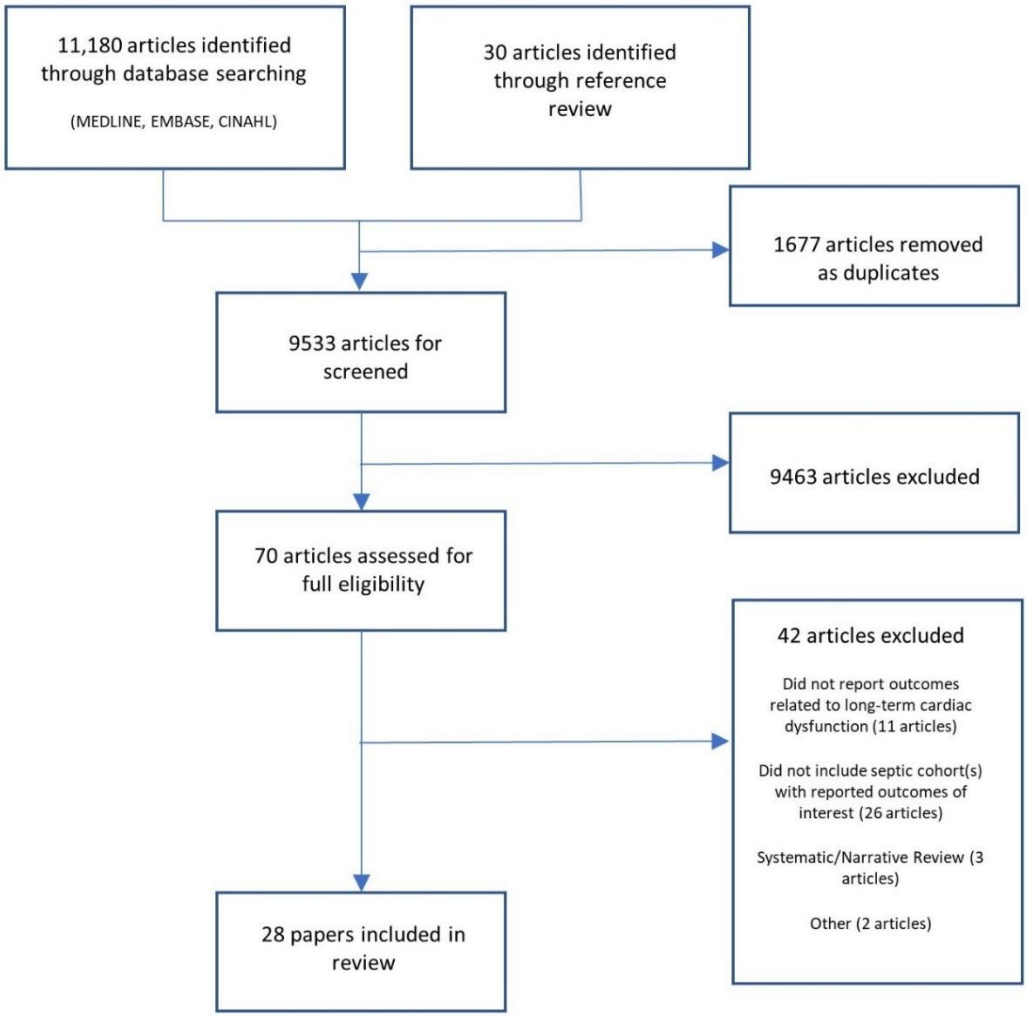

Figure 2-1 Flow diagram for scoping review

2.3.3 Research methodology

Included articles were either prospective 3/28(10.7%) or retrospective 25/28 (89.3%) observational cohort studies. Although there was one systematic review and meta-analysis, this was excluded from final analysis on the basis that it contained duplicate data from many of the articles presented. There was a wide range in methodology, with some studies comparing sepsis cohorts with hospitalised non-sepsis or population controls. Some studies used findings related to cardiovascular imaging 4/28 (14.3%) or biomarkers 3/28 (10.7%) to stratify patients into groups at varying risk of cardiovascular events. The scoping review found no randomised controlled trials investigating interventions related to reducing risk of adverse cardiovascular events following sepsis, although 3/28 (10.7%) retrospective observational studies focused on cohorts of patients prescribed statins or renin-angiotensin-aldosterone (RAAS) inhibitors versus those who were not.[169-171]

Table 2-2 Summary of articles included in scoping review

First Author	Year	Country	Context	Concept	Population	Comparator Cohort	Methodology	CV Outcomes Studied	Mechanisms of CV Dysfunction Assessed
Adamuz[172]	2014	Spain	Pneumonia	Predictor of 1 year mortality	Adults	Alive vs Dead	Prospective Cohort Study	MI, Cardiovascular Deaths	-
Aldas[173]	2020	Spain	Pneumonia	MACE	Adults	MACE vs No MACE	Prospective Cohort Study	HF, Arrhythmia, MI, All-cause mortality	-
Alnabelsi[174]	2020	USA	Sepsis	MACE	Adults	CT-CAC & Reduced LVEF vs No CT-CAC and normal LVEF	Retrospective Cohort Study	MI, Cardiovascular Deaths	Imaging, Biomarkers
Angriman[171]	2023	Canada	Sepsis	Risk Factors Associated with MACE	Adults	RAASi vs No RAASi	Retrospective Cohort Study	MI, All-cause mortality	Biomarkers
Angriman[163]	2023	Canada	Sepsis	RAASi and MACE	Adults	MACE vs No MACE	Retrospective Cohort Study	MI, All-Cause Mortality	RAASi Prescribing

Angriman[9]	2022	Canada	Sepsis	MACE	Adults	Sepsis vs Hospitalized Non-sepsis	Retrospective Cohort Study	MI, Cardiovascular Deaths	-
Beesley[175]	2021	USA	Sepsis	MACE	Adults	Normal vs Abnormal GLS	Retrospective Cohort Study	HF, MI, All-cause mortality	Imaging, Biomarkers
Chang[176]	2015	USA	Sepsis	Hospital Readmissions and Diagnoses	Adults	Sepsis vs MI vs HF	Retrospective Cohort Study	MI, Cardiovascular admissions	-
Corrales-Medina[177]	2009	USA	Pneumonia	Acute Coronary Syndrome	Adults	Pneumonia vs Hospitalized Control	Retrospective Cohort Study	MI	-
Corrales-Medina[178]	2015	USA	Pneumonia	MACE and Mortality	Adults	Pneumonia vs Hospitalized Control	Retrospective Cohort Study	MI, Cardiovascular Death	-
De Geer[179]	2018	Scandinavia	Sepsis	CV Mortality	Adults	Sepsis vs Hospitalized Non-sepsis	Retrospective Cohort Study	Cardiovascular Death	-
Gadre[180]	2019	USA	Sepsis	Hospital Readmissions	Adults	30-day readmission vs No 30-day readmission	Retrospective Cohort Study	Cardiovascular Admissions	-

Garcia[181]	2021	USA	Sepsis	MACE, Mortality	Adults	Normal vs Abnormal Troponin Values	Retrospective Cohort Study	HF, Arrhythmia, MI, All-cause mortality	Biomarkers
Gupta[182]	2018	USA	Sepsis	Coronary Artery Disease and Mortality	Adults	CAC Absent vs CAC present	Retrospective Cohort Study	MI, Cardiovascular Death	Imaging
Gupta[170]	2020	USA	Sepsis	Statin Prescribing following Admission with Sepsis	Adults	Statin indication vs No statin indication	Retrospective Cohort Study	MI, HF, Cardiovascular Death	Statin Prescribing
Ishani[183]	2005	USA	Sepsis	MACE	Adults with ESRF	Sepsis vs Population Control	Retrospective Cohort Study	HF, MI, All-cause mortality	-
Jafarzadeh[167]	2016	USA	Sepsis	MACE	Adults	Sepsis vs Hospitalized Non-sepsis	Retrospective Cohort Study	MI	-
Jentzer[184]	2023	USA	Sepsis	MACE	Adults	Sepsis vs Hospitalized Non-sepsis	Retrospective Cohort Study	Cardiovascular death, HF, IHD, MI, Arrhythmia, All-cause mortality	-

Lai[185]	2018	Taiwan	Sepsis	MACE	Adults	Sepsis vs Hospitalized Non-sepsis vs Population Control	Retrospective Cohort Study	MI	-
Menendez[186]	2019	Spain	Pneumonia	MACE	Adults	Early vs Late CVEs	Prospective Cohort Study	HF, Arrythmia, MI, All cause-mortality	Biomarkers
Ou[187]	2016	Taiwan	Sepsis	MACE	Adults	Sepsis vs Hospitalized non-sepsis vs Population control	Retrospective Cohort Study	HF, MI, Arrhythmia, All-cause mortality	-
Ou[169]	2021	Taiwan	Sepsis	MACE, RAASi prescribing	Adults	RAASi vs No RAASi	Retrospective Cohort Study	HF, MI, All-cause Mortality	RAASi prescribing
Prescott[188]	2017	USA	Sepsis	Hospital Readmissions	Adults	<65 years vs ≥65 years	Retrospective Cohort Study	Cardiovascular admissions	-
Shih[168]	2007	Taiwan	Sepsis	MACE	Adults with CKD	Sepsis vs Hospitalized Non-sepsis	Retrospective Cohort Study	HF, MI, All-cause mortality	-
Vallabhajos-yula[189]	2018	USA	Sepsis	Mortality, Heart Failure	Adults	Sepsis with LV dysfunction vs Sepsis No-LV dysfunction	Retrospective Cohort Study	HF, All-cause mortality	Imaging, Biomarkers

Walkey[190]	2014	USA	Sepsis	Mortality	Adults	No AF vs New-Onset AF vs Prior AF	Retrospective Cohort Study	HF, Arrhythmia, MI	ECG Analysis
Wu[191]	2019	Taiwan	Sepsis	MACE	Adults	MACE vs No MACE	Retrospective Cohort Study	MI, All-cause mortality	-
Yende[8]	2014	USA	Sepsis	MACE, Mortality	Adults	Sepsis (ICU & Non-ICU) vs Hospitalized Sepsis (ICU & Non-ICU) vs Population Control	Retrospective Cohort Study	MI	-

AF=Atrial fibrillation, CAC=Coronary artery calcification, CT=Computed tomography, CKD=Chronic kidney disease, CVE=Cardiovascular events, ECG=Electrocardiogram, End-stage renal failure, HF=Heart failure, ICU= Intensive care unit, IHD= Ischaemic heart disease, LV=Left ventricular, LVEF=Left ventricular ejection fraction, MACE=Major adverse cardiovascular events, MI=Myocardial infarction, RAASi= Renal angiotensin aldosterone inhibition, USA=United States of America

2.3.4 Cardiovascular outcomes

The included articles reported a variety of incident outcomes related to cardiovascular function following sepsis (Figure 2-2). 24/28 (85.7%) articles reported incidence of myocardial infarction (MI) or acute coronary syndromes (ACS) and 13/28 (46.4%) reported admissions or presentations with congestive heart failure. 20/28 (71.4%) articles reported either all-cause or cardiovascular mortality and 6/28 (21.4%) examined cardiovascular admissions to hospital. 2/28 (7.1%) of articles focused explicitly on hospital admissions and diagnoses following sepsis.

Other commonly reported outcomes related to long-term cardiovascular dysfunction included incidence of atrial fibrillation or other dysrhythmia, with 6/28 (21.4%) articles describing arrythmia in patients with sepsis at follow-up.

Despite a wealth of data describing incident outcomes such as congestive heart failure, myocardial infarction, or cardiovascular admissions, the review could find no papers which reported any objective cardiovascular symptoms and only one study referenced patient reported measures of functional impairment.[192]

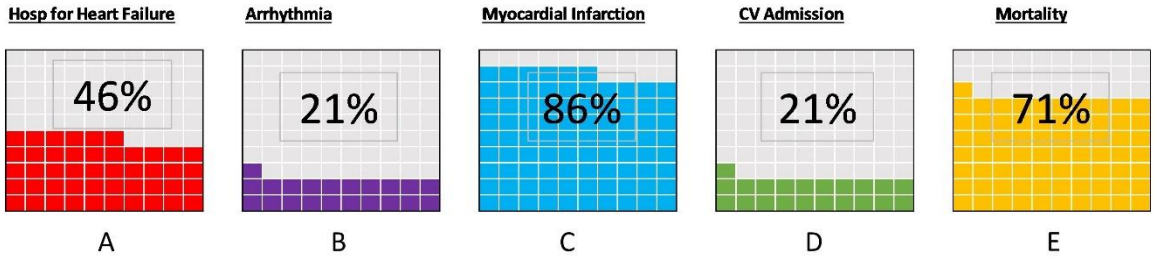

Figure 2-2 Cardiovascular outcomes used in literature examining cardiovascular dysfunction following admission with sepsis

Articles explore a predominately incident cardiovascular outcomes including hospitalisation for heart failure (A), arrythmia (B), myocardial infarction (C), cardiovascular admissions (D) and all-cause mortality (E).

2.3.5 Mechanisms of cardiovascular dysfunction following sepsis

11/28 (39.3%) articles reported variables or outcomes related to cardiac assessment modalities, which could give mechanistic insights into the incident outcomes reported (Figure 2-3). There was wide variation in methodology employed and modalities of cardiac assessment utilised. 6/28 (21.4%) studies reported cardiac or inflammatory biomarkers as a variable of interest. Five of

the included articles used troponin during index illness as a variable for inclusion in data analysis or to risk-stratify patients into separate cohorts for study. Only one study analysed other cardiac or inflammatory biomarkers (e.g NT-proBNP or acute phase inflammatory biomarkers). This particular study was the only article which described serial biomarkers that were sampled beyond admission.[186] 4/28 (14.3%) articles related findings on cardiovascular imaging to adverse cardiovascular outcomes.[174 175 182 189] All of these articles that examined mechanistic data and the association with cardiovascular outcomes used imaging during index illness employing a variety of methods (CT-Coronary Angiography or echocardiography) and grouped patients into hypothetical groups of cardiovascular risk based on imaging findings. One study stratified patients based on the presence of atrial fibrillation on ECG during sepsis admission and explored the association with long-term risk of cardiovascular events.[190] 2/28 (7.1%) studies explored the role of RAAS inhibition following admission with sepsis and found a reduction in risk of adverse cardiovascular events using retrospective cohort analysis that employed propensity score matching methodology.[169 171]

The review could find no prospective randomised controlled trials that explored the effect of preventative or disease modifying therapies on the risk of adverse cardiovascular events.

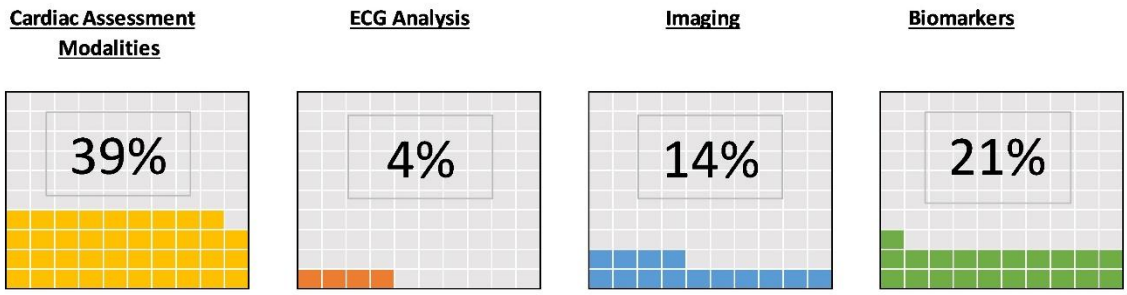

Figure 2-3 Modalities of cardiovascular assessment in the literature pertaining to cardiovascular dysfunction following sepsis

2.4 Discussion

This scoping review maps the literature pertaining to cardiovascular dysfunction following hospital admission with sepsis, the research methodologies employed and the extent to which the literature employs objective methods of cardiovascular assessment to explore this topic. The review demonstrates that

whilst there is an established body of evidence to suggest that sepsis is associated with a long-term risk of cardiovascular events, there are gaps in our understanding as to why this occurs. Only 3/28 (10.7%) of the included studies were prospective in nature and only 11/28 (39.3%) included objective measurements of cardiac assessment, cardiac injury or functional outcomes following admission. Whilst basic biological mechanistic research is out with the remit of this scoping review, it demonstrates a lack of articles highlighting broad clinical mechanisms by which these adverse events are mediated and several gaps in the literature for which there is a need to explore with further research. From the review, a hypothetical model of the risk of cardiovascular disease acquired as a consequence of sepsis is proposed (Figure 2-4). This led subsequently to the generation of research questions aimed at furthering how the field can help identify survivors most at risk of cardiovascular disease and whether they may be responsive to therapy that may alter recovery trajectory or reduce risk hospital readmission (Figure 2-4).

Firstly, despite a body of evidence suggesting that cardiac dysfunction following admission with sepsis is prevalent, the approach towards identifying at-risk groups on admission is less clear. Sepsis is one of the most common reasons for hospital and intensive care admission worldwide.[64 193 194] As such, this population represents a huge cohort of patients at risk of unrecognised cardiovascular disease that may benefit from established preventative or disease modifying therapy. This scoping review demonstrates there is recognition of the issue in the literature, however there is clearly a varied approach to collecting data pertaining to adverse cardiovascular outcomes and identifying which patients may be at risk. Many of the studies are retrospective and observational in nature, using administrative datasets with ICD codes to record variables and outcomes. There can be variability in recording these outcomes and as such they may be vulnerable to confounding. As such, it is difficult to know how much weight to ascribe to these studies when considering whether patient sub-groups should be screened for cardiovascular disease following admission with sepsis. Similarly, data pertaining to further risk-stratification of patients using cardiovascular imaging or biomarkers during admission were often from retrospective or single centre studies using different modalities of variable availability in clinical practice. Thus, it remains unclear whether objective

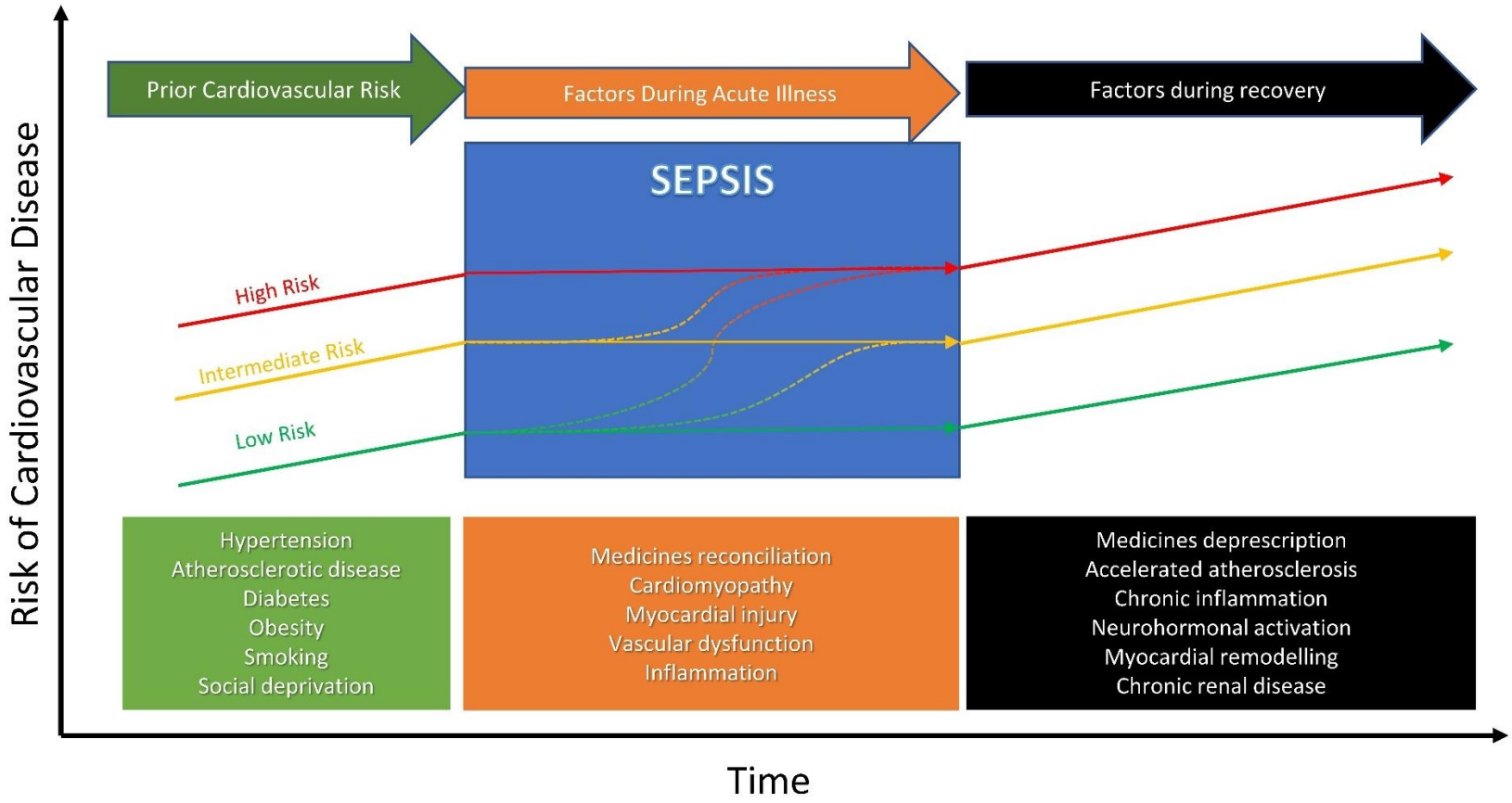

Figure 2-4 A model of cardiovascular risk following admission with sepsis

This thesis proposes that patients present to intensive care with a prior burden of cardiovascular risk due to the interplay between genetic predisposition and modifiable risk factors. Ther There are be multiple features of sepsis admission that may accelerate risk of cardiovascular disease and lead to the acquisition of further comorbidity or risk factors that increase the risk of future adverse events.

methods of cardiovascular assessment may be useful for these purposes. Understanding the relationship between sepsis and chronic cardiovascular disease, and the extent to which patients and sub-groups are at risk of adverse outcomes offers an opportunity to identify cohorts that may benefit from a host of established preventative or disease modifying therapies that may have demonstrable benefits. Further epidemiological study is required to delineate what patients are most at risk of cardiovascular events following admission with sepsis. Similarly, further prospective research is required, exploring how we can further stratify survivors and validate useful methods of identifying patients at risk of cardiovascular disease prior to discharge from critical care and hospital settings.

Secondly, the underlying mechanisms by which post-sepsis cardiovascular events occur remain unclear. In this scoping review, all included articles were observational cohort studies focusing on incident cardiovascular outcomes (e.g. incidence of myocardial infarction) but there was a paucity of data explaining how these events may be mediated from a clinical perspective. Less than half of articles included any objective assessment of cardiovascular dysfunction and related these to long-term outcomes. Only 21.4% explored relationships with cardiac biomarkers and 14.2% investigated imaging findings. Despite a focus on long-term cardiovascular outcomes, the review could only find one study that demonstrated prospectively collected mechanistic data beyond admission - in this case, cardiac and inflammatory biomarkers - to explore the relationship with adverse cardiovascular events. Thus, the mechanisms underlying the acquired cardiovascular risk related to sepsis are presently unclear. For example, there is little evidence examining whether sepsis has perhaps accelerated pre-existing chronic cardiovascular disease or whether it has occurred de novo. It remains unclear as to what extent this phenomenon is driven by atherosclerotic disease or whether myocardial inflammation might play a role. Studies that help characterise these underlying mechanisms of cardiovascular dysfunction and their prevalence - for example by prospectively utilising cardiac imaging or biomarkers of cardiac injury - during follow-up are required to investigate whether proposed clinical mechanisms can be confirmed or refuted in this population.

Table 2-3 Research gaps in the literature of cardiovascular dysfunction following sepsis

Identifying patients at risk
• To what extent do traditional cardiovascular risk factors play a role in determining cardiovascular risk following admission? • To what extent is unrecognised cardiovascular disease prior to admission (e.g. coronary artery disease) implicated in adverse cardiovascular risk following admission?
Risk stratifying patients during acute illness
• How does severity of acute illness impact risk of chronic cardiovascular disease? • What are the associations of biomarkers of cardiovascular injury and dysfunction with long-term risk of cardiovascular events? • Can biomarkers of cardiovascular dysfunction be used in this population in a similar manner to those used in conventional outpatient settings? • Are findings on cardiovascular imaging during admission correlated with those on discharge and what implications do these findings have in terms of cardiovascular risk? • How do alterations to cardiovascular therapies during hospital admission with sepsis impact cardiovascular risk on discharge?
Screening for and managing chronic disease
• What is the prevalence of cardiac dysfunction following admission with sepsis? • Should sepsis survivors be screened for cardiovascular disease following admission and what is the best strategy in which to do so? • What is the association of cardiovascular dysfunction and functional outcomes following admission with sepsis? • To what extent does sepsis influence the acceleration of atherosclerosis or the evolution of de-novo atheroma? • Do preventative or disease modifying cardiovascular therapies influence risk of cardiovascular events following admission with sepsis?
Understanding mechanisms of chronic cardiovascular disease following sepsis
• What is the pathogenesis of adverse cardiovascular events following admission with sepsis? • Is there a genetic or metabolic basis to the cardiovascular risk that is acquired following sepsis admission? • Does sepsis share similarities to other critical illness syndromes in how it mediates acquired cardiovascular risk?

Thirdly, the prevalence of chronic cardiovascular disease and how this affects survivors of sepsis on a day-to day-basis is unclear. The scoping review identified just one article which linked admission with sepsis or cardiovascular outcomes to patient-reported functional outcomes or measures or cardiovascular symptoms.[178] Given the frequency of cardiovascular admissions following sepsis, it seems plausible that a significant proportion of sepsis survivors may be affected by chronic heart failure or other chronic cardiovascular disease. Future research should aim to address the long-term impact on survivors and how this relates to functional outcomes.

Fourthly, given the potential prevalence of cardiovascular dysfunction in this large cohort of patients it is tempting to consider the potential for cardiovascular therapies to modify risk. This review found no randomised controlled trials to prospectively explore these types of question. Future prospective research should seek to study whether established cardiovascular therapies may lower risk of adverse cardiovascular events or indeed modify recovery trajectory.

Finally, there is significant overlap between literature examining cardiovascular outcomes in specific infective processes (e.g. pneumonia) and the sepsis syndrome. Our understanding of critical illness and how we define disease processes is changing, with the recognition that many classically labelled clinical syndromes may share pathophysiological mechanisms.[18] Although there may be differences in terms of initial pathophysiological insults at the time of acute illness, the mechanisms that mediate the underlying increase in cardiovascular risk may be similar. Previous research has demonstrated that survivors of sepsis and pneumonia have increased circulating levels of pro-inflammatory cytokines following discharge.[110 186 195] Similar inflammatory markers have been associated with occurrence of long-term adverse cardiovascular events, and critical illness in general is thought to induce immunometabolic changes associated with atherosclerotic disease.[107 196 197] Indeed, some literature included in this scoping review also identified an increased risk of cardiovascular events in survivors of critical illness with ‘non-sepsis’ aetiologies.[8] Further prospective research is required to understand this intersection between acute illness and chronic cardiovascular disease. As well as understanding how this risk is mediated in

conditions such as sepsis, it is also important to consider whether it might occur as long-term sequelae of critical illness in general.

There are a number of proposed mechanisms by which cardiovascular disease following critical illness may occur, including altered homeostatic reflexes; alterations in immune signalling and lipid metabolism; and cellular level changes that all predispose to chronic cardiovascular disease.[107] Previously, there has been burgeoning interest in the role inflammation may play in chronic heart failure and atherosclerotic disease and there have been exciting novel developments.[198 199] For example, the CANTOS trial demonstrated that administration of anti-IL-1ß antibodies to patients post-myocardial infarction and treated in accordance with current guidelines were at reduced risk of adverse cardiovascular events.[111] A subsequent subgroup analysis identified a significant reduction in hospitalisation or mortality from heart failure in patients who achieved low hs-CRP on treatment.[200] Whilst this offers promise of novel, targeted treatments for heart failure, it too offers an insight into mechanisms by which persisting inflammation following sepsis may mediate cardiovascular dysfunction and contribute to functional impairment.

2.4.1 Strengths and limitations

Strengths of this scoping review include the development of a robust search strategy developed in partnership with a librarian with extensive experience in the conduct of systematic review. Furthermore, it rigorously adheres to JBI guidelines and PRISMA-ScR standards.[164] The pilot phase of the search strategy ensured it was sensitive to collecting key papers that had previously been identified as highly relevant. Over 11,000 articles were screened by at least two independent reviewers who subsequently undertook detailed full text review of potential articles for inclusion. There was a deliberate focus on cardiovascular outcomes *following* an episode of sepsis and as such, there was an emphasis on the impact of cardiovascular disease on sepsis survivorship.

However, there are limitations. The focus was primarily on identifying literature pertaining to chronic cardiac dysfunction in the period following an episode of sepsis. As such, other outcomes such as acute stroke or venous thromboembolic events were not included. Whilst these conditions have similar aetiologies, the

assessment and long-term management of these conditions is different to that of heart failure and other cardiovascular diseases. Consequently, they were excluded from the review. Similarly, the review focuses on sepsis as a whole entity rather than discrete infection syndromes (e.g. pneumonia, urinary tract infection or cellulitis). Doing so would have led to an elaborate and inelegant search strategy that covered a wide range of infections of low severity that were not relevant to the outcomes of interest. Similarly, in articles where patients with other critical illness syndromes were included, the review was unable to differentiate between literature around cardiovascular dysfunction following sepsis vs critical illness as a whole, beyond exclusion of articles where <50% of patients had sepsis.

Lastly, the review did not include non-English articles in results. Whilst the strategy identified some articles that were published in more than one language, it is possible more articles may have been identified on the topic by inclusion of other languages. However, attempting to include these articles would have likely introduced errors in translation and consequently may have confounded the data set.

2.5 Conclusion

Whilst there is an evolving body of literature examining cardiovascular dysfunction following sepsis, there is still a lack of data examining underlying mechanisms by which this occurs and how it might translate to chronic cardiovascular disease and functional impairment. The strategy by which at-risk patient groups are identified and how chronic cardiovascular disease should be optimally managed on discharge is unclear. Further prospective studies are required to explore the underlying mechanisms and understand how future research and clinical interventions may mitigate increased cardiovascular risk, with the aim of improving the recovery trajectory of sepsis survivors.

The research presented in the following chapters pertains to a prospective, observational cohort study combining cardiac imaging, biomarkers and patient reported functional outcomes with the aim of elaborating on some of the questions raised by this scoping review.

Chapter 3 Methods

The work in the following chapter has been published in CHEST Critical Care in 2024, and is cited using the following reference:

Garrity K, Docherty C, Mangion K, Woodward R, Shaw M, Roditi G, Shelley B, Quasim T, McCall P, McPeake J. Characterizing Cardiac Function in ICU Survivors of Sepsis: A Pilot Study Protocol. CHEST Crit Care. 2024 Mar;2(1):100050.

 The original manuscript was drafted in full by the author of this thesis and has been amended for its inclusion. Dr Docherty, a clinical research fellow at University of Glasgow contributed to the design of the wider biomarker study and within which the following work is embedded. Recruitment and delivery of follow-up visits was done jointly by the author and Dr C Docherty. Prof J McPeake and Dr P McCall are supervisors for the following body of work and contributed revisions to the chapter.

3.1 Introduction

This chapter outlines the protocol which forms the basis of the subsequent results presented in this thesis (Chapters 4-7) which were undertaken on the same population of patients.

3.2 Ethical approval

The study was approved by an NHS Research and Ethics Committee (South-West Central Bristol), Reference: 22/SW/0082, Approval date - 7th July 2022.

3.3 Rationale for study

Sepsis is one of the most common reasons for intensive care unit (ICU) admission and mortality worldwide.[64 65] The impact of critical care admission is profound, and has been widely associated with a combination of physical, psychological or cognitive sequelae often termed, post-intensive care syndrome (PICS).[2] Despite increasing recognition of the profound impact of PICS on survivors, the

mechanisms that underly the associated impairments following critical illness are less clear.[96] Understanding mechanisms by which chronic impairments are acquired during convalescence is likely key to understanding how we can best improve care for survivors.

The adverse cardiovascular risk associated with sepsis has gained attention in recent years.[107] One recent meta-analysis demonstrated an association with sepsis and adverse cardiovascular outcomes in a magnitude compared to other cardiovascular risk factors such as hypertension or dyslipidaemia.[105] The scoping review in the previous chapter demonstrates there are many gaps in our understanding of cardiovascular dysfunction following sepsis. The hypothesis that adverse events such as myocardial infarction, acute decompensated heart failure or stroke might be mediated by ongoing inflammatory and immunometabolic changes following sepsis is intriguing and allows for consideration of sepsis as a non-traditional cardiovascular risk factor.[107]

The implications for survivorship are significant. Many survivors of critical illness - including sepsis - experience symptoms such as breathlessness and fatigue.[43 201] However, the extent to which cardiac dysfunction plays a role in these symptoms or the other functional impairments is unknown. Given the association of adverse cardiovascular events such as myocardial infarction or heart failure, it is plausible that survivors of sepsis may be at accelerated risk of chronic cardiovascular disease. There are several mechanisms described in the literature which may be associated with increased risk of cardiovascular disease and functional impairment following critical illness including myocardial injury during admission, deprescription of medications that may play a role in prevention of adverse cardiovascular outcomes and persistent inflammation and neurohormonal changes following sepsis that can increase propensity to adverse cardiovascular events.[107 184]

To that end, the study in this thesis sought to characterise cardiovascular function in ICU survivors of sepsis, exploring the associations between objective measures of cardiovascular function, injury, inflammation and patient-reported functional outcome measures (PROMs).

3.4 Research question

What is the prevalence of myocardial dysfunction following ICU admission with sepsis and to what extent might it be associated with physical impairments in PICS?

3.5 Study design

3.5.1 Objectives

The study was exploratory in nature and sought to combine cardiovascular magnetic resonance (CMR) imaging, biomarkers of cardiac injury or dysfunction, and PROMs.

The study aims were to:

- Understand feasibility of CMR imaging in this complex, heterogeneous and often frail cohort of patients.
- Describe prevalence of left and right ventricular (LV and RV) dysfunction and explore causative mechanisms (inflammation, scar, thrombus).
- Investigate biochemical changes associated with cardiac dysfunction and cardiac injury and their comparison to the general population.
- Describe the inflammatory profile of ICU survivors of sepsis 6-10 weeks following hospital discharge.
- Explore the relationship between functional impairment, detailed imaging, and cardiac biomarkers.

3.5.2 Study structure and timeline

The study was multimodal, incorporating CMR imaging, biomarker analysis and PROMs. It was embedded in a wider 69 patient biomarker study examining multiple long-term outcomes (including pain and inflammation) in ICU survivors of sepsis (Figure 3-1). Patients were recruited between August 2022 and August 2024.

Initially, these two projects were conceptualised as one cohort study with identical recruitment criteria, but investigating different outcomes. However, due to concerns regarding the inability to recruit otherwise eligible patients because of contraindications to CMR or prior cardiovascular disease, the CMR study was later embedded *within* the wider biomarker study with ethical approval granted for this in February 2023.

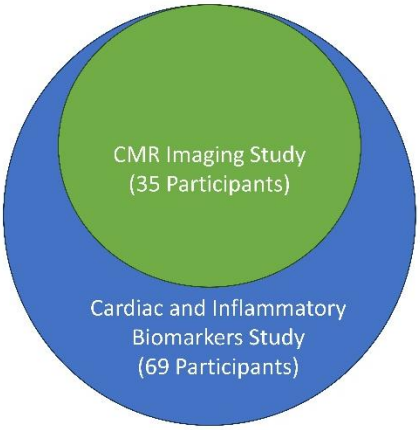

Figure 3-1 Structure of CONDUCT-ICU

The wider biomarker study aimed to investigate mechanisms of other long-term physical impairments (including inflammation and pain) following ICU admission with sepsis. Patients who met inclusion criteria for the wider biomarker study were also screened for inclusion in the embedded CMR study (additional criteria in italics below). Patients continued to be recruited to the embedded CMR study (if eligible), until 35 patients underwent follow-up imaging or if recruitment to the wider biomarker study was complete (69 patients) (Figure 3-2).

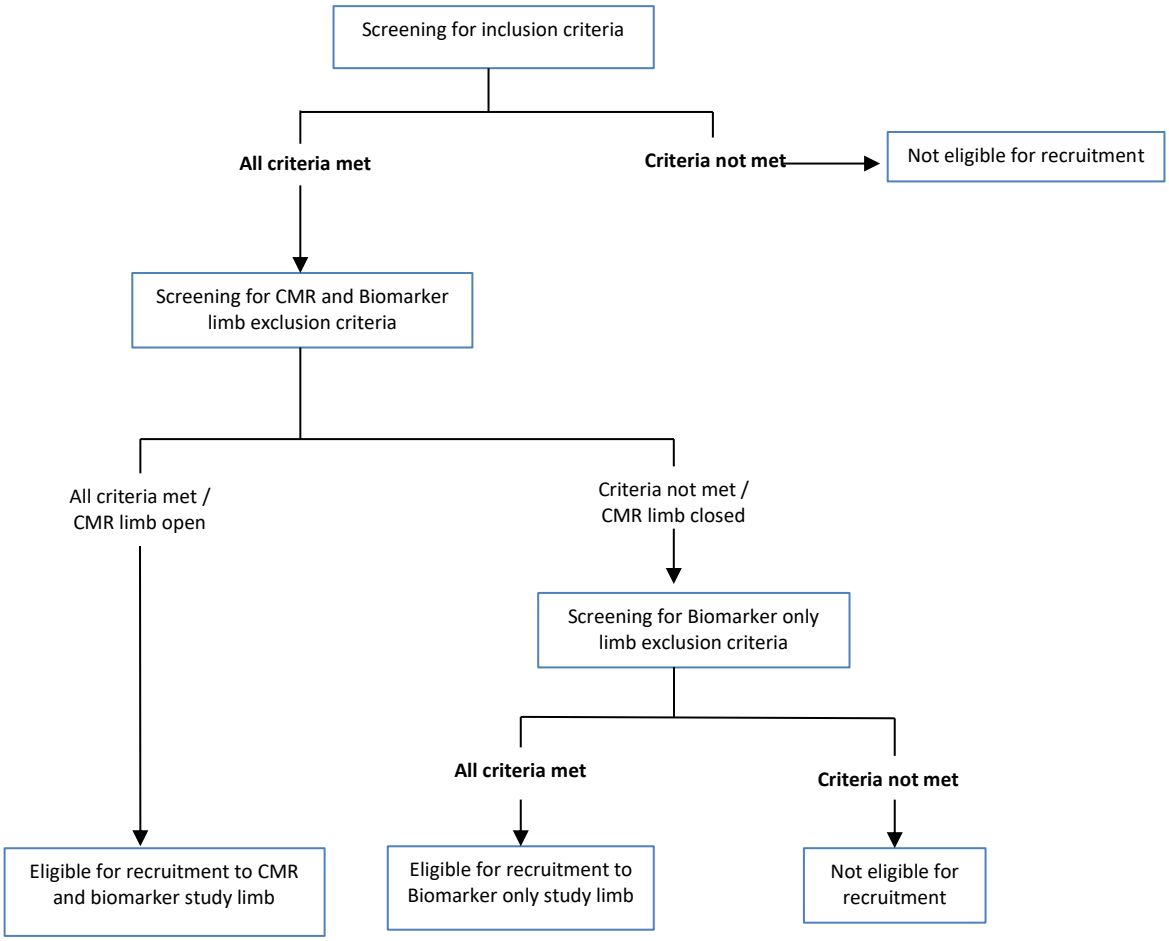

Figure 3-2 Recruitment structure in CONDUCT-ICU

3.5.3 Setting

The study was undertaken across two general ICUs, situated in the West of Scotland, covering a mix of medical and surgical patients. Imaging and follow-up was performed in a regional centre of excellence.

3.5.4 Population

Patients were recruited from the general ICU population. The study intentionally focused on the convalescent phase of critical illness, recruiting participants at the point from which they were transitioning towards recovery.

The patients presented in the following chapters are those that were eligible for participation in the CMR cohort of the study (Figure 3-1). Eligibility criteria for the CMR study are outlined below.

3.5.5 Eligibility criteria

- Provision of informed consent
- Age ≥ 18 years
- ICU admission with sepsis (According to The Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3])1
- Ability to comply with study procedures

3.5.6 Exclusion criteria

- Inability to give informed consent
- Ongoing participation in any investigational research that may undermine the scientific basis of the study
- Receipt of immune modulating drugs or biologic therapy either long term or during acute admission
- Patient considered by the clinical team to be very unlikely to survive to hospital discharge
- Hospital admission because of Covid-19
- Patients undergoing treatment for malignancy with systemic anti-cancer therapies
- Pregnancy
- Patients who are prisoners at time they would be otherwise eligible
- Exclusions to CMR study:
    - *Contraindications to cardiovascular magnetic resonance imaging*
    - *Known coronary artery disease prior to ICU admission*
    - *Previous myocardial infarction prior to ICU admission*
    - *Known chronic heart failure prior to ICU admission*

3.5.7 Screening

Patients were screened over the course of a two-year period between August 2022 and August 2024. Reasons for eligibility or ineligibility were prospectively recorded to help evaluate the feasibility of the study protocol.

3.5.8 Recruitment

Patients who were identified as being ready for discharge from intensive care by their local clinical care team were considered as eligible for screening. If eligibility criteria were met, patients were approached by recruiters.

Patients eligible for the CMR study were invited back for CMR imaging at 6-10 weeks following hospital discharge. In addition, cardiac and inflammatory biomarkers were collected in all patients in addition to a number of patient reported functional outcome measures (PROMs).

Patients were also consented for longer term follow-up and storage of biological samples for future analysis, pending further ethical approval.

3.5.9 Diagnosis of sepsis

Sepsis was defined using internationally recognised 'Sepsis 3' definitions i.e. life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined by a change in SOFA score ≥ 2 from baseline (where patients with no pre-existing organ dysfunction can be assumed to have a SOFA score of 0).[65]

3.5.10 Primary outcome and justification

A summary of outcomes assessed is depicted in Figure 3-3. The primary outcome for the study was prevalence of reduced left ventricular ejection fraction (LVEF) in the sample population at 6-10 weeks following hospital discharge. Reduced LVEF was considered <51% for women and <47% for men, aligned with a local control population and within parameters advocated by the European Association for Cardiovascular Imaging (EACVI).[202 203]

LVEF is fundamental to the assessment of cardiac function and is widely used in the heart failure population. Along with its inclusion in international guidelines, there is a well-established evidence base for treatment of heart failure, based upon ejection fraction phenotype e.g. heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF).[125] Thus, reduced left ventricular ejection fraction represents not only an objective and reproducible measure of cardiac function, but also a clinically meaningful endpoint for patients which is aligned with a vast evidence base for disease modifying treatments.[125 150]

Utilisation of gold-standard imaging techniques such as CMR in combination with biomarker analysis is novel in this population and provides objective findings in relation to myocardial inflammation and cardiac function which can be compared to other populations such as healthy controls or other vulnerable patient groups. Similar studies utilising CMR and biomarker analysis had been successfully delivered in the author's institution in other populations of patient including; covid-19, post lung resection surgery and post-myocardial infarction.[152 204 205] As such it was felt to be a feasible, accurate and reproducible method of measuring the primary outcome.

Given sepsis is associated with an increased incidence of heart failure following admission, CMR represents an important technique for advancing understanding and providing clinically important data that can be referenced and compared with key reference range data such as that published from UK biobank data.[138 206]

3.5.11 Secondary outcomes

3.5.11.1 Cardiac magnetic resonance imaging

CMR is a gold-standard method for assessing indices of cardiac function and a reference diagnostic method for assessing myocardial injury, including myocarditis and cardiomyopathy, with superior accuracy and precision when compared with echocardiography.[207 208]

CMR imaging was conducted at a local centre of excellence using a 3 Tesla scanner by Health and Care Professions Council accredited radiographers, 6-10

weeks following discharge. Indices of cardiovascular function were reported by a radiologist accredited in CMR reporting. Images were evaluated to calculate dimensions of cardiovascular structures and evaluate indices of function including: Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), LV Stroke Volume (LVSV), LV Mass, LV Ejection Fraction (LVEF), Cardiac Output; Right ventricular end-diastolic volume (RVEDV), right-ventricular end-systolic volume (RVESV) and Right Ventricular Ejection Fraction (RVEF). With the exception of LVEF and RVEF, these values can be indexed against body surface-area (BSA) to give standardised-indexed values.

The 6-10 week timepoint coincides with the point at which participating sites routinely follow-up critical illness survivors and as such the point at which we would normally evaluate and address ongoing comorbidity following critical care admission.[209 210] Whilst it is possible to detect myocardial inflammation earlier than this in other patient cohorts, there was a wish to minimise burden on patients in terms of follow-up at multiple appointments and ensure identification of findings at a time point where they are likely to have meaningful implications for patient recovery.

Sepsis-induced cardiomyopathy may occur in 10-70% of patients admitted with sepsis and has traditionally thought to have been reversible, with subsequent recovery of LV function.[162] However, to date there are few data to suggest this is the case, and we now know that sepsis is associated with an adverse risk of heart failure admission or myocardial infarction that persists long after index admission.[105] In other settings such as post LV assist device insertion, persistent molecular abnormalities persist even after cardiac function has improved.[211] Utilising gold-standard imaging provides a clear indication of the trajectory of cardiovascular function following intensive care admission.

In addition to determination of new or persisting myocardial dysfunction, CMR can be utilised to evaluate for evidence of myocarditis or new incidental pathology. Furthermore, there is scope for identification of any incidental or unexpected pathology (e.g. pulmonary arterial thrombus or incidental tumour).

CMR imaging also offers the ability to undertake parametric mapping. These techniques, including T1 and T2 mapping; LGE enhancement; and the calculation

of extra-cellular volume (ECV) through measurement of T1 values post-contrast can be used to identify areas of subtle fibrosis and oedema for which abnormal values have been identified in other populations.[140 141]

Native T1 mapping measures the longitudinal spin-lattice relaxation time and is described in more detail, along with associated techniques in Chapter 5.2.2. The main biological determinants of increased native T1 are *oedema* (e.g. acute infarction or inflammation) and *increased interstitial space* (e.g. fibrosis or amyloid deposition).[141] The use of gadolinium-based contrast, along with haematocrit allows the calculation of the ECV, a more robust measure of myocardial fibrosis with better reproducibility.[212]

T2 mapping refers to measurement of the loss of transverse magnetisation following application of a radiofrequency pulse and has long been associated with myocardial oedema.[213] Similar to T1, T2 values can be rendered onto pixellated maps of myocardial tissue, indicating areas of oedema. T2 values are significantly prolonged in a variety of pathologies and can help in evaluating cardiac disease such as acute coronary syndromes, myocarditis, transplant rejection and dilated cardiomyopathy.[214]

T1, T2, ECV values were determined by the author following initial scan reports. An initial sample of 10 scans were dual reported by a cardiologist accredited in parametric mapping techniques and intra-class correlation coefficients were calculated to ensure inter-rater reliability, prior to further assessment of the CMR imaging dataset.

In combination, these T1 and T2 criteria (or derived parameters) can be used to accurately diagnose myocardial inflammation and are supported in expert consensus guidelines by means of criteria such as the modified Lake-Louise criteria.[140] As such, this thesis will utilise native T1, native T2 and ECV to compare values in ICU survivors of sepsis to population reference ranges to evaluate for evidence of myocardial fibrosis, oedema and inflammation.

3.5.11.2 Echocardiography

Echocardiography findings during index admission were recorded in patients who participated in the CMR study. Many patients with sepsis and septic shock will undergo echocardiography in ICU, for assessment and refinement of diagnoses or to tailor supportive therapies.[215] Echocardiography involves use of non-invasive ultrasound imaging to acquire measurements of heart structure and function. It is commonly undertaken in a 'focused' manner by clinicians in ICU in and these images can be analysed retrospectively and correlated with other clinically meaningful endpoints. Acute LVSD was defined as LVSD identified and reported by an accredited echocardiographer during the patients ICU stay.[215 216]

3.5.11.3 Biomarker analysis

All biomarkers were collected at recruitment (approximating to the time of ICU discharge) and at follow-up (6-10 weeks following hospital discharge). Samples were transferred on day of collection to an NHS Greater Glasgow and Clyde Biorepository where they were processed by laboratory staff and kept in freezer storage at -80°C for later analysis.

Samples were later batch analysed at the Glasgow Biomarker Research Unit (GlasBRU) and returned to storage in the biorepository. A summary of biomarkers utilised in the study is displayed below (Table 3-1).

All biomarkers were compared with published general population reference ranges, or to reference ranges for normal endogenous values provided by test manufacturers. This is aligned with local clinical practice and laboratory reference ranges in the West of Scotland.

3.5.11.4 Cardiovascular, renal and inflammatory biomarkers

Long-established and novel markers of cardiovascular function were collected including: N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity Troponin-T (hs-TnT), Ca-125 and Mid Regional Pro-Adrenomedullin (MR-proADM). In addition, biomarkers of renal dysfunction commonly associated with major adverse cardiovascular events such as Cystatin-C were collected.[217]

NT-proBNP is a sensitive biomarker of myocardial dysfunction, released due to increased myocardial wall stress and is recommended in national and international guidelines for assessment and diagnosis of heart failure.[125 150] In a critical care setting, NT-pro-BNP values during ICU stay have been identified as predictive of mortality following discharge from ICU.[151]

Hs-TnT is a biomarker of cardiomyocyte injury most frequently used in the diagnosis of myocardial infarction.[143 144] Troponin values are associated with mortality in ICU settings and with other markers of disease severity including acute physiology scoring systems such as the acute physiology and chronic health evaluation (APACHE) II score.[114 145 146] It has been shown to be associated with other objective markers of cardiac dysfunction such as need for vasoactive drugs and wall motion abnormalities on echocardiography.[147] High-sensitivity troponin has also been associated with an increased risk of adverse cardiovascular events in a community setting.[148]

MR-proADM is a biomarker of endothelial dysfunction which has been associated with poor prognosis in both sepsis and heart failure.[218 219] Ca-125 is a membrane associated glycoprotein, which is most commonly known as a biomarker of ovarian and other cancers.[153] However, more recently CA-125 has been investigated as a novel marker of heart failure [154] and has been shown to be associated with clinical outcomes including mortality and hospital admission.[155]

Similarly, Cystatin-C, a biomarker traditionally associated with renal dysfunction [156], has also shown promise as a biomarker for cardiac dysfunction, especially when used in combination with NT-proBNP.[157] Cystatin-C has been shown to be a predictor of mortality and cardiac events in patients with heart failure.[158 159]

3.5.11.5 Inflammatory biomarkers

In addition to biomarkers of myocardial injury and dysfunction, biomarkers of inflammation on ICU discharge were collected at 6-10 weeks following hospital discharge. These biomarkers: (hs-CRP, procalcitonin, IL-1ß, IL-6, IL-8, and IL-10 and TNF-α) have been associated with adverse cardiovascular events and were collected with a view to exploring mechanistic underpinnings of observed cardiovascular outcome measures.[220 221]

Table 3-1 Biomarkers used to explore association between cardiovascular function, inflammation and patient reported outcomes following sepsis.

Biomarker	Rationale
NT-proBNP	Biomarker of ventricular wall/myocardial stretch and widely utilised in diagnosis and prognostication of heart failure.[222]
hs-TnT	Sensitive biomarker of myocardial injury and utilised internationally in definitions and diagnosis of myocardial infarction.[223]
Cystatin-C	Biomarker of renal dysfunction, produced by multiple tissue sites in humans and better predicts risk of future cardiovascular events than creatinine alone.[224]
Creatinine	Biomarker of renal function, use of which is featured widely in international guidelines in diagnosis and management of acute and chronic kidney disease.[225]
hs-CRP	Acute phase inflammatory protein used to diagnose and monitor acute inflammation. Has been associated with adverse cardiovascular events in the general population.[226]
IL-1β	Pro-inflammatory cytokine that triggers local inflammation and leukocyte production as part of the NLRP3 inflammasome pathway. Has been implicated in pathogenesis of atherosclerosis and plaque instability.[227]
IL-6	Pro-inflammatory cytokine promoting accelerated atherosclerosis and plaque formation. Stimulated by other cytokines such as IL-1β. Successfully targeted in other critical illness syndromes.[228]
IL-10	Anti-inflammatory cytokine that is thought to be involved in suppression of inflammation, reducing myocardial fibrosis remodelling following myocardial infarction. However has been positively associated with risk of CVD.[229]
TNF-α	Acute phase inflammatory protein, contributing to myocardial remodelling atherosclerosis and vascular dysfunction. Blockade has not been successful in reducing risk of chronic heart failure.[113 230]
MR-proADM	Biomarker of endothelial dysfunction and associated with adverse outcomes in both heart failure and sepsis.[231]

Abbreviations: Hs CRP=High sessitivity C reactive protein, hs-TnT=high sensitivity troponin T, IL-1β=Interleukin-1β, IL-6=Interleukin 6, IL-10=Interleukin 10, MR-proADM=Mid-regional pro-adrenomedullin, NT-proBNP=N-Terminal Brain Natriuretic Peptide, TNF-α=Tumour necrosis factor-α

3.5.11.6 Patient reported outcome measures (PROMs)

Patient reported outcome measures (PROMs) and their association with findings on cardiac imaging and biomarkers were explored. These included established PROMs utilised in assessment of functional capacity and breathlessness: Duke

Activity Status Index (DASI), Medical Research Council (MRC) Dyspnoea Scale and EuroQol 5-Dimension 5-Level (EQ-5D-5L).[22-26] To assess outcomes pertaining to fatigue, the vitality domain of SF-36 health questionnaire was collected.[232 233]

3.5.11.7 Feasibility

The feasibility of CMR scanning in this population is of significance to further studies in the ICU survivor population. To the author's knowledge, this is the first prospective cardiac imaging study undertaken prospectively in this population in combination with PROMs and biomarker analysis.

A screening log, rates of recruitment and follow-up attendance was collected to evaluate feasibility of the protocol.

ICU discharge	6-10 weeks post-hospital discharge
Baseline Demographics (Age, Frailty, Comorbidities, Length of Stay, Diagnosis, Treatments and Therapies, SOFA Score, APACHE Score)	Patient Reported Outcome Measure (EQ-5D-5L, DASI, SF-36 Vitality Domain, MRC Breathlessness Scale, HADS, Brief Pain Inventory, ID-Pain)
Biomarkers (U&E, Cystatin C, Ca-125, hs-TnT, NT-proBNP, CRP, IL-1β, IL-6, IL-10, TNF-α)	Biomarkers (U&E, Cystatin C, Ca-125, hs-TnT, NT-proBNP, CRP, IL-1β, IL-6, IL-10, TNF-α)
Echocardiography (LV/RV Size/Function)	Cardiac Magnetic Resonance Imaging (CMR) (LV/RV function, LV/RV Wall Motion, Myocardial Perfusion, Tissue Characterisation (T1/T2 native mapping, LGE, ECV)

Figure 3-3 Summary of outcomes recorded in the study at the point of ICU discharge and follow-up (6-10 weeks post-hospital discharge).[234]

3.5.12 Study management

This study was conducted in line with the current Guidelines for Good Clinical Practice in Clinical Trials and STROBE guidelines.[235]

3.6 Statistical approach

3.6.1 Statistical considerations

3.6.1.1 Sample size

Given the exploratory nature of this study and paucity of data available for CMR outcomes in a post-critical illness population, it was difficult to undertake an accurate power calculation for prevalence of LV dysfunction.

There is a wide-ranging estimated prevalence of LV dysfunction (10-63%) in patients with sepsis in ICU.[189 236] Taking a conservatively estimated 12% prevalence of LV dysfunction following ICU, and ensuring 80% power and a significance of 0.05, then 35 patients would be required to determine a statistically significant difference in comparison to population prevalence of left ventricular systolic dysfunction, estimated at 2.2%.[237]

3.6.2 Data analysis

The data in this thesis are presented as median (Q1, Q3) or mean (sd) depending on whether variables conform to non-parametric or normal distributions. Comparisons are assessed using students-t test or Wilcoxon rank sum test for continuous variables depending on whether they are normally distributed. Chi squared or Fisher's exact tests are used to test comparisons of categorical variables.

To help visualise biomarker data, all biomarkers have been plotted using violin plots. These plots display key statistics such as median values and interquartile range (IQR), however also indicate the cumulative density of observed values so as to appreciate the distribution of observed data. The anatomy of a violin plot is described in Appendix 6.

To explore relationships between variables, linear and logistic regression models were constructed to explore the associations between dependent outcome variables and predictor variables. In this thesis, the outcome variables considered were those thought to be of clinical importance in assessment and management of heart failure (e.g. LVSD or LVEF assessed by CMR), biomarkers of

cardiovascular dysfunction (e.g. NT-proBNP) or patient reported outcome measures (e.g. DASI). Predictor variables include key patient demographics, features related to illness severity, or biomarkers of cardiovascular dysfunction and inflammation.

3.6.2.1 Linear regression modelling

For continuous outcome variables, linear regression models are used. Linear regression models are built by generating a line of 'best fit' which predicts an outcome variable by a desired predictor variable. The line of best fit is defined by the equation:

$$y = \beta_0 + \beta_1 x + e$$

Where 'y' denotes the outcome variable, β_0 denotes the value of 'y' when 'x' is 0 and 'β_1' denotes the slope of the linear regression line, such that the equation can be interpreted as 'for every unit increase in x, we would expect y to increase or decrease by a multiple of β_1'. The term 'e' denotes the 'error' and is described below. The linear regression line is determined by using the 'sum of least squares' method, where the sum of vertical distances between measured data points ('residuals') and the regression line is at a minimum Figure 3-4.

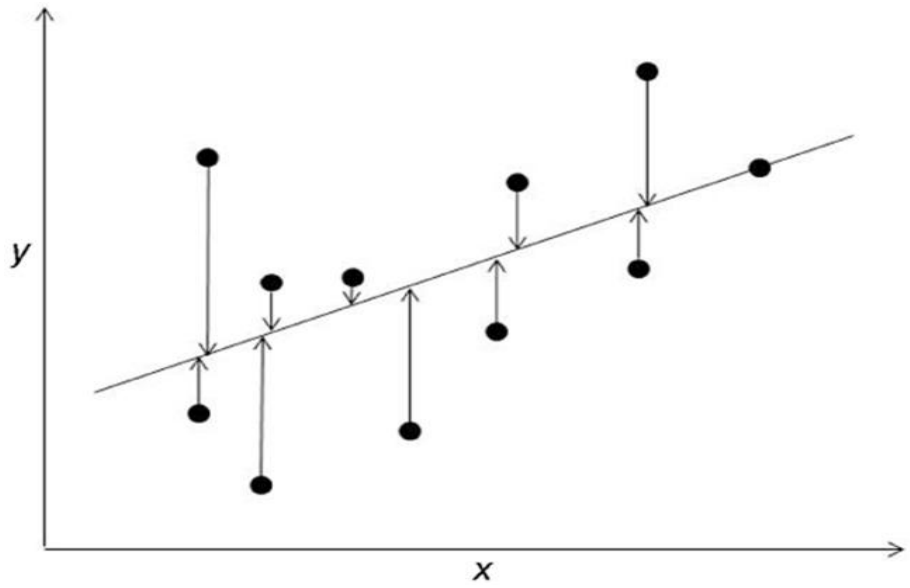

Figure 3-4 Linear regression line and associated residuals

The regression line is determined by that created when the sum of squared value of the residuals is at a minimum. Reprinted with permission from John Wiley and Sons.[238]

There are two assumptions underpinning linear regression. Firstly, there is an underlying assumption that outcome and predictor variables are normally distributed. The second is that the magnitude of spread around the residual line is evenly distributed across the length of the regression line. This is often denoted by the 'error', which is assumed to be normally distributed with a mean of '0' and standard deviations around the regression line.

As such, in constructing linear regression models in this thesis, effort has been taken to ensure that variables of importance have been assessed for normality of distribution so as to ensure model integrity. Normality has been assessed with 'goodness of fit' tests including Kolmogorov-Smirnov (KS), Anderson-Darling (AD) and Cramer-von Mises (CVM) tests. If variables were non-normally distributed then they were log transformed and reassessed.

Following model construction, underlying assumptions have been checked by assessing for normality of residuals using KS, AD and CM tests against residual values. Additionally, models were further tested using simulated data. Simulated data have been generated from each datapoint the using the constructed models, with each observed value from the original dataset mapped to the cumulative density function of the simulated values. From the simulated data, QQ plots can be generated to assess for normality of the observed and simulated residuals. Observed values can also be standardised against simulated data using their cumulative density function, such that if all of the simulated datapoints are above that of the observation observed, its 'scaled' residual has a value of 0.[239] If all of the simulated residuals are lower than the observed value, this generates a value of 1. If the observed residual has half greater and half lower, it has a value of 0.5. Scaled residuals can then be plotted in a standardised fashion in comparison to ranked model predictions. If the model is predictive across its range, the scaled residuals will deviate in a uniform manner, with homoscedasticity of the scaled residuals indicating that the model assumptions are met across the range of observed values (Figure 3-5). This method is undertaken using the DHARMa package in 'R' version 4.4.3 as described by Hartig.[239]

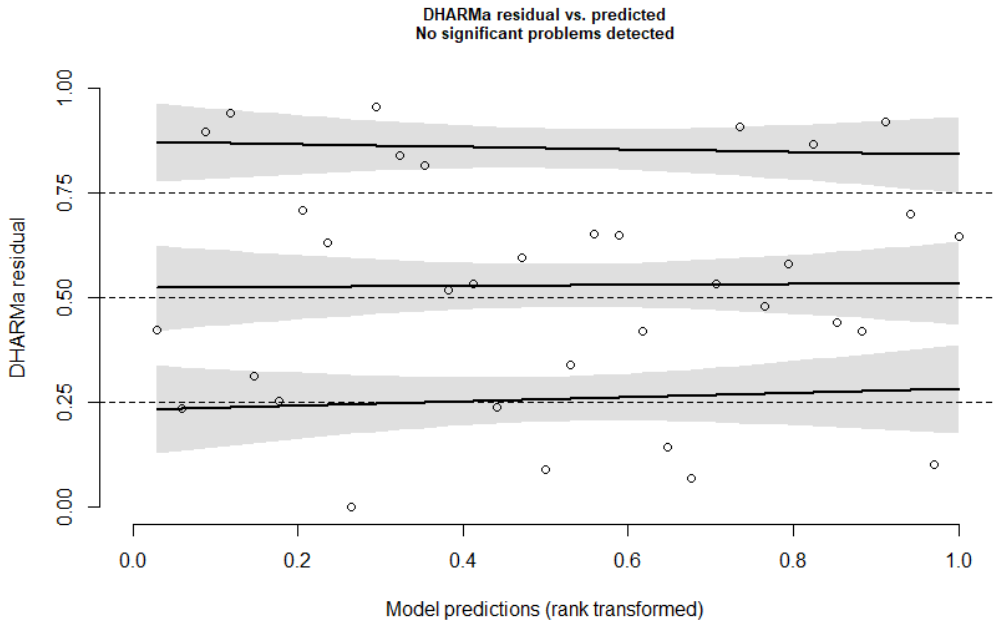

Figure 3-5 Simulated model residuals plotted against scaled (DHARMa) residuals

There is homoscedasticity of observed (scaled) residuals when plotted against ranked model predictions. Across all simulated values ranked, the scaled residuals from observed data are evenly spread, with no quantile deviation indicating the above the assumptions of the model are met.

3.6.2.2 Logistic regression modelling

Associations with categorical outcomes (e.g. LVSD) are explored in this thesis through use of logistic regression modelling. Logistic regression modelling deals with the odds of occurrence of a binary dependent variable based on exposure to a predictor variable. Whilst the relationship between outcome and predictor variables do not need to be linear, the relationship between predictor variables and the 'log odds' of the outcome should be broadly linear.

Two-sided p values set at <0.05 were used in this thesis to determine statistical significance. All analyses were conducted in 'R' version 4.4.3 (http://www.r-project.org) by the author of this thesis, with support from an experienced statistician.

3.7 Discussion

The study presented in this thesis is a prospective, observational, multi-site imaging and biomarker cohort study of ICU survivors of sepsis with the aim of characterising cardiovascular function and functional impairments following admission with sepsis. The approach is novel in this population, allowing

exploration of potential mechanisms that mediate adverse cardiovascular events associated with sepsis admission. The study aimed to provide objective measurements of cardiac function, myocardial inflammation, oedema and scar and explore associations with cardiac and inflammatory biomarkers in addition to patient reported outcome measures.

Critical illness such as sepsis are associated with chronic immune activation and immunometabolic changes similar to those seen in chronic cardiovascular disease.[107] These inflammatory and metabolic changes may result in atherosclerosis or cardiac remodelling that may ultimately predispose to chronic cardiovascular disease such as hypertension, ischaemic heart disease or heart failure. ICU survivors represent a huge population of patients at potential risk of chronic cardiovascular disease. The work in this thesis aimed to prospectively collate evidence to support or refute proposed clinical mechanisms and identify a group at patients who may be responsive to established therapeutics.

The study aimed to recruit a deliberately heterogenous cohort of patients in terms of comorbidity, admission diagnosis and hospital trajectory. In doing so, it was designed to minimise selection bias and ensure the findings are as generalisable as possible. As such, the screening, recruitment and follow-up data is imperative to evaluation of the protocol described in this thesis. The study provides key data regarding attrition rates, sample size and feasibility of outpatient investigations in this population. Incorporating a CMR imaging study into a wider cohort of patients undergoing biomarker analysis was done in part to minimise the impact of attrition from the imaging arm of the study.

There are limitations to the study. Whilst the methodology excludes patients with established coronary artery disease or heart failure, it is recognised there may be patients who may have had unrecognised cardiovascular disease at the point of recruitment, potentially confounding results. The methodology represents a pragmatic approach to recruiting this patient cohort, balancing exclusion of confounders against exposure to the burden of additional coronary imaging or invasive angiography during what is often a prolonged and complicated stay. Exclusion of patients unable to give consent may have resulted in selection bias, for example through exclusion of patients due to delirium which has not yet resolved. Inclusion of these patients via other means such as

proxy consent would have presented considerable logistical and ethical challenges on follow-up and as such, these patients were excluded from the study.

The results described going forward give fundamental mechanistic insights into adverse cardiovascular outcomes following admission to ICU with sepsis. They may provide initial understanding in to the role cardiovascular dysfunction may play in post-intensive care functional impairment. Furthermore, they provide key operational and pilot data for larger studies investigating mechanisms of post-intensive care cardiac dysfunction and how it may be implicated in functional impairment in the recovery period.

Chapter 4 Generic results

4.1 Introduction

The following chapter presents patient demographics, illness characteristics and data pertaining to hospital stay for participants in the study. It will describe the cohort at the point of recruitment to the study (approximating to discharge from ICU), and at 6-10 weeks post-hospital discharge before considering differences between those who attended follow-up and those who did not. Subsequently, it will present a brief comparison of the cohort relative to other large observational studies describing characteristics of patients admitted to hospital with sepsis in similar healthcare settings. Finally, it will consider underlying reasons for changes in the cohort from recruitment to follow-up 6-10 weeks post hospital discharge.

4.2 Recruitment and follow-up

Recruitment took place between August 2022 and August 2024. In total 192 patients were screened with 89 participants eligible to participate and 69 ultimately recruited to the wider biomarker study within which the CMR imaging study was embedded (Figure 4-1).

Due to initial study eligibility criteria, 4 patients were excluded from participation in any limb of the wider study cohort on account of known coronary artery disease, recent MI or contraindications to CMR. Subsequent changes to eligibility criteria (outlined in Chapter 3.5.2) allowed these participants with prior cardiac disease to be recruited to a wider study cohort focusing on chronic pain and inflammation. These participants with prior heart failure or ischaemic heart disease did not undergo cardiac imaging. The group of participants with prior heart failure, ischaemic heart disease or CMR contraindications is referred to as the ‘biomarker only’ cohort is not dealt with in subsequent chapters in this thesis.

Of the 69 patients recruited, 19 had prior cardiac disease or contraindications to cardiac magnetic resonance (CMR) imaging and as such were recruited to the biomarker only limb of the study.

50 patients were recruited for CMR follow-up. Of these patients, 2 patients died prior to the follow-up visit and 2 became ineligible during the follow-up period (one patient diagnosed with malignancy requiring urgent systemic anti-cancer therapy, one patient was still in hospital following closure of the study). 12 patients withdrew from the study of their own accord. Consequently, there were 34 patients in total who underwent CMR follow-up, representing a study retention rate of 68%. All patients who attended CMR scanning tolerated the scan without issue, with the exception of 1 participant who experienced some pain adjacent to an old scar site. Despite appropriate MRI safety checks, it was felt in the participant's best interests to stop scanning after only basic CMR sequences were acquired.

As outlined previously, details in the following chapters will pertain to participants that were recruited to the CMR limb of the study (n=50). Participants who were able to undergo CMR follow up will be termed 'CMR' participants. Those who did not undergo follow-up due to withdrawal from the study for any reason will be termed the 'No CMR' participants.

4.3 Participant demographics

Table 4-1 displays overall characteristics of the recruited study cohort. Of the 50 patients recruited to the CMR limb of the study, the median age was 58 (50, 68) and 21/50 (42%) were female. 10/50 (20%) of participants had a clinical frailty scale (CFS) ≥5 prior to admission, and the median Charlson comorbidity index (CCI) was 2 (1, 3). 50% of participants had a postcode that corresponded to an area of the lowest quintile of the Scottish Multiple Index of Deprivation (SIMD). 3/50 (6%) participants were of Asian ethnicity, with the remaining participants 47/50 (94%) of white ethnicity. In terms of cardiovascular risk factors, 16/50 (32%) of participants had hypertension and 8/50 (16%) had diabetes mellitus. 11/50 (22%) of participants were active smokers.

In terms of factors related to sepsis admission and severity of disease, the median SOFA and APACHE II scores on admission to ICU were 5 (2, 8) and 17 (11, 21) respectively. In terms of sepsis source, 17/50 (34%) had lower respiratory tract infection, 12/50 (24%) hepatobiliary, 9/50 (18%) soft tissue and 8/50(16%),

urinary tract (16%), 2/50 (4%) bone/joint and 1/50 (2%) had central nervous system (CNS) sources of sepsis.

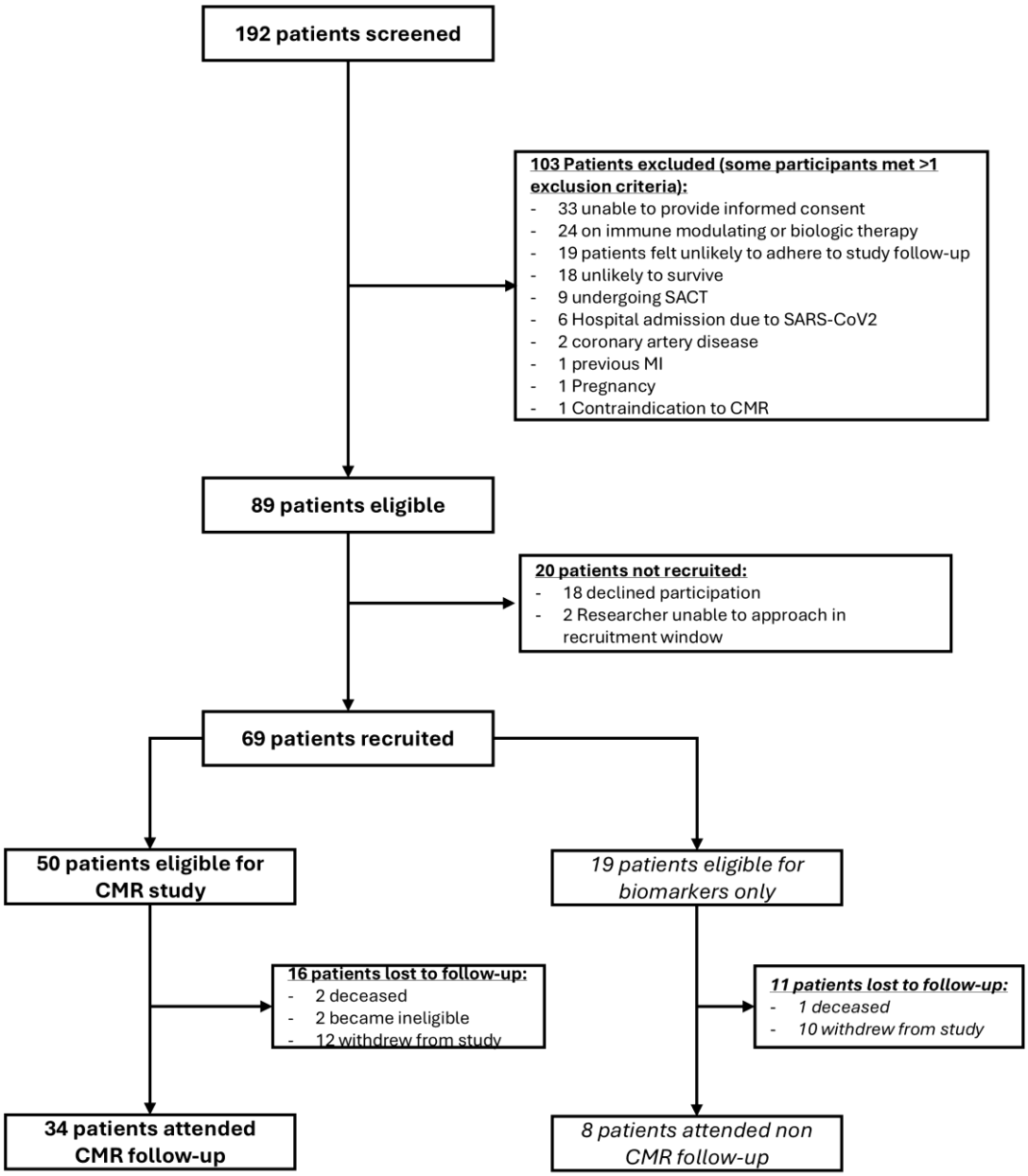

Figure 4-1 Participant flowchart

69 patients were recruited to the wider study within which the CMR study is embedded. Of these, 50 patients were eligible for CMR imaging and 34 patients went on to have CMR follow-up.

Regarding organ support, 20/50 (40%) participants required invasive mechanical ventilation, 36/50 (72%) required cardiovascular support and 10/50 (20%) underwent renal replacement therapy. 8/50 (16%) participants were identified as having left ventricular systolic dysfunction during their admission, and 2/50

(4%) had right ventricular dysfunction. Overall peak hs-TnT in ICU across the cohort had a median value of 56pg/mL (4, 281pg/mL).

The median length-of-stay (LOS) in ICU was 6 (2, 14) days and the median hospital LOS was 16 (8, 29) days.

Median NT-proBNP at time of recruitment (approximating to time of ICU discharge) was 1446 (306, 4115) pg/mL and hs-TnT was 19 (12, 57) pg/mL.

Table 4-1 Overall characteristics of patients recruited for CMR follow-up

Patient Characteristics	**N = 50[1]**
Age	58 (50, 68)
Sex (Female)	21 (42%)
Clinical Frailty Scale	3 (2, 3)
Clinical Frailty Scale >/= 5	10 (20%)
SIMD Quintile	
1	25 (50%)
2	9 (18%)
3	5 (10%)
4	5 (10%)
5	6 (12%)
Ethnicity	
Asian	3 (6%)
White	47 (94%)
BMI	29 (25, 33)
Charlson Comorbidity Index	2 (1, 3)
Hypertension	16 (32%)
Diabetes	8 (16%)
CKD	1 (2.3%)
Previous Stroke	0 (NA%)
Alcohol Excess	5 (10%)
Previous Arrhythmia	3 (6%)
COPD	2 (4%)
Smoking History	11 (22%)

Illness Characteristics	
APACHE II Score	17 (11, 21)
SOFA Score	5 (2, 8)
Source of Sepsis	
Bone/Joint	2 (4.0%)
Central Nervous System	1 (2.0%)
Intrabdominal/Hepatobiliary	12 (24%)
Lower Respiratory Tract	17 (35%)
Skin/Soft Tissue	9 (18%)
Urinary	8 (16%)
Other	1 (2%)
Required Invasive Mechanical Ventilation	20 (40%)
Duration of Mechanical Ventilation (days)	8 (5, 15)
Required Non-Invasive Ventilation / Nasal High-Flow Oxygen	19 (38%)
Duration of Non-Invasive Ventilation (days)	1.25 (0.5, 4)
Required Cardiovascular Support	36 (72%)
Duration of Cardiovascular Support (days)	1 (0, 4)
Required renal replacement therapy	10 (20%)
Duration of renal replacement therapy (hrs)	9 (3, 20)
Cardiovascular dysfunction or injury during illness	
LVSD during admission	8 (16%)
RVD during admission	2 (4.1%)
ECG Changes in ICU	13 (27%)
Maximum hs-TnT	56 (4, 281)
Maximum CRP	339 (250, 446)
Peak Lactate	1.75 (1.00, 3.10)
ICU discharge characteristics	
ICU Length of Stay (days)	6 (2, 14)
Hospital Length of Stay (days)	16 (8, 29)
Discharge NT-proBNP (pg/mL)	1446 (306, 4115)
Discharge hs-TnT (pg/mL)	19 (12, 57)
Discharge hs-CRP (mg/L)	79 (18, 148)

[1]Median (Q1, Q3); n (%). Abbreviations: APACHE II= Acute Physiology and Chronic Health Evaluation II, BMI=Body Mass Index, CKD=Chronic Kidney Disease, CRP=C reactive protein, COPD=Chronic Obstructive Pulmonary Disease, ECG=Electrocardiogram, hs-TnT= high sensitivity troponin T, ICU=Intensive care unit, LVSD=Left ventricular systolic dysfunction, NHFO=Nasal high flow oxygen NIV=Non-invasive ventilation, NT-proBNP=N type pro-B-type natriuretic peptide, RVD=Right ventricular dysfunction, SOFA=Sequential Organ Failure Assessment

4.4 Demographics of participants undergoing CMR follow-up

Table 4-2 displays comparisons between patient demographics and illness characteristics of No CMR participants in comparison to CMR participants. Median time to follow-up CMR visit from hospital discharge was 51 days (47, 60).

Comparing No CMR versus CMR participants, there were statistically significant differences. Median age was 67 vs 56, p = 0.036. There were significant differences in the proportion of participants who required non-invasive ventilation (NIV) or nasal high-flow oxygen (NHFO). 2/16(12.5%) No CMR participants required NIV/NHFO whilst in ICU vs 17/34 (50%) CMR participants (p = 0.011). However, there was also a significant difference in duration of NIV/NHFO with median durations of 11.2 vs 1.3 days (p=0.028) in the respective groups. Although not statistically significant, No CMR participants had longer durations of mechanical ventilation (10 vs 8 days, p=0.792), cardiovascular support (2 vs 1 day(s), p=0.550) and renal replacement therapy (16 vs 9 days, p=0.889).

In the No CMR participants, 5/16 (32%) had a frailty score of CFS ≥5 in comparison to 5/34 (15%) CMR particpants, although this was not statistically significant (p = 0.256). There was no difference in comorbidity as measured by Charlson comorbidity index, with each cohort demonstrating a median of 2 (p = 0.229). There were no significant differences demonstrated in proportion of cardiovascular comorbidities such as hypertension (7/16 (44%) vs 9/34 (25%), p = 0.222), diabetes (2/16 (13%) vs 6/34 (18%), p>0.999) and chronic kidney disease (CKD) (0/16 (0%) vs 1/34 (3.4%), p>0.999). There was no significant difference in the prevalence of key lifestyle factors such as smoking (4/16 (27%) vs 7/34 (21%), p=0.716) or excess alcohol consumption (3/16 (19%) vs 2/34 (6.1%), p=0.307).

In terms of illness severity, there was no difference in APACHE II scores (17 (11, 20) vs 17 (12, 23), p = 0.6) or SOFA scores on admission (5 (2, 8) vs 4 (3, 8), p = 0.9) when comparing No CMR versus CMR participants.

Table 4-2 Characteristics of patients who attended CMR follow-up in comparison to those who did not attend

Patient characteristics	No CMR follow-up N = 16[1]	CMR follow-up N = 34[1]	p-value[2]
Age	67 (54, 74)	56 (44, 62)	**0.036**
Sex (Female)	5 (31%)	16 (47%)	0.291
Clinical Frailty Scale	3 (2, 5)	3 (2, 3)	0.197
Clinical Frailty Scale ≥ 5	5 (31%)	5 (15%)	0.256
Charlson Comorbidity Index	2 (1, 3)	2 (0, 3)	0.229
SIMD Quintile	1.5 (1, 4.5)	1.5 (1, 3)	0.696
Ethnicity			>0.999
Asian	1 (6.3%)	2 (5.9%)	
White	15 (94%)	32 (94%)	
BMI	30 (23, 35)	29 (25, 32)	0.850
Hypertension	7 (44%)	9 (26%)	0.222
Diabetes	2 (13%)	6 (18%)	>0.999
CKD	0 (0%)	1 (3.4%)	>0.999
Previous Stroke	0 (NA%)	0 (NA%)	
Alcohol Excess	3 (19%)	2 (6.1%)	0.307
Previous Arrhythmia	**3 (19%)**	**0 (0%)**	**0.029**
COPD	1 (6%)	1 (3%)	0.542
Smoking History	4 (27%)	7 (21%)	0.716
Illness characteristics			
APACHE II Score	17 (12, 23)	17 (11, 21)	0.747
SOFA Score	4 (3, 8)	5 (2, 8)	0.734
Source of Sepsis			0.362
Bone/Joint	1 (6.3%)	1 (3.0%)	
Central Nervous System	0 (0%)	1 (3.0%)	
Intrabdominal/Hepatobiliary	6 (38%)	6 (18%)	
Lower Respiratory Tract	4 (25%)	13 (39%)	
Other	0 (0%)	1 (1%)	
Skin/Soft Tissue	4 (25%)	5 (15%)	
Urinary	1 (6.3%)	7 (21%)	
Required Invasive Mechanical Ventilation	6 (38%)	14 (41%)	0.804
Duration of Mechanical Ventilation (days)	10 (4, 17)	8 (5, 15)	0.792
Required NIV/NHFO	**2 (12.5%)**	**17 (50%)**	**0.011**
Duration of NIV/NHFO (days)	**11.2 (6.4, 16)**	**1.3 (0.5, 2)**	**0.028**
Required CV Support	12 (75%)	24 (71%)	>0.999
Duration of CV Support (days)	2 (0, 6)	1 (1, 3)	0.550
Renal Replacement Therapy	2 (13%)	8 (24%)	0.498
Duration of Renal Replacement Therapy (days)	16 (1, 30)	9 (3, 20)	0.889

Cardiovascular dysfunction or injury during illness			
LVSD during admission	0 (0%)	8 (24%)	0.087
RVSD during admission	0 (0%)	2 (5.9%)	>0.999
ECG Changes in ICU	6 (40%)	7 (21%)	0.178
Maximum Troponin	33 (4, 76)	67 (4, 479)	0.521
Maximum CRP	345 (284, 472)	326 (200, 442)	0.270
Peak Lactate	1.00 (0.90, 4.25)	1.80 (1.10, 3.00)	0.466
ICU discharge characteristics			
ICU Length of Stay (days)	7 (4, 28)	6 (2, 12)	0.287
Hospital Length of Stay (days)	24 (11, 37)	15 (8, 26)	0.287
Time from discharge to follow-up (days)	NA (NA, NA)	51 (47, 60)	NA
Discharge NT-proBNP (pg/mL)	1926 (371, 4076)	1254 (185, 4115)	0.439
Discharge Troponin (pg/mL)	26 (17, 56)	17 (10, 62)	0.439
Discharge hs-CRP (mg/L)	109 (22, 172)	60 (12, 136)	0.287

[1]Median (Q1, Q3); n (%) [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; NA; Wilcoxon rank sum exact test. APACHE II= Acute Physiology and Chronic Health Evaluation II, BMI=Body Mass Index, CKD=Chronic Kidney Disease, CRP=C reactive protein, COPD=Chronic Obstructive Pulmonary Disease, ECG=Electrocardiogram, hs-TnT= high sensitivity troponin T, ICU=Intensive care unit, LVSD=Left ventricular systolic dysfunction, NHFO=Nasal high flow oxygen NIV=Non-invasive ventilation, NT-proBNP=N type pro-brain natriuretic peptide, RVD=Right ventricular dysfunction, SOFA=Sequential Organ Failure Assessment

CMR participants had a shorter median ICU LOS (6 days (2-12) vs 7 days (4-28), p = 0.3) and hospital LOS (15 days (8, 26) vs 24 (4, 28), p = 0.2), albeit these were not statistically significant.

There were no differences in rates of myocardial injury or dysfunction during ICU admission in CMR participants compared to No CMR participants. However, 8/34 (24%) CMR participants were identified as having LVSD during their ICU admission. In both cohorts, levels of cardiovascular biomarkers on ICU discharge were markedly elevated, above the 99th percentile of the general population reference range, with median NT pro-BNP values of 1926pg/mL (371-4076, p = 0.4) vs 1254pg/mL (185–4115, p = 0.4) in No CMR versus CMR participants. There was also a non-significant difference in hs-CRP (60mg/L (12,136) vs 109mg/L (22, 172), p = 0.3).

4.5 Discussion

To the author's knowledge, this is the first study describing the prospective recruitment of participants to an ICU follow-up study combining cardiac imaging, biomarkers and patient reported functional outcome measures. The CMR imaging arm embedded within a wider biomarker study allowed for maximisation of recruitment to the imaging component of the study, whilst allowing for the collation of key feasibility data such as participant retention, thus informing future work.

4.5.1 Protocol feasibility

Given the novelty of the study design, it was unclear whether it would be possible to recruit and retain patients for a study of this nature, such is the profound impact of ICU admission. ICU survivors are likely to have a high burden of acquired comorbidity as a consequence of their admission[5 240], and prior comorbidity has been associated in multiple observational studies to be correlated with adverse long-term outcomes.[7 151] As such, it was unclear whether participants would be willing to re-attend for further investigations including a lengthy MRI scan, which potentially added to their burden of healthcare interactions and follow-up.

In this study, 68% percent of participants who agreed to take part in the CMR study proceeded with their follow-up scan. This is in keeping with other larger scale prospective studies of ICU survivors. For example, in a study examining one year outcomes of patients, Herridge et al followed up approximately 70% of recruited participants surviving until ICU discharge.[31] In another landmark study examining post-intensive care cognitive impairment, 54% (448/821) of participants who underwent initial evaluation in hospital were able to undergo follow-up cognitive testing.[57] Thus, despite the relatively high attrition rate of 32%, data here are in-keeping with other large scale studies of post-intensive care populations and perhaps reflective of the burdensome acquisition of multimorbidity following critical illness.

Nonetheless, the majority of patients recruited attended for CMR follow-up, with all patients who attended able to comply with a CMR study sufficient enough to acquire, at lease, a basic dataset. This supports the feasibility of the

research protocol and the concept that if participants are willing and able, CMR scanning and similar modalities of diagnostic testing are likely to be well tolerated in this patient cohort.

In terms of the CMR cohort versus no CMR cohort, participants were significantly younger and also had a reduced prevalence of frailty. Although there were reductions in duration of organ support (if required) the prevalence of participants who required mechanical ventilation, cardiovascular support or renal support was reduced in participants who did not undergo follow-up scanning.

4.5.2 Overview of the study population

Table 4-3 highlights key participant demographics and how the CMR study cohort compares to two observational studies of sepsis patients utilising contemporary datasets.

Patient demographics are broadly comparable. The median age in the study was 58, with 42% of participants female and 20% having a clinical frailty score greater than 5. Participants also had a median Charlson Comorbidity Index of 2, again, broadly in keeping with other large scale datasets of UK patients who have been admitted to intensive care with sepsis.[241]

Severity of illness - measured using outcomes such as APACHE II scores – was lso comparable to other large observational datasets. In the study by Prescott et al, nearly 100,000 patients were included that were admitted to intensive care between 2017 and 2019, with an APACHE II score of 14.[241] Similarly, in Shankar-Hari's epidemiological comparison of sepsis 2 and 3 definitions including nearly 200,000 ICU patients, there was a mean APACHE II of 13.7.[64] In comparison, the median APACHE II score in the study in this thesis was 17, marginally higher and corresponding to a predicted mortality rate of approximately 25%.[71]

Table 4-3 Comparison of key patient demographics with two large observational datasets

Characteristic	Shankar-Hari (2017)[64] N = 197,142	Prescott (2024) N = 99,948[241]	Garrity (2025) N = 50
Definition	Sepsis-3	Sepsis-3	Sepsis 3
Age[1]	66	66	58
Sex female (%)	45	43.7	42
% Mild-Moderate Frailty/ Dependency[2]	29.3	-	20
Site of Infection n(%)			
- Cardiovascular	4264 (2.2)	1,742 (1.7)	0 (0.0)
- Respiratory	98,785 (50.0)	61,321 (61.4)	17 (35.0)
- Urinary	12,796 (6.5)	13,426 (13.4)	8 (16.0)
- Gastrointestinal	50799 (25.8)	8970 (9.0)	12 (44.0)
- Neurological	5,815 (3.0)	3409 (3.4)	1 (2.0)
- Musculoskeletal/Soft Tissue	10,499 (5.3)	3,379 (3.5)	11 (22.0)
- Other	14,185 (7.2)	7693 (7.7)	1 (2.0)
APACHE II[1]	18.5	14	17
ICU LOS (days)	3.8	4	6
Hospital LOS (days)	-	14	17

[1]Mean/Median value. Mild/moderate dependency if not explicitly defined in the study corresponds to a clinical frailty score (CFS) ≥ 5. Abbreviations: APACHE=Acute physiology and chronic health evaluation. ICU=Intensive care unit. LOS=Length of stay.

72% of participants required cardiovascular support, 40% required invasive mechanical ventilation and 20% required renal replacement therapy, indicating a high level of acuity. ICU and hospital LOS were 6 and 16 days respectively, again similar to other published studies in similar cohorts. Thus, it would seem the degree of illness severity is comparable to other similar ICU settings.[64 241 242]

In terms of cardiovascular injury during intensive care admission, left ventricular dysfunction was prevalent, in keeping with observational studies examining cardiac function during sepsis in intensive care.[189 236] Furthermore, the majority of participants had NT-proBNP values well above the 99th centile in comparison to values in the general population.[243] There are few data that describe sepsis as an independent cause of markedly raised NT-proBNP, although there have been studies that correlate abnormal NTproBNP values to increased mortality following ICU admission.[151] Biochemical evidence of cardiac injury - manifesting as elevated high sensitivity troponin - was also prevalent in the study cohort,

with values remaining abnormal even around the point of discharge. Raised troponin is known to be associated with mortality and adverse cardiovascular events in critical illness, again supporting the premise that this is a population that are at risk of significant cardiac injury whilst in intensive care and may be at risk of adverse outcomes following discharge from intensive care.[114 181]

In-patient mortality seen in this study from the point of recruitment was only 4% (2/50), much lower than anticipated for corresponding APACHE II (17 (12, 23)) or SOFA (5 (2, 8)). The protocol deliberately had a focus on survivorship, with participants only eligible for recruitment if expected to survive. In addition, participants required capacity to consent to the study procedures and were therefore not delirious at the point of recruitment. This deliberate selection of a cohort of ICU survivors is likely to contribute to the low mortality rate in the presence of similar illness severity scales, despite similar rates of participant retention.

4.5.3 Limitations

The research protocol does have limitations. Rather than set a maximum number of recruits to the CMR study, this was instead set by the wider observational biomarker study within which the CMR study was embedded, and recruitment to the CMR scanning was only planned to stop once 35 participants were scanned. This was for two reasons. Firstly, the CMR study was powered to detect prevalence in LVSD in comparison to prevalence in the general population and secondly, embedding the CMR study within a larger biomarker study ensured that funding allocated for CMR scanning was fully utilised and recruitment continued to this limb of the study could continue, even if prior recruited participants withdrew from follow-up. However, it is possible that the cohort of patients (34/50), who ultimately presented for CMR scanning are reflective of younger, less frail participants who had a reduced hospital LOS. Furthermore, the deliberate focus on survivors and those that were not delirious may also potentially bias the cohort towards patients who are less frail and comorbid.

Lastly, although the prior burden of cardiovascular disease was assessed at screening, it is impossible to fully assess for cardiovascular exclusions that may have been present prior to ICU admission, such as asymptomatic cardiac

dysfunction or coronary artery disease. To include patients that had not had prior cardiac or coronary artery imaging would have been impractical within the confines of resources available and meant the cohort was not reflective of the typical ICU population.

4.6 Conclusion

Utilising the protocol described in Chapter 3, this study successfully recruited a representative population of ICU survivors with sepsis, with similar patient demographics and prevalence of cardiac injury to published data. This approach provides key feasibility data for future imaging studies and the findings contained in the forthcoming chapters are likely to be applicable to future work and other similar ICU cohorts.

Chapter 5 Cardiovascular Magnetic Resonance imaging in intensive care unit survivors of sepsis

5.1 Introduction

This chapter describes the cardiovascular magnetic resonance (CMR) imaging findings of 34 patients admitted to intensive care with sepsis who were recruited to the study described in Chapters 3 and 4 and subsequently had follow-up cardiac imaging. It will describe key principles in CMR imaging, how it can be utilised to assess left and right ventricular function and how novel parametric mapping techniques can be used to assess for the presence of myocardial inflammation, oedema and scar. It describes the methodology utilised to obtain the CMR dataset and subsequently characterise the cardiac function of the study population, the prevalence of left and right ventricular (LV and RV) dysfunction and how the CMR findings differ if participants belong to these separate groups. Finally, it will discuss the implications of these findings in the wider context of the study and implications for future research and clinical practice before considering the limitations of the work.

5.2 Cardiovascular magnetic resonance imaging

CMR is a gold-standard non-invasive method of assessing cardiovascular mass and function.[244] Typically performed by acquiring electrocardiogram-gated (ECG-gated), clinicians can then manually contour the outline of cardiac structures to make detailed assessments, with higher reproducibility than 2D echocardiography. This has particular relevance for research, where the higher interstudy reliability can be utilised to reduce sample sizes and achieve greater power in cardiac imaging studies.[208]

5.2.1 A brief overview of CMR physics

A Magnetic Resonance Imaging (MRI) system comprises of three main electromagnetic coils, which each generate their own magnetic fields (Figure 5-1). These three types of magnetic field can be applied to a subject in combination to produce magnetic resonance (MR) signals and encode images.[245]

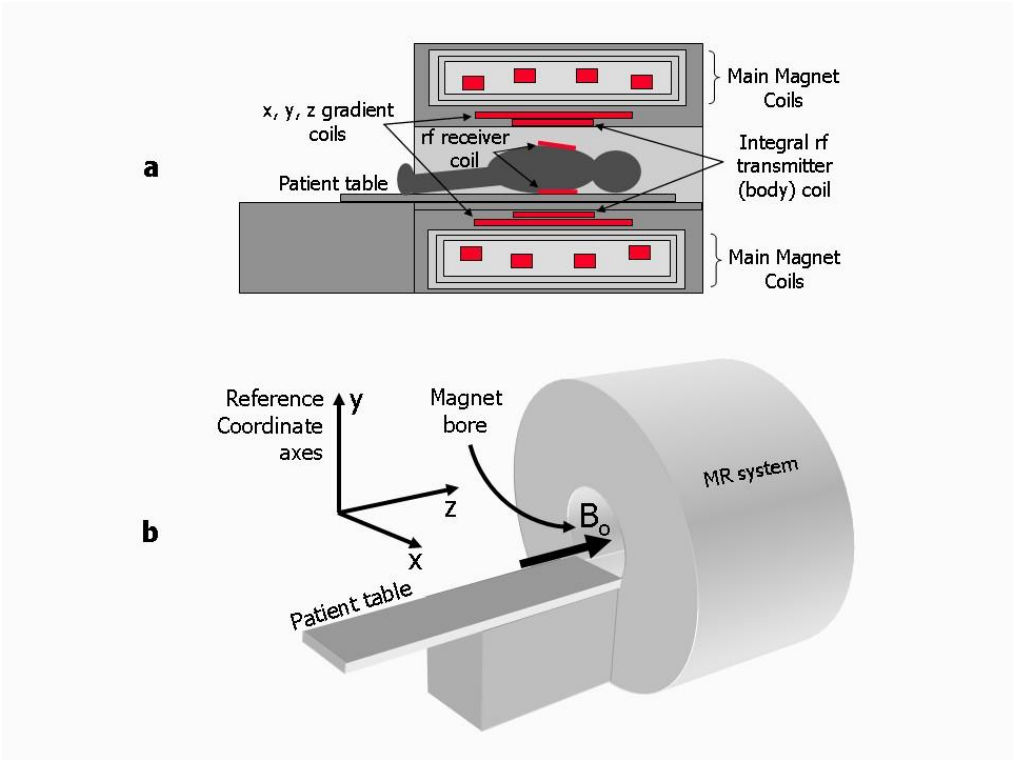

Figure 5-1 Magnetic Resonance (MR) system components

a) Relative locations of the main magnet coils; x, y and z gradient coils; and the integral radio frequency (rf) transmitter and receiver coils. b) Typical arrangement for a cylindrical bore MR system showing the magnet core and reference co-ordinate axes with the static B_0 field direction along the horizontal axis.

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The 'strength' of the MR system is defined by the operating strength of the continuous main magnet, denoted by the symbol B_0 and measured in units of Tesla (T), where 1 Tesla is equal to approximately 20,000 times the power of the earth's own magnetic field. [245]

A gradient electromagnetic field is generated by three gradient coils mounted inside the main magnet, which can be switched on and off rapidly. They are aligned with B_0, but with a strength that differs according to their position in the x, y or z axes, according to which gradient coil is used. Thus, the strength of the B_0 magnetic field increases (or decreases) along the direction of the applied gradient field.[245]

MR imaging utilizes the innate properties of protons and their behaviour in magnetic fields, in particular, the hydrogen ions found in abundance in biological tissues.[246] Each proton has its own 'spin' and magnetic moment,

essentially a magnetic field which lies along a spatial vector. These are normally randomly orientated in biology such that the net magnetic moment is zero. However, in the presence of a strong external magnetic field, such as that in the MRI scanner, the protons 'spin-up' or 'spin-down' to align in the direction of B_0, whilst rotating around the central axis of B_0 in a process known as precession (Figure 5-2).[246] This causes the particles to be arranged with an overall net longitudinal magnetisation.

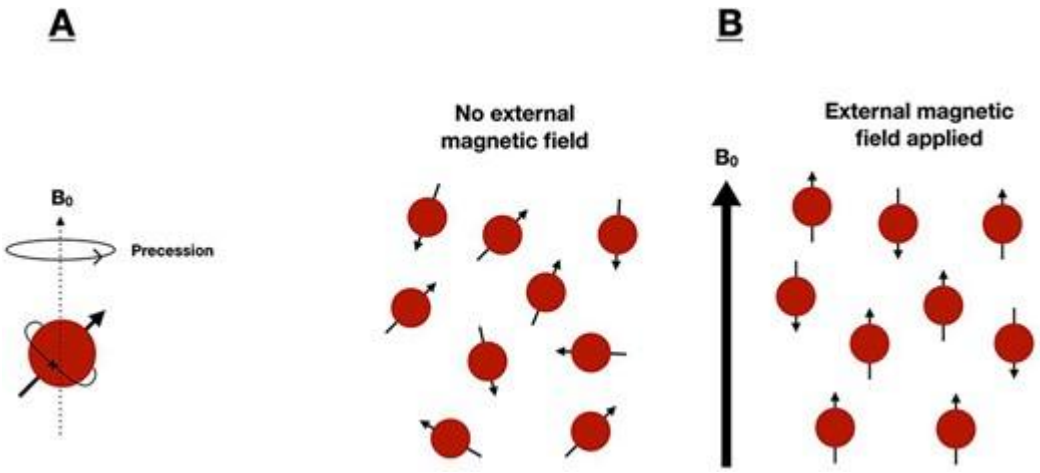

Figure 5-2 Response of protons to application of a radiofrequency pulse

A) An external magnetic field creates a torque on the proton such that it rotates around the central axis. B) With no magnetic field, the protons are randomly orientated. When an external magnetic field is applied, protons either spin-up or spin-down, resulting in a small net longitudinal magnetisation. From Azhar et al (2023). Reproduced with permission from Oxford University Press.[246]

Whilst this magnetisation cannot be directly measured in the same longitudinal plane as B_0, the application of an additional magnetic pulse by the radiofrequency coil (rf pulse) at 90° in the transverse plane, can cause some particles to spin-down resulting in an overall reduction in net magnetisation. Furthermore, the magnetic field generated by the rf pulse creates additional torque on adjacent protons such that they precess in-phase in the transverse plane, resulting in a net transverse magnetisation in the x and y planes (Figure 5-3).

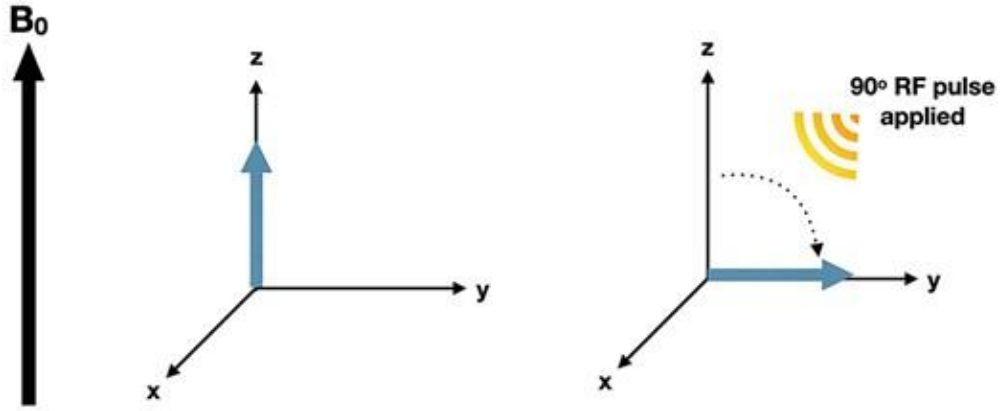

Figure 5-3 Overall net magnetisation following application of a radiofrequency pulse

When an external magnetic field is applied, the net magnetisation is aligned parallel to B0. After application of a radiofrequency (rf) pulse, the net magnetisation is displaced in the transverse plane. From Azhar et al (2023). Reproduced with permission from Oxford University Press.[246]

When the rf pulse is subsequently switched off, the protons 'relax' over time and revert to their default state. This causes the net longitudinal value to regrow and return to its original value (T1 relaxation), as they switch back to their net spin-up state and realign with B_0. This also causes the net transverse magnetisation to decay as the protons de-phase randomly and can be measured (T2 relaxation) (Figure 5-4).

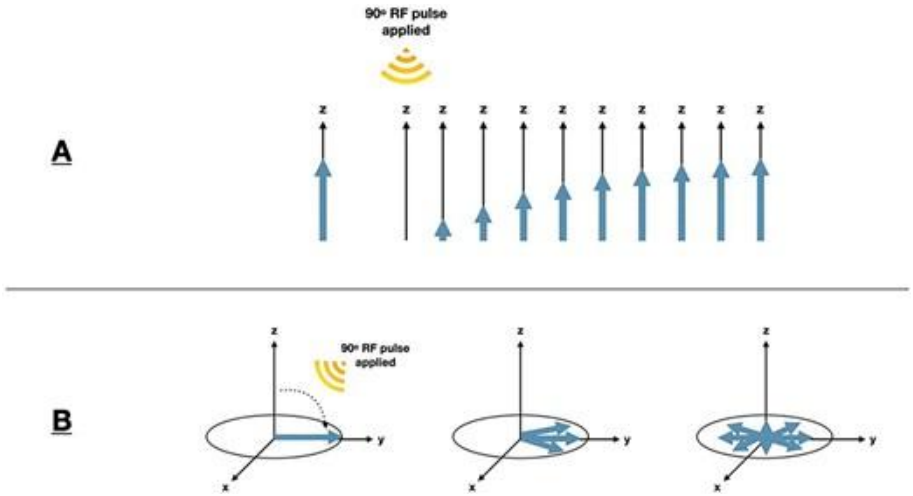

Figure 5-4 Schematic diagram of T1 and T2 relaxation

A) T1 relaxation. After a radiofrequency pulse is applied, longitudinal magnetisation becomes 0. When the rf pulse is turned off, the longitudinal magnetisation grows back to its original value. B) T2 relaxation. After a radiofrequency pulse is applied, net magnetisation is displaced into the transverse plane with proton spins precessing in phase with each other. When the rf pulse is turned off, protons de-phase randomly and the net transverse magnetisation decreases. From Azhar et al (2023). Reproduced with permission from Oxford University Press.[246]

5.2.2 T1, T2 Relaxation and late gadolinium enhancement

5.2.2.1 Native T1

T1 relaxation (Figure 5-5) is an exponential process with a time constant and refers to the time taken for the net magnetisation (M_z) in the B_0 plane to recover to 63% of its value at equilibrium. The native T1 value has a relationship to the water content of the tissue from which the relaxation rate is measured. Normally, water-based tissues with high macromolecular content (e.g. cardiac myocytes) have shorter T1 values, however in the presence of increased water content (e.g. due to an inflammatory process) this time will be prolonged.[245] This means that T1 can be utilised for assessment of both cardiac disease (e.g. myocarditis, coronary syndromes, diffuse fibrosis) and cardiac manifestations of systemic disease (e.g. siderosis, cardiac amyloid etc).[247]

5.2.2.2 Post-contrast T1 mapping and extra cellular volume

After administration of a gadolinium-based contrast agent, myocardium containing fibrosis appears as a high signal intensity area, allowing the identification of scar tissue through late-gadolinium enhancement (LGE). However, if the fibrosis is diffuse and not regional, then this cannot be detected by LGE.[247]

Post-contrast T1 time in normal myocardium is shorter than native T1 time, due to the presence of residual gadolinium within the interstitium. This effect is further amplified in patients with diffuse fibrosis or with regional scarring, by the increased volume of retained gadolinium.

The concentration of contrast in the myocardium relative to the blood is used to calculate extra-cellular volume (ECV), essentially reflective of the expansion of extra-cellular space that occurs in fibrosis and tissue remodelling.[247] The determination of ECV involves creating pre and post-contrast T1 maps. The ECV is then calculated based on the values of these maps, using the ratio of the differences between native T1 and post-contrast T1 values. Myocardial ECV is derived by correcting for the haematocrit level using the following equation:

$$ECV = (1 - Haematocrit) \times \frac{\Delta R1(myocardium)}{\Delta R1(LV\ blood\ pool)}$$

$$(R1 = 1/T1,\ \ \Delta R1 = \ postcontrast\ R1 - precontrast\ R1)$$

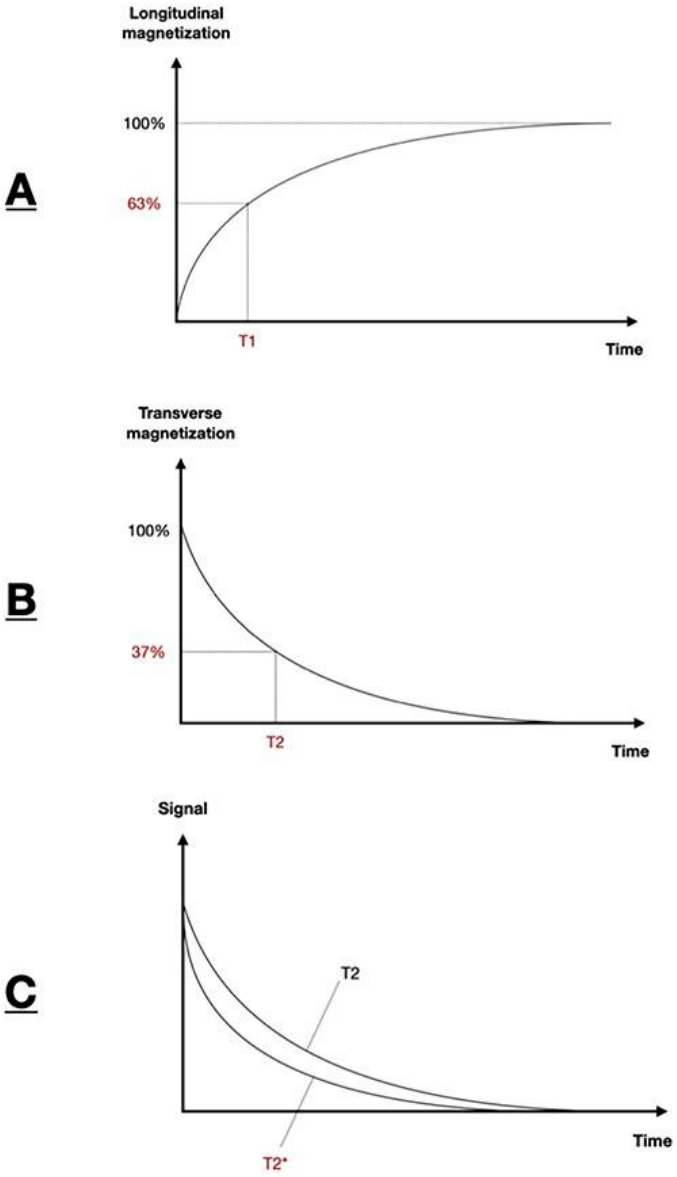

Figure 5-5 Measurement of T1 and T2 relaxation time

A) **T1 Relaxation B) T2 relaxation C) T2* relaxation. (A) T1 relaxation is a measure of the overall longitudinal magnetization of particles in the magnetic field over time relative to B_0, following application of an RF pulse. There is initially complete loss of overall longitudinal magnetisation, which gradually recovers over time, with T1 relaxation reflecting the time to recover 63% of the overall value of longitudinal magnetisation. In contrast, T2 recovery (B) reflects the overall decay of transverse magnetisation following application of an RF pulse, and is determined following 37% loss of the maximum T2 value. T2* reflects the T2 value if magnetization occurred within a perfectly homogenous field and accounts for presence of other magnetic inhomogeneities within the field. From Azhar et al (2023). Reproduced with permission from Oxford University Press.**[246]

ECV gives a physiologically intuitive unit of measuring tissue remodelling, and with the exception of amyloid disease, increased values are often due to excessive collagen deposition and thus a marker of myocardial fibrosis.[247]

5.2.2.3 T2 mapping and T2* mapping

T2 relaxation time (Figure 5-5) refers to the amount of time it takes for the overall decay of transverse magnetisation to 37% of its maximum value. Free water molecules that are spread far apart tend to have longer T2 relaxation times due to the reduced spin-spin interaction, however tissues containing water bound to large macromolecules (e.g. muscle) will have greater spin-spin interaction and this will cause reduction in T2 decay. Similar to T1, inflammatory processes can cause prolongation of T2 values due to increased tissue water content.[245]

T2* relaxation described the decay of transverse magnetisation under an ideal, perfectly homogenous B0 field.[246] In practice, the magnetic field is often less homogenous due to presence of other materials within it, causing more rapid dephasing. T2* describes the combined effects of tissue-specific dephasing and additional dephasing from B_0 inhomogeneities, and is always shorter than T2 relaxation.[246]

It is important to understand that T1 and T2/T2* relaxation are fundamentally independent processes and are specific, dependent on the given B_0 in the scanner. The complexities of how these signals are acquired and subsequently spatially mapped to form the high-quality images that can be used to assess cardiac tissue and its function are beyond the scope of this thesis.

However, these MRI techniques fundamentally bring the key advantage of being able to differentiate between types of soft tissue in a manner that can be considered superior to other forms of cardiac imaging.[208] In combination with standard views of the left and right structures of the heart, these signals can be used to create a highly detailed animated series of ‘cine’ images across different phases in the cardiac cycle to evaluate its function.[248]

5.2.3 Assessment of left ventricular function using CMR

The society of cardiovascular magnetic resonance (SCMR) recommend that left ventricular (LV) function is assessed using 6 key components[249]:

- LV end-diastolic volume (LVEDV) - The total amount of blood (ml) in the LV after maximal filling,
- LV end-systolic volume (LVESV) - The total amount of blood in the LV (ml) after maximal emptying,
- LV stroke volume (LVSV) – the amount of blood (ml) pumped per cardiac cycle (LVEDV – LVESV),
- LV ejection Fraction (LVEF) – the fraction or percentage (%) of blood that leaves the heart during systole (LVSV/LVEDV)
- LV cardiac output (LVCO) – defined as LVSV multiplied by heart rate, and
- LV mass (LV mass) – the LV myocardial volume multiplied by 1.05 in grams.

The SCMR recommends indexing volumes to body surface area (BSA) for the above measurements, with the exception of ejection fraction.[249] In addition, they recommend commenting on presence of regional wall motion abnormalities using a 17 segment model as described by the American Heart Association; presence of aneurysm and; optional measurement of strain.[249 250]

Common images used for assessment of LV function include 2 chamber, 3 chamber and 4 chamber views in addition to a short axis 'stack' from which LV volumes can be assessed and calculated (Figure 5-6).[251] For LV chamber quantification, epicardial and endocardial borders can be identified across the stack in the systolic and diastolic phases of the cardiac cycle. The LVEDV should be calculated from the image with the largest LV blood volume, with closure of the mitral valve and opening of the aortic valve used to assist in orientation. The full stack should be evaluated and one phase should be identified for all of the short axis locations.[251]

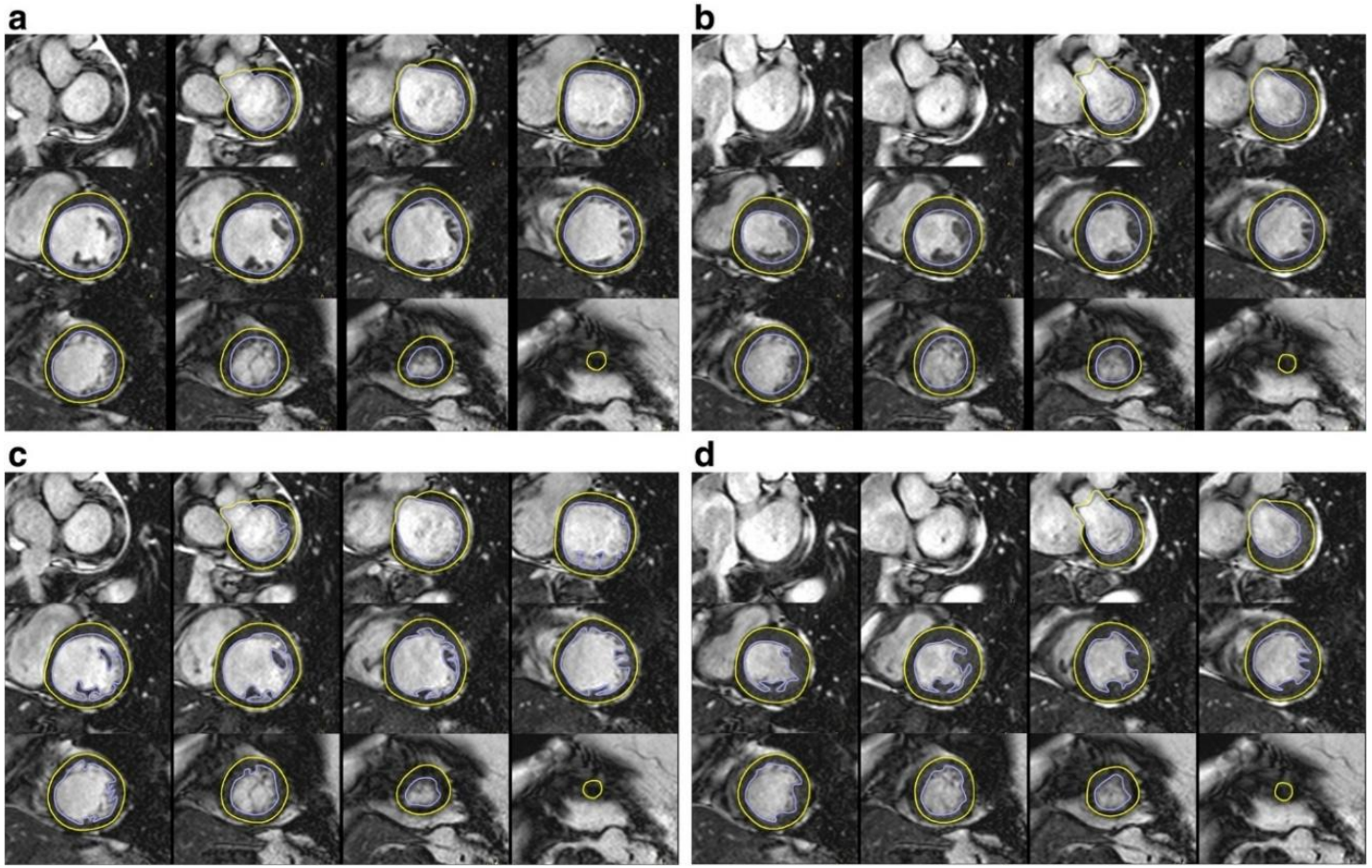

Figure 5-6 Left ventricular chamber quantification

The epicardial borders are highlighted in yellow and endocardial borders highlighted in blue with the diastolic phase included (left) and systolic phase (right). a + b illustrate the approach with inclusion of papillary muscles and c + d illustrate the approach with exclusion of the papillary muscles. From Schulz-Menger et al. Reproduced from Elsevier under CC-BY licence.[251]

Similarly the end systolic image for calculation of LVESV should be chosen as the image with the smallest blood volume, again, with all stacked images from the same phase included in the assessment. Papillary muscles should ideally be included for assessment of LV mass, but due to ongoing discussion around exact delineation of papillary muscles, they are often not included.[251] Approach should be consistent throughout all analyses.

LV Mass is calculated by the difference between the total epicardial volume minus the difference in endocardial volume, which is then multiplied by the specific density of myocardium (1.05g/ml).

5.2.4 Assessment of right ventricular function using CMR

Similarly to left ventricular function, the SCMR recommend 6 measurements to describe right ventricular function. Whilst these are currently considered 'optional', they are as follows[249]:

- RV end-diastolic volume (RVEDV) – the total volume of blood (ml) in the right ventricle after maximal filling.

- RV end-systolic volume (RVESV) – the remaining volume of blood (ml) after maximal emptying.

- RV stroke volume (RVSV) – the amount of blood pumped per heart beat (i.e. RVEDV-RVESV)

- RV Ejection Fraction (RVEF %) – the fraction or percentage (%) of blood that leaves the RV during systole (RVSV / RVEDV)

- RV Cardiac Output (RVCO) – defined as RVSV multiplied by heart rate

- RV Mass (RVM) – indicated in conditions such as hypertrophic cardiomyopathy or pulmonary hypertension.

Again, it is recommended to index volumes to BSA.[249] For acquisition of contours, images can be acquired from either axial stacks of RV cines, for example to identify the tricuspid valve annular plane; or using short axis stacks,

which may help in delineating the inferior wall (Figure 5.6).[251] In a similar process to assessment of LV function, contours are drawn around endocardial borders in the systolic and diastolic phases of the cardiac cycle, with each stack of images acquired from the same phase.[251] RV volumes are taken as the sum of volumes from individual 2D slices, accounting for any interslice gap and slice thickness. RV trabeculae and papillary muscles are typically included in routine assessment.[251] RV mass is not a routinely recommended measurement, but can be commented on in cases where relevant (e.g. pulmonary hypertension where RV hypertrophy is often present).[251]

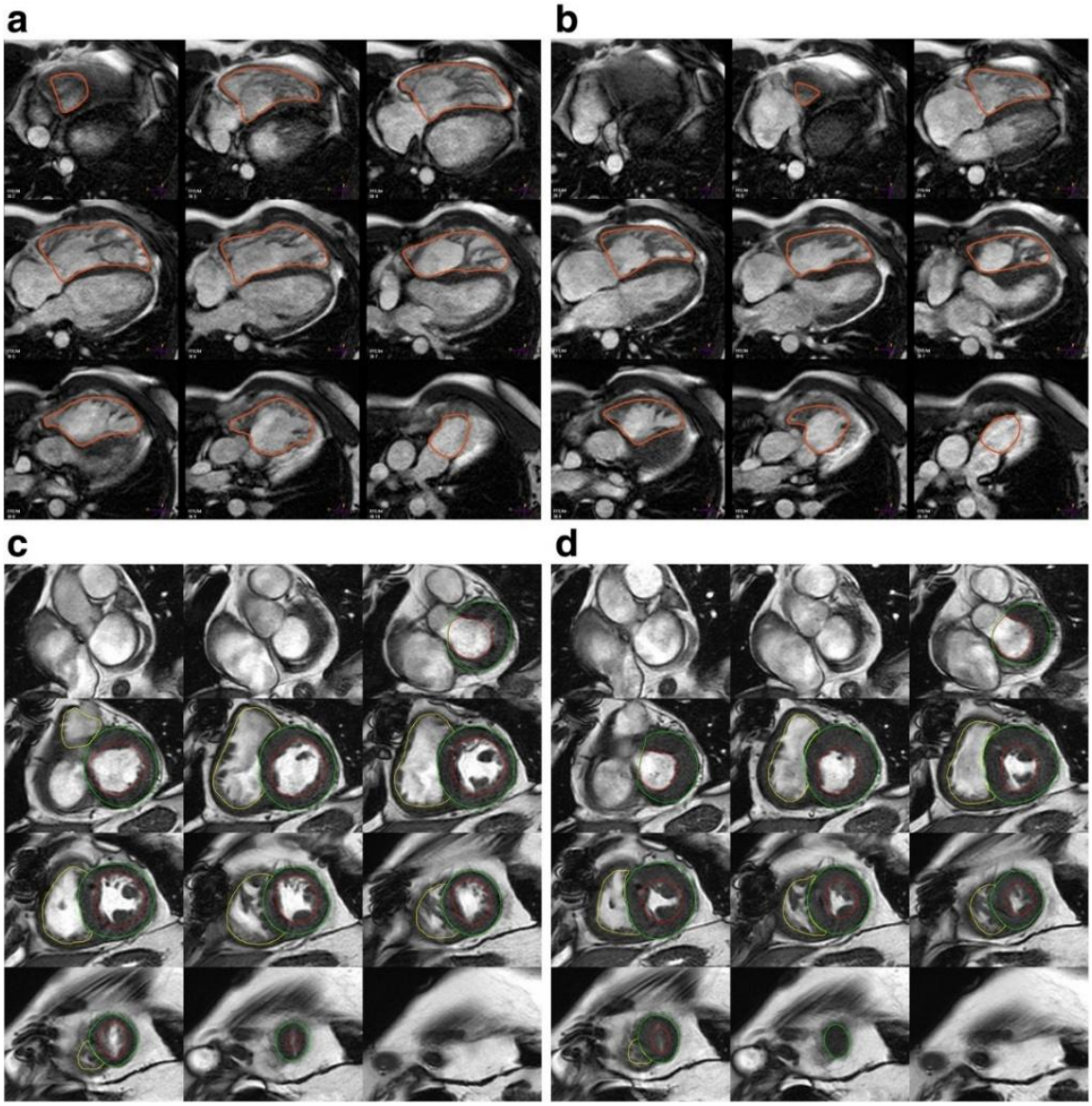

Figure 5-7 Right ventricular chamber quantification

The RV volumes are calculated by delineation of the ventricle in systolic (a + c) and diastolic (b + d) phases of the cardiac cycle. Here, the red contours in a stack of trans-axial slices (a+b) covering the whole RV are shown. Alternatively, short axis stacks (c+d) can be used with the yellow contours highlighting the endocardial borders of the right ventricle. From Schulz-Menger et al. Reproduced from Elsevier under CC-BY licence.[251]

5.2.5 Parametric mapping

In terms of image acquisition, relaxation times are calculated on a pixel-by-pixel basis by fitting the image intensity of the MR series against the parameter that is used to vary the relaxation time weight.[252] Images need to account for variation in other factors in imaged tissue (such as different relaxation times or diffusion) and there needs to be negligible physical displacement of the structures assessed between images within the series. This makes imaging myocardium challenging given the contractile nature of the tissue and the presence of normal diaphragmatic contraction.[252] As such, MR images are often acquired using techniques such as ECG-gating, where image slices are acquired according to phases in the cardiac cycle, and breath holding techniques to minimise motion artefact.[252]

The Modified Look-Locker Inversion recovery (MOLLI) sequence is widely used for acquisition of T1 maps. A detailed explanation of the underlying technical detail of this technique is beyond the scope of this thesis. Briefly, single shot images are acquired intermittently during 3-5 heartbeats following the inversion pulse with images spaced by the R-R interval along the T1 recovery curve.[253] MOLLI is felt to offer excellent T1 diagnostic precision for pre and post contrast maps and is used widely in clinical practice.[252 254]

The SCMR publish recommendations for analysis of parametric mapping. [251] For T1 analysis, the image series should be visually analysed and verified for image quality. For global assessment and diffuse disease, a single region of interest (ROI) should be drawn on the septum on the mid cavity short axis to reduce image artefact from adjacent tissues. For focal disease, further ROIs can be drawn and assessed on areas of abnormal appearance on visual inspection.[251]

ECV estimation requires T1 mapping acquisition before contrast (native T1) and subsequently more than 10 minutes after contrast to ensure steady state conditions. To calculate ECV, a ROI should be drawn in the centre of the blood pool in the native and the post-contrast T1 map (excluding papillary muscles and trabeculae).[251] Ideally, haematocrit on the same day should be available, however there are other means of calculating values, such as synthetic ECV.[251 255]

In terms of T2 mapping, the SCMR recommend visual inspection to detect regions with a potential signal intensity increase as a marker of increased free water content and therefor oedema.[251] In terms of quantitative mapping, for global assessment and diffuse disease, a single ROI can be drawn conservatively on the septum on mid-cavity short axis maps to reduce the susceptibility to image artefact from adjacent tissues.[251]

The specific protocol for analysing the images reported in this study is included in sections below.

5.3 Methods

5.3.1 Participant recruitment

Participant recruitment was described in detail in Chapter 3. In short, participants admitted to ICU with sepsis (as defined by Sepsis 3 criteria) were invited to attend a follow-up visit 6-10 weeks post-hospital discharge where CMR scanning was performed. In addition, investigators collected biomarkers of cardiovascular function and inflammation and collected patient reported outcome measures of functional capacity and health related quality of life.

Exclusion criteria included: inability to give informed consent, receipt of immune modulating or systemic anti-cancer therapies, prior known ischaemic heart disease, known heart failure or cardiomyopathy, pregnancy, prisoner status and contraindications to CMR imaging.

5.3.2 CMR protocol

CMR imaging took place in a local imaging research centre of excellence using a research-dedicated 3.0 Tesla MRI scanner (MAGNETOM Prisma, Siemens Healthineers) with a standard phased-array surface coil. The protocol is available in Appendix 7.

5.3.2.1 CMR set-up and patient preparation

Informed consent was obtained from participants at study recruitment and revisited by research and radiography staff on the date of their follow-up visit. Participants must have satisfied local safety criteria for CMR, including recent renal function (eGFR >45ml/min) to ensure safety for gadolinium contrast administration.

Following completion of an MRI safety checklist, an intravenous cannula was inserted and participants were guided into the scanner, positioned and (if required) given reassurance. ECG electrodes were applied in addition to headphones allowing for communication between the radiography team and the participant.

5.3.2.2 CMR acquisition

The MRI protocol included the following images as outlined below and in Table 5-1:

- Standard localisers
- Cine imaging for cardiac dimensions including vertical long axis (VLA), horizontal long axis (HLA) and left-ventricular outflow tract (LVOT) acquisitions.
- T2 mapping (short axis stack (SA) and horizontal long-axis (HLA))
- T1 mapping (3 SA slices and HLA in rest protocol)
- First pass perfusion imaging
- Cine imaging of the LV short axis stack
- Late gadolinium enhancement imaging
- Post-contrast T1 mapping (3 x short axis MOLLI)

Table 5-1 CMR protocol.

	Acquisition method	Guidance
PRE-CONTRAST SCAN	Localisers/ Planning (heart)	X1 Bright blood, 4, 3 & 2 chamber
	T2 mapping (heart)	SA Full stack, HLA
	T1 mapping (heart)	SA Basal, SA Mid-LV, SA Apex, HLA
	Contrast injection	
POST-CONTRAST SCAN	Cardiac Perfusion	3 of 5 SA
	Cine SSFP	SA full stack, 4,3 & 2 chamber
	Late gadolinium enhancement	SA Full stack, 4,3 & 2 chamber
	T1 mapping (heart)	SA Basal, SA Mid-LV SA Apex

Abbreviations: SA= Short Axis, HLA=Horizontal Long Axis, LV= Left Ventricular, SSFP= Steady state free precession

The CMR map included three orthogonal 'white blood' sequences (axial, sagittal and coronal) and a long axis cine image to identify the left ventricular outflow tract (LVOT).

T2 mapping used a T2 weighted SSFP sequence to acquire a short axis LV stack from the mitral valve to the apex. T1 maps were acquired using a MOLLI technique to acquire 3 short axis (basal, mid and apical) perfusion slices and one four chamber series.

Gadolinium based contrast was used at a dose of 0.05mmol/kg at 4 mls/second, followed by 20mls of 0.9% saline flush. Subsequently, images were acquired to assess cardiac perfusion, with acquisition of 3 short axis slices.

Left-ventricular function cines were then obtained, with a short-axis stack aligned to the native T1 maps in addition to 2, 3 and 4 chamber orthogonal sequences.

Imaging for LGE enhancement occurred at least 10-15 minutes after contrast administration. A full stack of short axis images in addition to orthogonal 2, 3 and 4 chamber sequences. Post-contrast T1 images were acquired again using MOLLI techniques to match pre-contrast T1 maps.

5.3.2.3 Patient tolerance

If patients were deemed to be tolerating the scan poorly, due to claustrophobia or other issues, an a-priori accelerated protocol focused on acquisition of post-contrast cine images to assess LV function and LGE to assess for scar. This was in-keeping with locally agreed protocols in the imaging centre and was initiated on discretion of the radiography team conducting the scan.

5.3.2.4 Image storage

Patient images were saved on to the hard-drive of the scanner and subsequently backed-up on the imaging centre's database in an anonymised format with the patient's study number. Aligned with our ethical approval (REC South-West Central Bristol, Ref 22/SW/0082) and local governance protocols within the health board, images were also transferred onto the national Picture Archiving and Communication System (PACS) and matched with the participants own health records should CMR images or reports be required by the patient or responsible healthcare providers in the future.

5.3.3 CMR analysis

Aligned with local safety and governance policy, images were analysed and reported by an accredited cardiovascular radiologist with over 15 years' experience. Ventricular volumes, mass, ejection fraction and motion-corrected T1 and T2 sequences were analysed using dedicated post-processing software (cvi42 software for cardiovascular MRI, version 5.1, Circle Cardiovascular).

A CMR report was generated with key indices of LV and RV function as outlined in SCMR guidance described above in section 5.2.3 and section 5.2.4. Any abnormalities in perfusion or presence of scar on LGE was included in the CMR safety report and acted on by the author of this thesis if necessary.

Further T1, T2 and ECV mapping was conducted by the author. Initial training was conducted by a consultant in cardiovascular imaging with >10 years' experience, with subsequent blinded inter-rater reliability assessment on a subset of 10 patients (described below) to ensure integrity of the parametric mapping dataset. Individual images were reviewed, and ECV maps were created by manual drawing of epicardial and endocardial borders on pre and post contrast T1 maps. Right ventricular insertion points were subsequently used to segment the myocardium according the American Heart Association's 16 segment model.[250] Mapping was later reviewed for errors and artefact once the data analysis was complete.

5.3.4 Outcomes

The primary outcome for the study was prevalence of left ventricular systolic dysfunction (LVSD). As outlined in Chapter 3.5.10, LVSD was considered <51% for women and <47% for men, aligned with a local control population and parameters defined by the European Association of Cardiovascular Imaging (EACVI).[202 203] Participants were also assessed for RV systolic dysfunction (RVSD), which was defined as presence of RVEF <40% in males and <45% in females, again in line with local control populations.[202]

Other CMR outcomes assessed included:

- Indices of LV function: LVEDV (mls), LVESV (mls), LVSV (mls), LVEF (%), CO (mls/min) and LVM (g)

- Indices of RV function: RVEDV (mls), RVESV (mls), RVSV (mls), RVEF (%)

- Parametric assessment of fibrosis, oedema and scar: Native T1 (ms), T2 (ms) and ECV (%) values

All volumetric indices of LV and RV function were indexed to BSA. Indices of left and right ventricular function were compared to published national reference ranges. Reference ranges for parametric mapping were determined by local reference ranges used in prior conducted studies within the author's institution.[138 256]

5.3.5 Statistical analysis

Participant demographics, illness characteristics, biomarkers and CMR outcomes are presented as median (Q1, Q3) or mean (SD) if continuous variables, depending on whether parametric or non-parametrically distributed. Categorical variables are displayed in proportions as n(%). Overall summary values are tabulated, and subsequently categorised by presence of LVSD and RVSD. Values of normally distributed data were assessed using an independent t-test or a one-way analysis of variance (ANOVA) if appropriate. Non-parametrically distributed data between groups were analysed using Wilcoxon-rank sum test or Kruskal-Wallis test as appropriate.

To assess reliability of parametric mapping analysis, these data were assessed with intra-class correlation coefficients for both absolute agreement and consistency with values indicating poor (<0.5), moderate (0.5-0.75), good (0.75-0.9) and excellent (>0.9) reliability .[257] Bland-Altman plots were subsequently generated to further assess bias between raters and potential differences in agreement over the range of values.

Univariate logistic regression analysis was undertaken to investigate association between LVSD at 6-10 weeks post hospital discharge and patient or illness characteristics and biomarkers during admission. On assessment of NT-proBNP and hs-TnT, both variables were significantly affected by marked right skew. As such, both variables were log transformed in order to account for outlier values and ensure improved reliability of logistic or linear regression models. Given the importance of NT-proBNP thresholds in the diagnosis and management of heart failure in the outpatient setting, follow-up values of NT-proBNP were also categorised into thresholds commonly used in clinical practice (NTproBNP <125pg/mL, NTproBNP 125-400pg/mL and NTproBNP >400pg/mL) in-keeping with local and international guidelines.[125 258] These thresholds were included in logistic regression analysis to explore their relationship with reduced LVEF. Logistic regression analyses are displayed as “OR (95%CI 0.025, 0.975), p-value”.

Univariate linear regression analysis was used to investigate the discrete relationship with LVEF (%). Models are displayed as β (95%CI 0.025, 0.975), p-value, and plotted with regression lines in blue with dark grey shading to

indicate their standard deviation. Spearman or Pearson correlation coefficients were calculated as appropriate, depending on distribution of the data.

Given the small sample size, data for all linear and logistic regression models of statistical significance were plotted and further assessed with overall goodness of fit testing and across residual quantiles to ensure adequacy of the model. All statistical analyses were performed with R software (version 4.4.3, http://www.r-project.org) by the author of this thesis and support from an experienced statistician.

5.4 Results

5.4.1 Overall cohort

5.4.1.1 Participant demographics

Thirty-four participants underwent CMR scanning. Their overall demographics are displayed in Table 5-2 and described in more detail in the previous chapter. Median age was 56 (44, 62) and 47% of participants were female. 9/34(26%) participants were known to have hypertension, 6/34(18%) had known diabetes and 7/34 (21%) had a history of smoking. 5/3 (15%) of participants had a clinical frailty score (CFS) greater than or equal to 5. Median acute physiology and health evaluation (APACHE) II score was 17 (11, 20) and admission SOFA scores were 5 (2, 8). 41% of participants required invasive mechanical ventilation and 50% required non-invasive ventilation or nasal high flow oxygen. Almost a quarter (24%) required renal replacement therapy.

Twenty-four percent of participants were identified as having new LV dysfunction during their intensive care stay. The cohort had a median maximum troponin value of 67 (4, 479). 21% had ECG changes identified during their ICU stay.

Median ICU LOS was 6 days (2, 12), median hospital LOS was 15 days (8, 26) and median time to follow up was 56 (47, 60) days. NT-proBNP and troponin levels on discharge had a median value of 1254pg/ml (185, 4115) and 17pg/mL (10, 62) respectively.

Table 5-2 Characteristics of CMR participants

Characteristics	N = 34[1]
Patient characteristics	
Age	56 (44, 62)
Sex (Female)	16 (47%)
BMI	29 (25, 32)
SIMD	1.5 (1, 3)
Ethnicity	
Asian	2 (6%)
White	32 (94%)
Charlson Comorbidity Index	2 (0, 3)
Hypertension	9 (26%)
Diabetes	6 (18%)
CKD	1 (3.4%)
Previous Stroke	0 (0%)
Smoking History	7 (21%)
Alcohol Excess	2 (6.1%)
Previous Arrhythmia	0 (0%)
COPD	1 (2.9%)
Anxiety	4(12%)
Depression	4 (12%)
Clinical Frailty Scale (CFS)	3 (2, 3)
CFS ≥ 5	5 (15%)
Sepsis severity and characteristics	
APACHE II Score	17 (11, 20)
SOFA Score	5 (2, 9)
Source of Sepsis	
Bone/Joint	1 (3%)
Central Nervous System	1 (3%)
Intrabdominal/Hepatobiliary	6 (18%)
Lower Respiratory Tract	13 (39%)
Skin/Soft Tissue	5 (15%)
Urinary	7 (21%)
Other	1 (3%)
Required Invasive Mechanical Ventilation	14 (41%)
Duration of Mechanical Ventilation (days)	8 (5, 15)
Required NIV/NHF	17 (50%)
Duration of NIV/NHF (days)	1.25 (0.5, 2)
Required CV Support	24 (71%)
Duration of CV Support (days)	1 (1, 4)
Renal Replacement Therapy	8 (24%)
Duration of Renal Replacement Therapy (hrs)	9 (3, 20)

Maximum CRP	326 (200, 442)
Peak Lactate	1.80 (1.10, 3.00)
Cardiac injury during ICU admission	
LVSD during admission	8 (24%)
RVSD during admission	2 (5.9%)
ECG Changes in ICU	7 (21%)
Maximum Troponin	67 (4, 479)
Discharge Characteristics	
ICU Length of Stay (days)	6 (2, 12)
Hospital Length of Stay (days)	15 (8, 26)
Time from discharge to follow-up (days)	51 (47, 60)
Discharge NT-proBNP	1,254 (185, 4,115)
Discharge Troponin	17 (10, 62)

[1]Median (Q1, Q3); n (%). APACHE=Acute physiology and chronic health evaluation, CFS=Clinical frailty score, CKD=Chronic kidney disease, COPD=Chronic obstructive pulmonary disease, SOFA=Sequential organ failure assessment,

5.4.1.2 CMR findings

Overall CMR findings of the cohort are included in Table 5-3. Seven patients (20.6%) had reduced LVEF. Median values of LVEDV/BSA, LVESV/BSA, LVSV/BSA, LVEF and CI were 81ml/m^2 (65, 92), 34ml/m^2 (28, 47), 42 ml/m^2 (35, 51), 56% (50, 60) and 3.04mls/min/m^2 (2.59, 3.86). Right ventricular indices of RVEDV/BSA and RVESV/BSA and RVEF were 87 ml/m^2 (69, 100), 41 ml/m^2 (33, 51) and 50% (47, 68).

The cohort had median global native T1 values of 1231ms (1211, 1268), global T2 was 39ms (37, 42) and ECV values were 29% (27, 32), (Ref range <27.4%). No participants had LGE in either an ischaemic or non-ischaemic distribution.

5.4.2 Reliability of parametric mapping techniques

Intra-class correlations were 'good' for all measurements of parametric mapping, indicating reliability between assessors (Table 5-4). ICC for agreement were 0.822 (0.446-0.952) p<0.001 for native T1 values and 0.828 (0.393-0.956) p=0.001 for native T2 values respectively. ICC for agreement was 0.766 (0.036-0.945) p=0.020 for ECV values indicating good reliability. Bland-Altman plots displaying interrater agreement are shown in Figure 5-8, plotting differences and mean values between raters.

Table 5-3 CMR Characteristics of the overall cohort

Cardiac MRI Findings	N = 34[1]	Reference Range
Left ventricular dimensions and function		
LV End Diastolic Volume/BSA (mls/m^2)	81 (65, 92)	54-94
LV End Systolic Volume/BSA (mls/m^2)	34 (28, 47)	19-40
LV Stroke Volume/BSA (mls/m^2)	42 (35, 51)	21-49
LV Ejection Fraction (%)	56 (50, 60)	51-70
LV Mass/BSA (g/m2)	52 (41, 61)	35-70
Reduced LVEF n(%)	7 (20.5)	-
Cardiac Index (mls/min/m2)	3.04 (2.59, 3.86)	1.8-4.2
Right ventricular dimensions and function		
RV End Diastolic Volume/BSA (mls/m^2)	87 (69, 100)	53-99
RV End Systolic Volume/BSA (mls/m^2)	41 (33, 51)	17-46
RV Ejection Fraction (RVEF) (%)	50 (44, 57)	47-68
Reduced RVEF n(%)	5 (14.7)	-
Parametric Mapping		
Global native T1 (ms)	1,31 (1211, 1268)	1107-1234
Global native T2 (ms)	39 (37, 42)	35-44
ECV (%)	29 (27, 32)	<27.4

[1]n (%), median (Q1, Q3). BSA=Body surface area, ECV=Extra cellular volume, LV=Left ventricle, RV=Right ventricle

Table 5-4 Inter-observer variation for T1, T2 and ECV parametric mapping analysis

Represented as Intra-class correlation coefficients (ICC) calculated as two-way effects models for both consistency and agreement (n=10).

Characteristic	ICC Consistency (95% CI)	ICC Agreement (95% CI)
Native T1 (ms)	0.813 (0.414-0.950) p=0.001	0.822 (0.446-0.952) p<0.001
Native T2 (ms)	0.868 (0.558-0.966) p<0.001	0.828 (0.393-0.956) p=0.001
ECV (%)	0.874 (0.575-0.967) p<0.001	0.766 (0.036-0.945) p=0.020

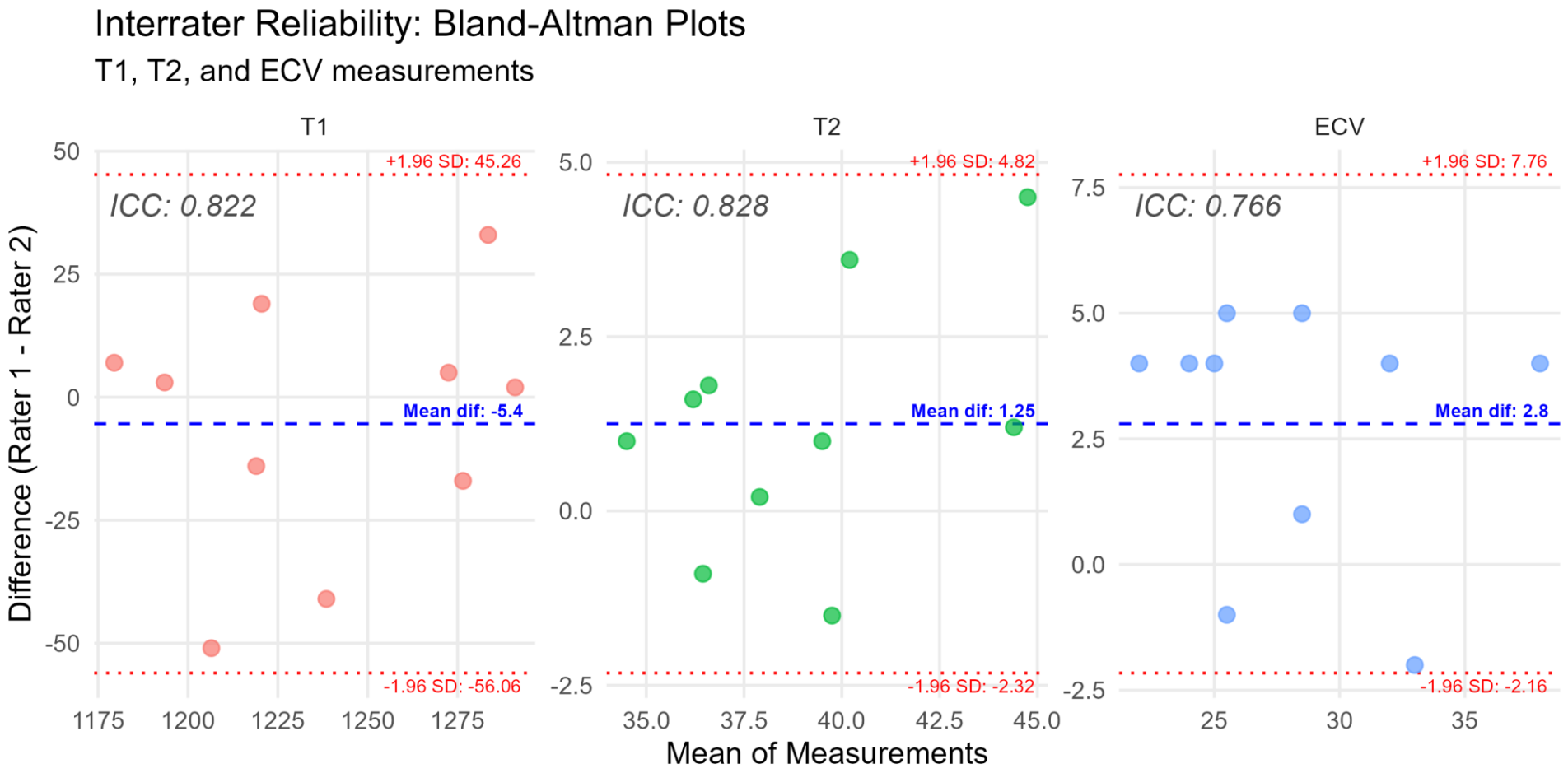

Figure 5-8 Bland-Altman plots of inter-rater reliability for parametric mapping analysis

ICC demonstrates "good" reliability for Native T1 (ms):, B: Native T2 Values (ms), and C: ECV Values(%). Differences between raters for each data point are plotted against the mean value of measurements. Mean difference between raters indicated by blue dashed lines with associated 1.96 standard deviations indicated by the red dashed lines. (T1 -5.4ms (-56.06, 45.26), T2 1.25ms (-2.32, 4.82) and ECV 2.8% (-2.16, 7.76)).

5.4.3 CMR findings in participants with and without left ventricular systolic dysfunction

Table 5-5 displays CMR characteristics of participants grouped by presence of normal LVEF and those with LVSD. LVESV/BSA was 32mls/m^2 (27, 38) in participants with normal LVEF vs 50mls/m^2 (39, 64), $p < 0.01$. Consequently, LV stroke volume was 45mls (36, 52) vs 36mls (30-51), $p = 0.027$ between groups.

Table 5-5 CMR characteristics tabulated by participants with and without LVSD

CMR Characteristic	No LVSD N = 27[1]	LVSD N = 7[1]	p-value[2]	Reference Range[3]
LV End Diastolic Volume/BSA (mls/m^2)	80 (65, 89)	82 (69, 110)	0.314	54-94
LV End Systolic Volume/BSA (mls/m^2)	**32 (27, 38)**	**50 (39, 64)**	**<0.001**	19-40
LV Stroke Volume/BSA (mls/m^2)	**45 (36, 52)**	**36 (30, 41)**	**0.027**	21-49
LV Ejection Fraction (%)	**57 (54, 61)**	**40 (28, 44)**	**<0.001**	51-70
LV Mass/BSA (g/m^2)	50 (40, 57)	61 (49, 83)	0.054	35-70
Cardiac Index (mls/min/m2)	3.11 (2.59, 3.87)	2.76 (2.33, 3.12)	0.357	1.8-4.2
RV End Diastolic Volume/BSA (mls/m2)	87 (69, 100)	86 (68, 107)	>0.949	53-99
RV End Systolic Volume/BSA (mls/m^2)	38 (32, 49)	48 (37, 65)	0.199	17-46
RV Ejection Fraction (%)	**53 (46, 58)**	**40 (31, 50)**	**0.003**	47-68
Native T1 (ms)	1221 (1209, 1253)	1252 (1230, 1275)	0.346	1107-1234
Native T2 (ms)	39.0 (37.0, 41.0)	40.0 (38.0, 42.0)	0.527	35-44
ECV (%)	29.0 (27.0, 31.0)	33.0 (29.0, 36.0)	0.127	<27.4

[1]Median (Q1, Q3) [2]Wilcoxon rank sum exact test; Wilcoxon rank sum test. [3]Reference range for functional indices is based on UK biobank data published by Petersen et al.[138] Reference range for parametric mapping is based on a local control cohort published by Morrow et al.[256]
BSA=Body surface area, ECV=Extra cellular volume, LV=Left ventricle, RV=Right ventricle

Figure 5-9 and Figure 5-10 display LVEF and RVEF in participants with LVSD those without. The median value of LVEF was 40% (28, 44) vs 57% (54, 61) in participants with and without LVSD. Participants with LVSD also had significantly reduced RVEF 40% (28, 44) vs 53% (46, 58), p = 0.003 in those with normal LVEF. This reduction is below local and national reference ranges for both males and females.[202]

There were no differences in global native T1 1221ms (1209, 1253) vs 1252ms (1230, 1275) p = 0.346, global native T2 39ms (37, 40) vs 40 (38, 42) p = 0.527 and ECV 29 (27, 31) vs 33 (29, 36), p = 0.127 in patients with normal LV function and those with LVSD. Participants with LVSD had global native T1 values and ECV values above the local reference range.

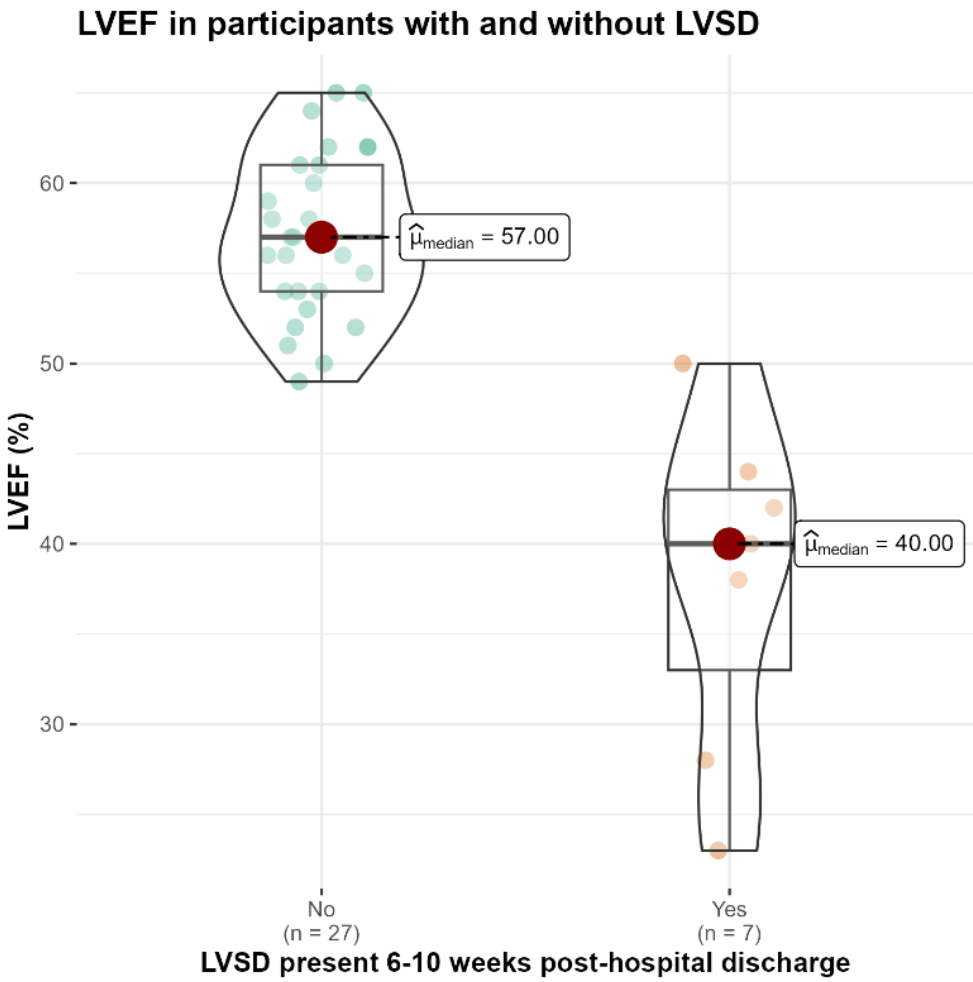

Figure 5-9 Left Ventricular Ejection Fraction in participants with and without LVSD at 6-10 weeks post-hospital discharge

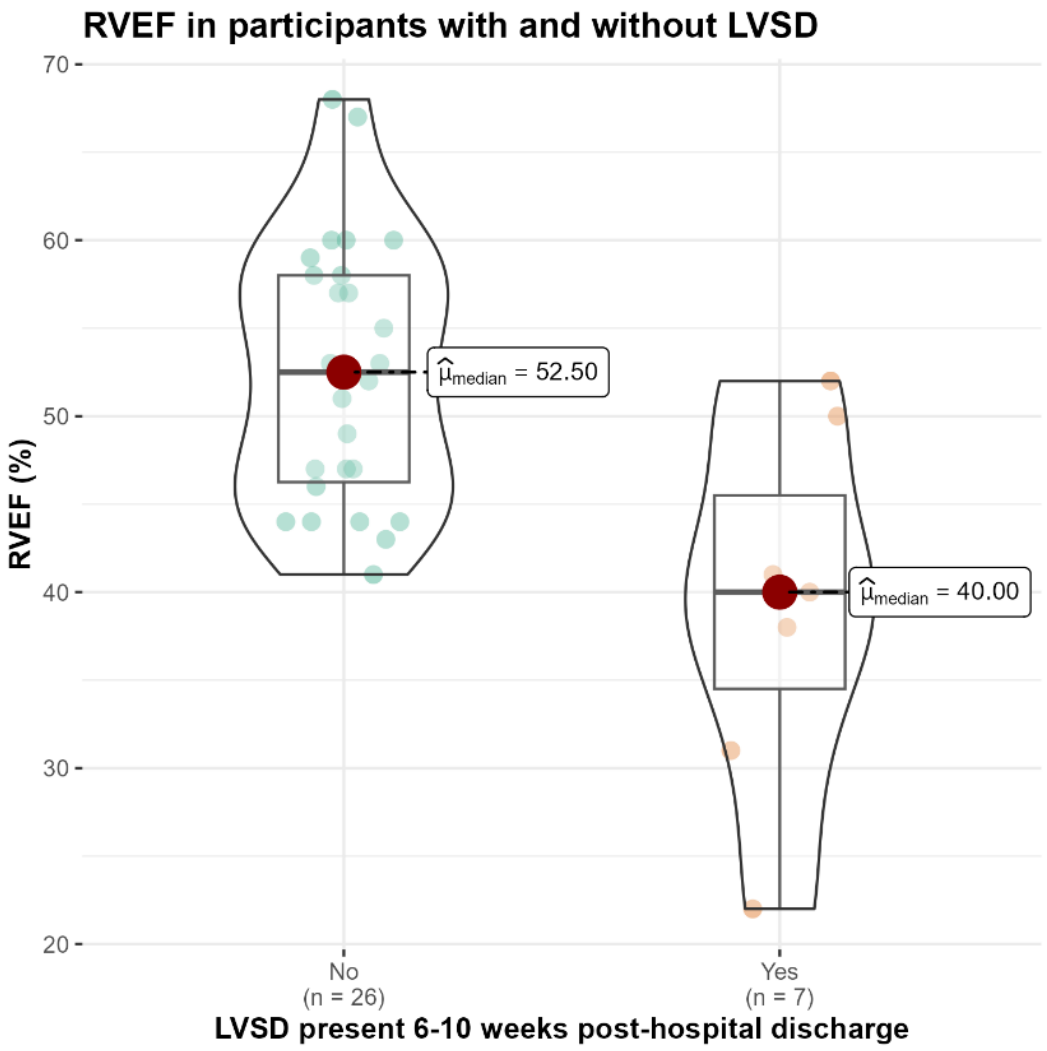

Figure 5-10 Right ventricular ejection fraction in participants with and without LVSD at 6-10 weeks post-hospital discharge

5.4.4 Relationship between left ventricular systolic dysfunction and patient, sepsis or discharge characteristics

Table 5-6 demonstrates the univariate logistic regression analyses exploring the ability of patient demographics, illness characteristics and biomarkers to predict LVSD 6-10 weeks post-hospital discharge. There was no relationship demonstrated with patient characteristics such as age (OR 1.02 (0.95, 1.09) p=0.628), frailty (OR 3.20 (0.35, 25.0) p=0.262) or key cardiovascular risk factors such as hypertension (OR 2.63 (0.2, 15.5) p=0.986, diabetes (OR 2.3 (0.27, 15.8), p=0.280) or smoking (OR 0.58 (0.03, 4.45), p=0.646). There was no relationship with illness severity as measured by APACHE II (OR 1.03 (0.93, 1.14) p=0.499) or SOFA score (OR 1.14 (0.93, 1.14), p=0.240). There was no association with requirement for invasive mechanical ventilation (OR 2.27 (0.42, 13.6) p=0.342),

non-invasive ventilation (OR 0.7 (0.42, 13.6), p=0.672), cardiovascular support (OR 1.05 (0.18, 8.43), p=0.956) or renal replacement therapy (OR 3.30 (0.52, 20.4), p=0.190).

Acute LVSD was the only factor that demonstrated an increase in odds of LVSD at follow-up 6-10 weeks post-hospital discharge (OR 7.67, (1.26, 54.5), p=0.030). There was no relationship observed between LVSD at 6-10 weeks and ICU LOS (OR 1.01 (0.99, 1.11), p=0.166) or hospital LOS (OR 1.01 (1.00, 1.04) p=0.124).

Log transformed values of NT-proBNP (OR 2.55 (1.33, 7.76) p=0.032) and hs-TnT (OR 3.37 (1.21, 13.0) p=0.037) at 6-10 weeks post hospital discharge also demonstrated significant ability to predict LVSD at 6-10 weeks post-hospital discharge. When categorized into clinically important cut-offs, NTproBNP values >400pg/mL at 6-10 weeks post hospital discharge demonstrated association with LVSD (OR 19.0, (1.8, 468) p=0.025).

Table 5-6 Univariate logistic regression of patient demographics, sepsis characteristics, cardiovascular injury during ICU and discharge factors and their relationship to reduced left ventricular ejection (LVEF%) fraction 6-10 weeks following discharge from hospital

Patient Characteristics	OR	95% CI	p-value
Age (years)	1.02	0.95, 1.09	0.628
Male Sex	1.24	0.23, 7.31	0.803
Clinical frailty scale	1.51	0.81, 2.95	0.198
Clinical frailty score ≥5	3.20	0.35, 25.0	0.262
Charleson Comorbidity Index	1.07	0.56, 2.01	0.829
BMI kg/m2	1.00	0.87, 1.13	0.892
Hypertension	2.63	0.42, 15.5	0.986
Diabetes	2.30	0.27, 15.8	0.280
Asthma	0.96	0.04, 8.16	0.972
Smoking History	0.58	0.03, 4.45	0.646
Alcohol excess	4.17	0.15, 116	0.337
Sepsis severity and requirement for organ support			
APACHE II Score	1.03	0.93, 1.14	0.499
SOFA Score	1.14	0.93, 1.44	0.240
Required invasive mechanical ventilation	2.27	0.42, 13.6	0.342
Required NIV or NHF Oxygen	0.70	0.12, 3.75	0.672
Required CV Support	1.05	0.18, 8.43	0.956
Required RRT	3.30	0.52, 20.4	0.190

Cardiac injury or dysfunction during ICU admission			
Acute LV dysfunction in ICU	**7.67**	**1.26, 54.5**	**0.030**
Acute ECG changes in ICU	4.31	0.65, 28.6	0.119
Peak hs-TnT (pg/mL)	1.00	1.00, 1.00	0.293
Peak CRP (mg/L)	1.01	1.00, 1.01	0.124
Peak Lactate (mmol/L)	1.06	0.79, 1.35	0.639
ICU Discharge and follow-up data			
ICU length of stay (Days)	1.04	0.99, 1.11	0.166
Hospital length of stay (Days)	1.01	1.00, 1.04	0.124
Log NTproBNP (pg/ml) at ICU discharge	1.67	1.02, 3.29	0.077
Log hs-TnT (pg/ml) at ICU discharge	1.73	0.83, 3.98	0.159
Log NTproBNP (pg/ml) 6-10 weeks post-hospital discharge	**2.55**	**1.33, 7.66**	**0.032**
Log hs-TnT (pg/ml) 6-10 weeks post-hospital discharge	**3.37**	**1.21, 13.0**	**0.037**
BNP Level 6-10 weeks post-hospital discharge			
NT-proBNP <125pg/ml	—	—	—
NT-proBNP 125-399pg/ml	0.90	0.04, 8.53	0.935
NTproBNP >400pg/ml	**19.0**	**1.80, 468**	**0.025**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio. APACHE=Acute physiology and chronic health evaluation, CRP=C reactive protein, ECG=Electrocardiogram, hs-TnT=High sensitivity troponin T, ICU=intensive care unit, NHF=Nasal high flow, NIV=Non-invasive ventilation, NT-proBNP=N terminal pro-B-type natriuretic peptide, CV, RRT, SOFA

5.4.5 Relationship of left ventricular ejection fraction and illness severity or duration of hospital admission

Table 5-7 displays univariate linear regression analyses exploring the association between patient and illness characteristics, key clinical biomarkers of cardiac injury and dysfunction, and LVEF. There were significant associations with severity of illness scores, duration of organ support and with biomarkers of injury and dysfunction both at the time of ICU discharge and at 6-10 weeks post-hospital discharge.

5.4.5.1 Illness severity scores

In terms of ability to predict LVEF at 6-10 weeks post-hospital discharge, there was no statistically significant association with APACHE score (ß=-0.27 (-0.67, 0.13) p=0.200). SOFA score demonstrated a significant ability to predict LVEF(%) 6-10 weeks post-hospital discharge (Figure 5-11 Association of SOFA score on ICU

admission and LVEF (%) at 6-10 weeks post-hospital dischargeFigure 5-11), β=-0.99 (-1.8, -0.16), p=0.027 with a moderately negative correlation between values (r = -0.38, p = 0.03).

Table 5-7 Univariate linear regression models of continuous variables and their relationship to LVEF.

There are significant relationships with LVEF and biomarkers of cardiovascular injury and dysfunction at both discharge from ICU and 6-10 weeks post hospital discharge

Illness severity and duration of organ support	Beta	95% CI	p-value
APACHE II Score	-0.27	-0.67, 0.13	0.200
SOFA Score	**-0.99**	**-1.80, -0.16**	**0.027**
Duration of mechanical ventilation (days)	**-0.41**	**-0.69, -0.14**	**0.010**
Duration of cardiovascular support (days)	**-0.57**	**-0.97, -0.17**	**0.010**
Duration of RRT (days)	**-0.70**	**-1.00, -0.38**	**<0.001**
Peak Lactate mmol/L)	-0.78	-1.80, 0.28	0.158
Length of ICU and hospital stay			
ICU length of stay (days)	**-0.34**	**-0.54, -0.14**	**0.002**
Hospital length of stay (days)	**-0.11**	**-0.18, -0.04**	**0.003**
Biomarkers at time of ICU discharge			
log NT-proBNP at time of ICU discharge (pg/mL)	**-1.7**	**-3.2, -0.13**	**0.042**
log hs-TnT at ICU discharge (pg/mL)	-2.1	-5.1, 0.84	0.169
CRP at ICU Discharge (mg/L)	0.01	-0.02, 0.04	0.485
Biomarkers at 6-10 weeks post hospital discharge			
log NT-proBNP at 6-10 weeks post-hospital discharge (pg/mL)	**-3.1**	**-4.7, -1.5**	**0.001**
log hs-troponin at 6-10 weeks post-hospital discharge (pg/mL)	**-5.8**	**-9.4, -2.1**	**0.004**
CRP at 6-10 weeks post-hospital discharge (mg/L)	-0.03	-0.48, 0.43	0.913

APACHE=Acute Physiology and Chronic Health Evaluation, CI = Confidence Interval, CRP=C reactive protein, hs-TnT = high sensitivity Troponin T, ICU=Intensive care unit, NT-proBNP=N-terminal pro-B type natriuretic peptide, RRT= Renal replacement therapy, SOFA=Sequential organ failure assessment.

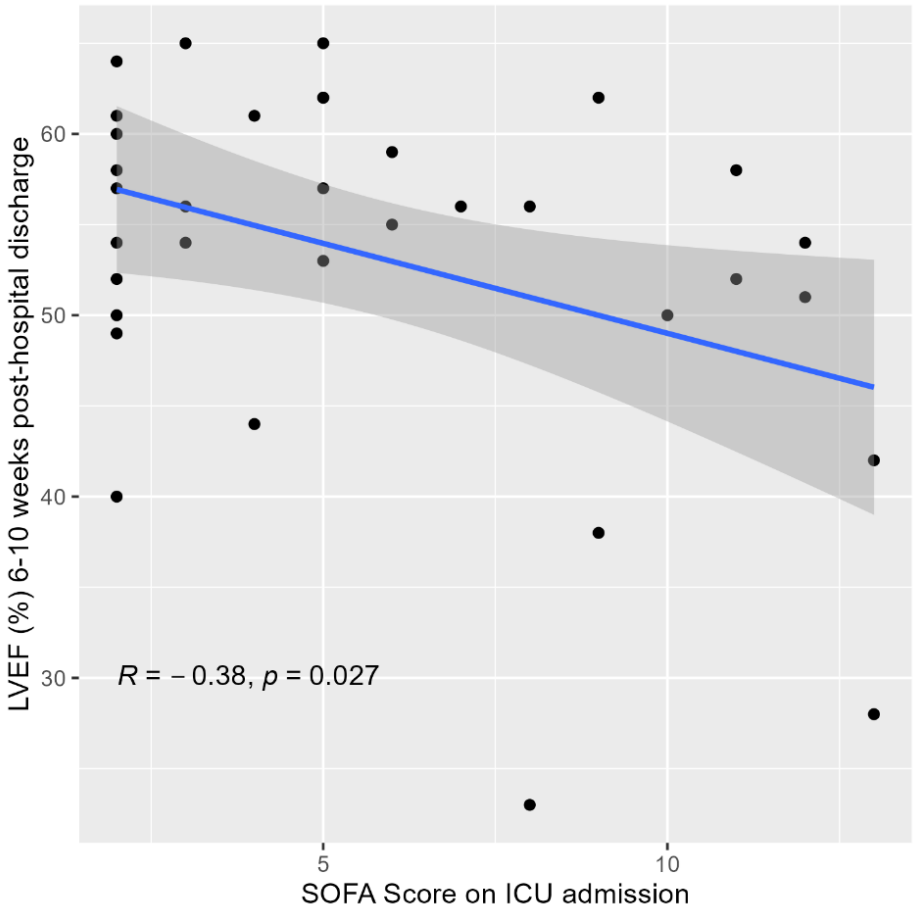

Figure 5-11 Association of SOFA score on ICU admission and LVEF (%) at 6-10 weeks post-hospital discharge

SOFA score demonstrated significant ability to predict LVEF (%) at follow-up, with corresponding moderately negative correlation between values.

5.4.5.2 Duration of organ support

Linear relationships were demonstrated with duration of mechanical ventilation (β -0.41 (-1.80, 0.16), p=0.010), cardiovascular support (β -0.57, (-0.97, -0.17), p=0.010) and duration of renal replacement therapy (β -0.70 (-1.00, -0.38), p<0.001) in participants who received these therapies. However, on visual inspection (Figure 5-12-Figure 5-14) the models of duration of mechanical ventilation, cardiovascular support and RRT were likely influenced by significant outliers. Goodness of fit testing demonstrated these predictor variables were not normally distributed, and only duration of cardiovascular support was robust on across all quantiles of scaled residuals. Thus, the predictive value of these models should be interpreted with caution.

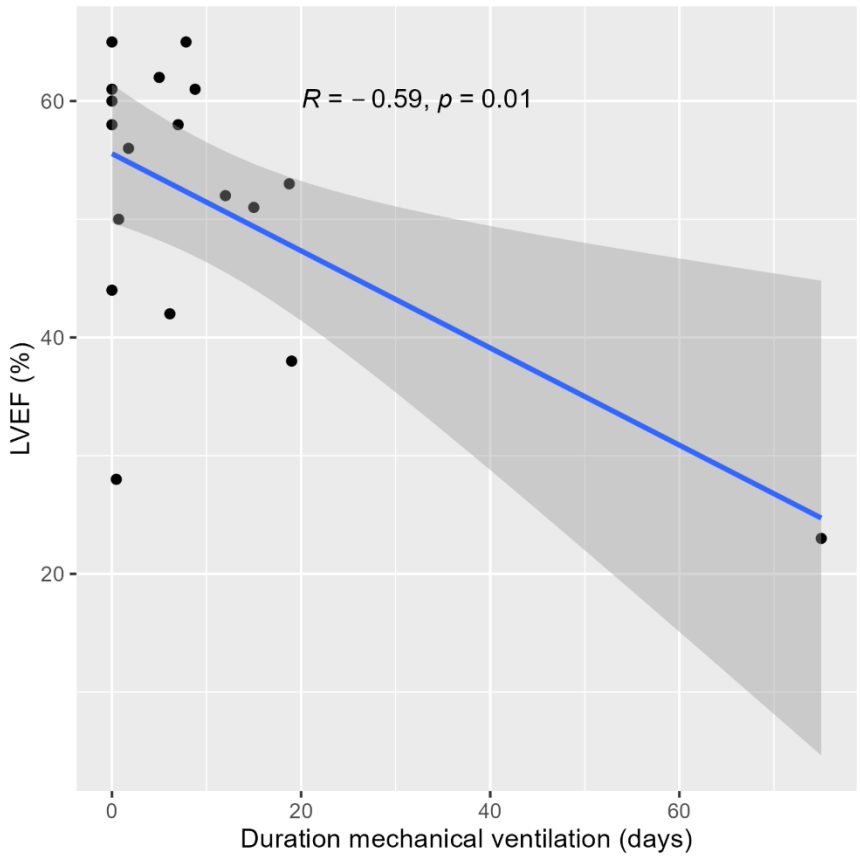

Figure 5-12 Relationship of LVEF (%) and duration of mechanical ventilation (days)

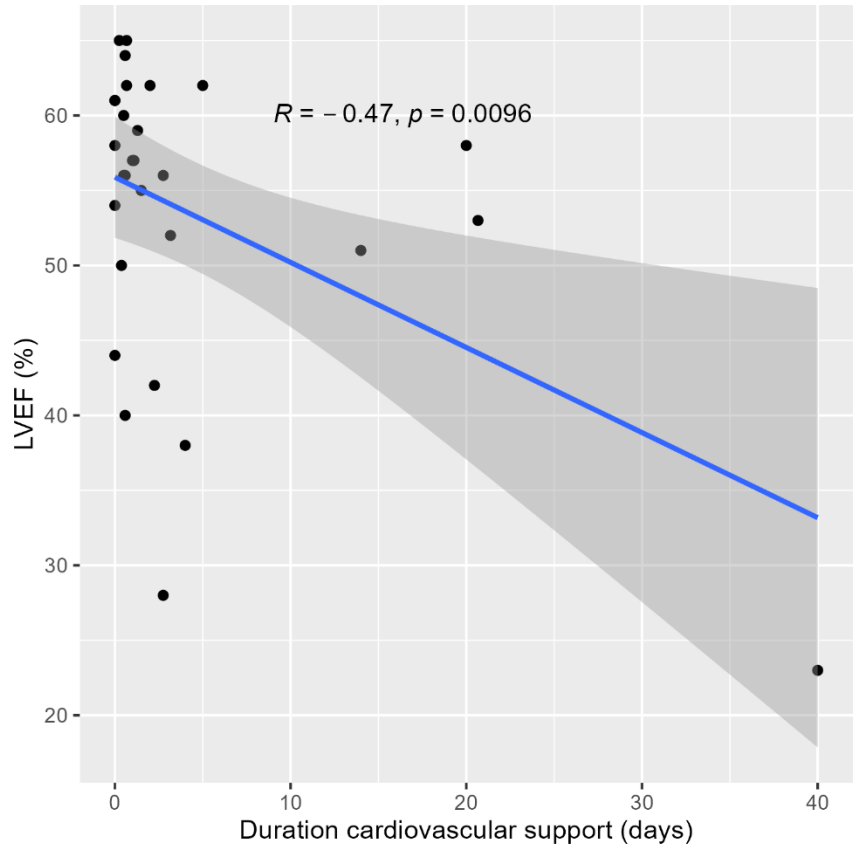

Figure 5-13 Relationship of LVEF (%) and duration of cardiovascular support (days)

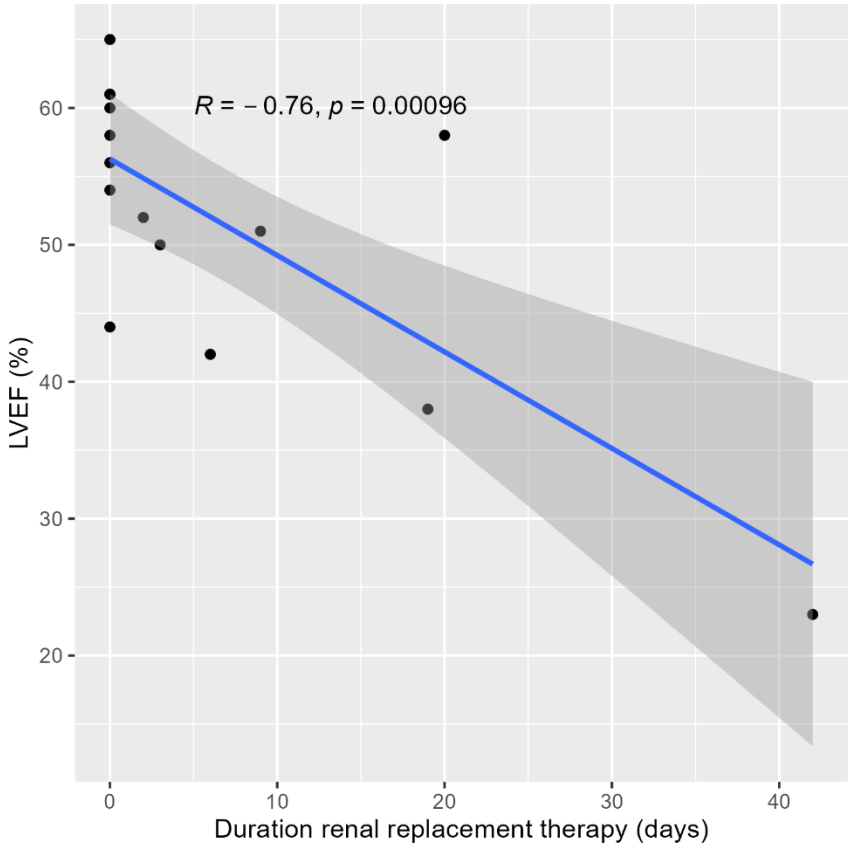

Figure 5-14 Relationship of LVEF (%) and duration of renal replacement therapy (days)

5.4.5.3 ICU and Hospital length of stay

Similar associations were seen with hospital (ß -0.34 (-0.54, 0.14), p=0.002) and ICU (ß -0.11, (-0.18, -0.04), p=0.003) LOS, but were potentially influenced by outliers with prolonged ICU or hospital stay (Figure 5-15). Again, visual inspection demonstrated significant outliers. Overall goodness of fit-testing and assessment of scaled residuals demonstrated only ICU length of stay had consistent ability to predict LVEF (%). Nonetheless, the degree of skew means these models must also be interpreted with caution.

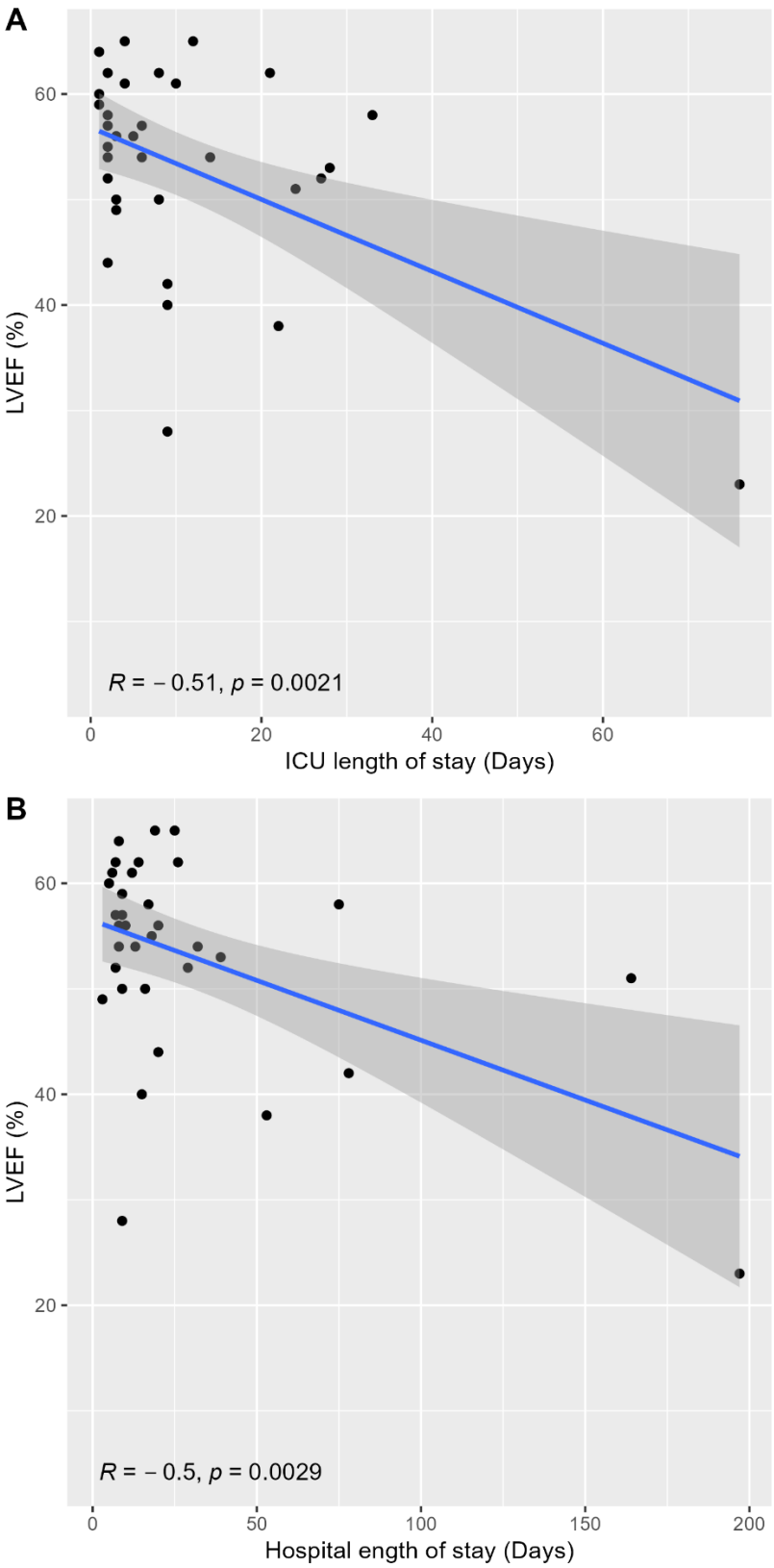

Figure 5-15 Relationship of LVEF (%) with length of stay

ICU (A) and hospital (B) length of stay (days). Although there are significant correlations that align with regression modelling, these are likely to be influenced by outliers who had prolonged length of stay.

5.4.6 Relationship between LVEF and biomarkers of cardiovascular dysfunction and injury

There were linear associations between LVEF and log-transformed values of NT-proBNP (Figure 5-16), both at ICU discharge (β -1.7 (-3.2, -0.13), p=0.042), and at 6-10 weeks post hospital discharge (β=-3.1 (-4.7, -1.5), p<0.001). Whilst log NT-proBNP on ICU discharge had a linear association with LVEF at follow-up visits, values demonstrated a weak correlation (r = -0.32, p = 0.042). Log transformed NT-proBNP values at follow-up 6-10 weeks post hospital discharge on the other hand demonstrated a moderate correlation in values (r = -0.56, p<0.001).

There was no significant relationship between log transformed values of hs-TnT (Figure 5-17) at ICU discharge (β -2.1 (-5.1, 0.84), p=0.169), neither was there significant correlation in values (r = -0.24, p = 0.17). However at 6-10 weeks post-hospital discharge, log hs-TnT was predictive of LVEF (β -5.8 (-9.4, -2.1), p=0.004), with moderately correlated values (R =-0.48, p=0.004).

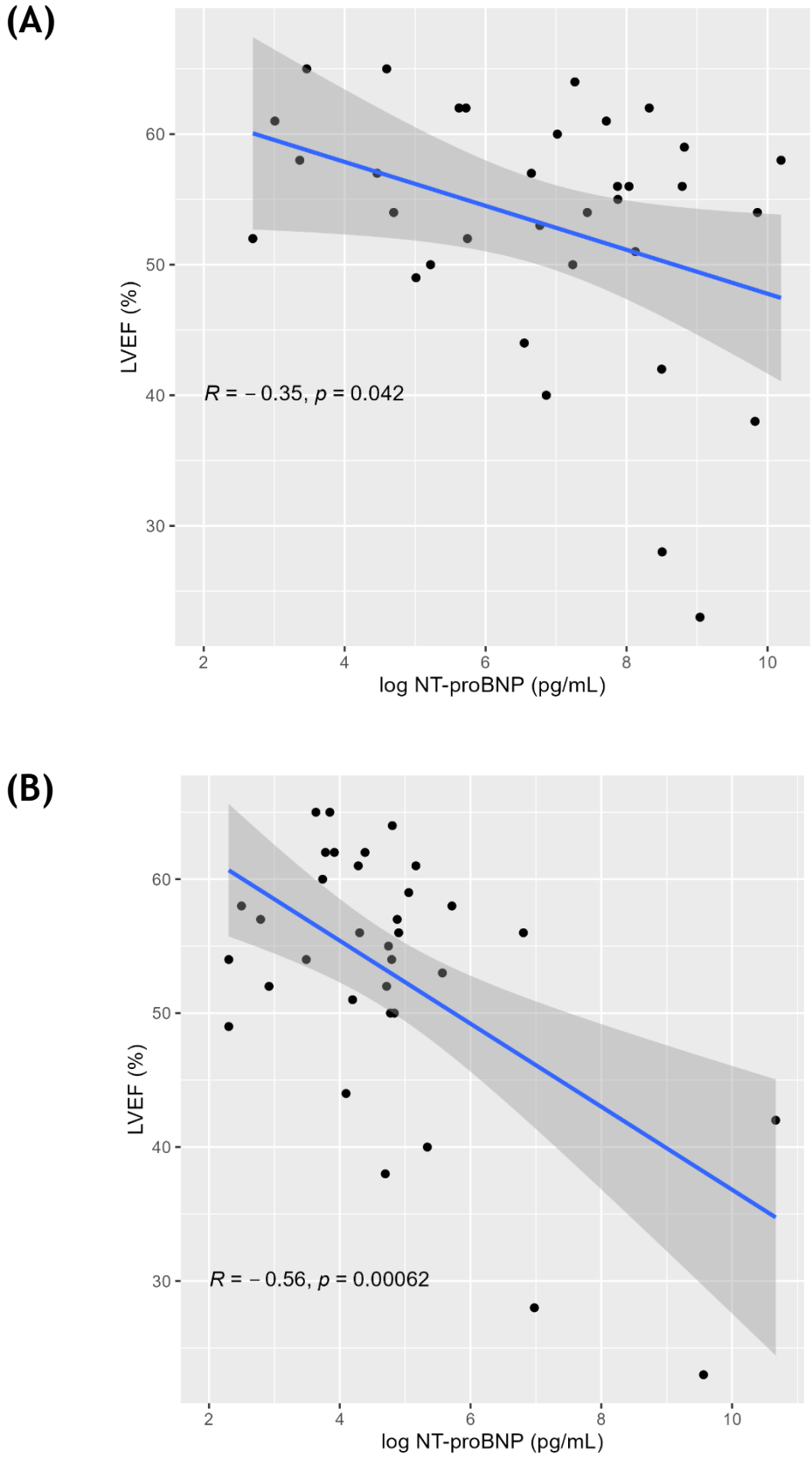

Figure 5-16 Relationship of LVEF (%) at 6-10 weeks post ICU discharge and NT-proBNP in study participants

There were significant associations between NTproBNP both at ICU discharge (A) and at 6-10 weeks post-hospital discharge (B).

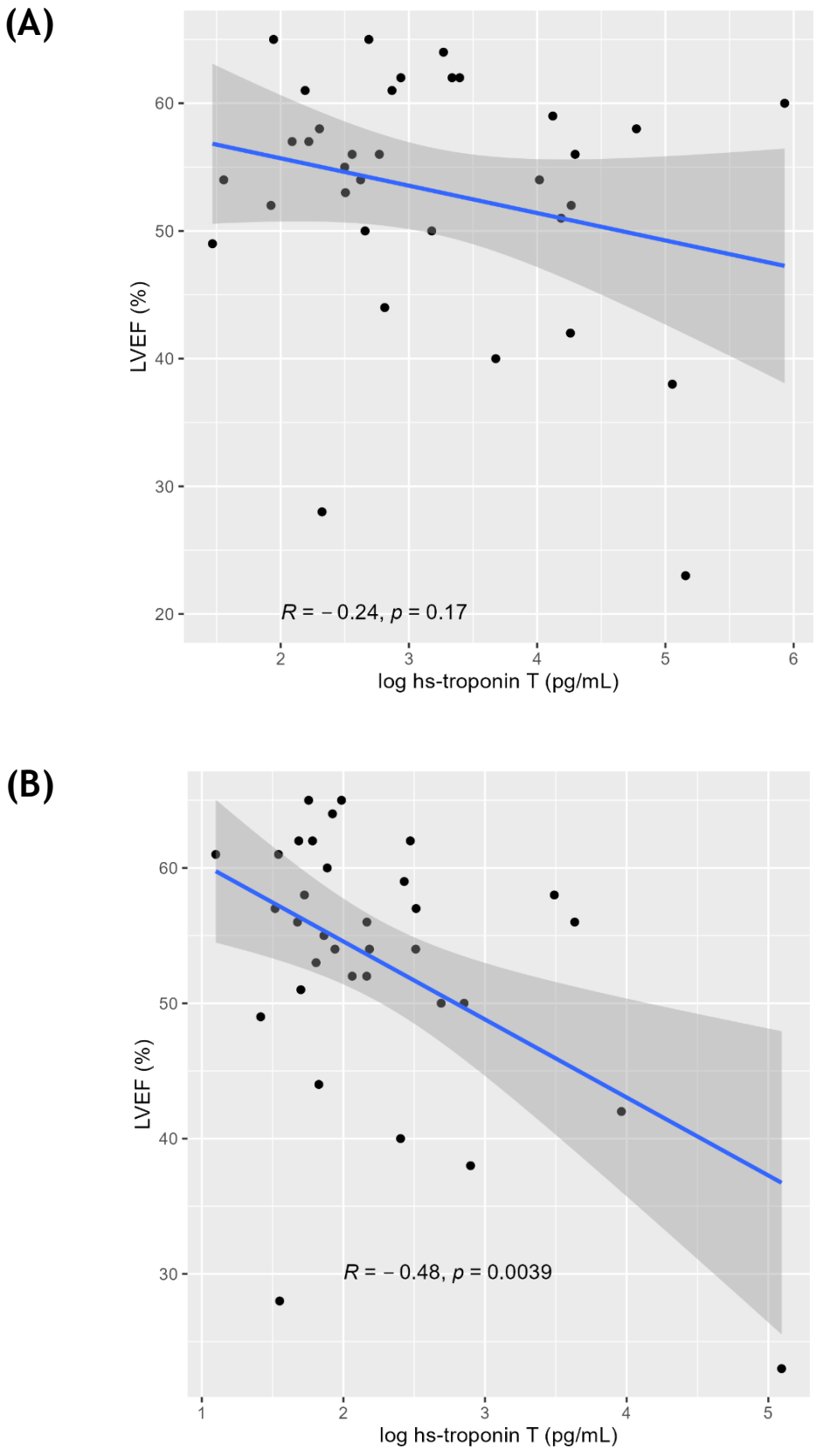

Figure 5-17 Relationship of LVEF(%) at 6-10 weeks post ICU discharge and hs-TnT in study participants

Hs-TnT values on ICU discharge were not significantly predictive of LVEF (%), however hs-TnT at 6-10 weeks demonstrate significant ability to predictive LVEF (%) at the same timepoint. Hs-TnT values and LVEF(%) at 6-10 weeks post-hospital discharge are moderately correlated (r= -0.48, p<0.001).

5.4.7 Reduced right ventricular systolic function

Five patients (14.7%) had RVSD. Table 5-5 CMR characteristics tabulated by participants with and without LVSDTable 5-8 displays CMR characteristics of participants grouped by presence of RVSD and those without. RVEF was 52% (47, 58) vs 38% (31, 40) in respective groups. Participants with RVSD had reduced LVEF 38% (28, 44, p<0.01) vs 56% (53, 61) compared to those without RVSD.

Table 5-8 CMR characteristics tabulated by participants with normal and reduced RVEF

CMR Characteristic	No RVSD N = 29[1]	RVSD N = 5[1]	p-value[2]	Reference Range
LV End Diastolic Volume/BSA (mls/m2)	83 (65, 92)	69 (58, 82)	0.539	54-94
LV End Systolic Volume/BSA (mls/m2)	33 (28, 42)	42 (39, 50)	0.135	19-40
LV Stroke Volume/BSA (mls/m2)	45 (37, 52)	30 (28, 31)	0.002	21-49
LV Ejection Fraction (%)	56 (53, 61)	38 (28, 44)	0.002	51-70
LV Mass/BSA (g/m2)	52 (41, 58)	52 (44, 71)	0.741	35-70
Cardiac Index (mls/min/m2)	3.11 (2.65, 3.87)	2.61 (2.33, 2.80)	0.080	1.8-4.2
RV End Diastolic Volume/BSA (mls/m2)	87 (74, 100)	68 (58, 87)	0.338	53-99
RV End Systolic Volume/BSA (mls/m2)	46 (33, 53)	37 (33, 41)	0.827	17-46
RV Ejection Fraction (%)	**52 (47, 58)**	**38 (31, 40)**	**<0.001**	**47-68**
Native T1 (ms)	1231 (1209, 1268)	1230 (1213, 1267)	0.876	1107-1234
Native T2 (ms)	39.0 (37.0, 42.0)	39.0 (38.0, 40.0)	0.547	35-44
ECV (%)	29.5 (27.0, 32.0)	29.0 (26.0, 32.0)	0.707	<27.4

[1]Median (Q1, Q3)[2]Wilcoxon rank sum exact test; Wilcoxon rank sum test. [3]Reference range for functional indices is based on UK biobank data published by Petersen et al.[138] Reference range for parametric mapping is based on a local control cohort published by Morrow et al.[256] BSA=Body surface area, ECV=Extra cellular volume, LV=Left ventricle, RV=Right ventricle

5.5 Discussion

This chapter presents CMR findings at 6-10 weeks post-hospital discharge for 34 patients admitted to intensive care with sepsis and their associations with patient demographics, illness characteristics, and key cardiac biomarkers on ICU discharge and at the time of CMR imaging. To the authors knowledge, this is the

first presentation of CMR findings from prospectively recruited patients in this population.

There was a high prevalence of LVSD in ICU survivors of sepsis. The observed prevalence of 20.6% is much higher than that observed in large general population datasets where the overall prevalence is between 1-3%.[237 259] This prevalence is much more akin to populations with traditional cardiovascular risk factors where the risk of heart failure is much higher. For example, in patients with type II diabetes, prevalence of heart failure has been recorded in excess of 20% and in patients with hypertension the lifetime risk of heart failure is estimated at approximately 8%.[260 261] This raises the concept of sepsis as a non-traditional cardiovascular factor and is in keeping with observational data demonstrating higher incidence of adverse cardiovascular outcomes following an episode of sepsis.[105 106]

The prevalence of acute (in ICU) LV dysfunction (24%), diagnosed by echocardiography, is in keeping with prior studies of LV dysfunction during sepsis in intensive care where prevalence has been reported from 10-70%.[162 189] The presence of LV dysfunction at follow-up was associated with this acute cardiac dysfunction. Previously, acute LVSD in sepsis, so-called 'septic cardiomyopathy' was felt to be reversible in nature. Whilst there is often a resolution of cardiac dysfunction during convalescence, it may be that the implications are further reaching than previously thought. Indeed, it is not clear in this study whether the LVSD observed at follow-up simply reflects the nadir of LVEF(%) following intensive care admission or whether this represents the early stages of a subsequent decline.

There were also associations between biomarkers of cardiac dysfunction such as NT-proBNP during sepsis episodes and at follow-up. NTproBNP has been independently associated with increased mortality in patients following admission to critical care.[151] Similarly in populations with acute decompensated heart failure, there is association between NT-proBNP at discharge and adverse follow-up outcomes such as readmission.[262 263] In chronic heart failure, the diagnostic and prognostic significance of NT-proBNP has led to its widespread adoption in clinical guidelines.[125] The association of NT-proBNP values at follow-up and LVSD in ICU survivors, support the hypothesis that it may be potentially

useful in prognostication and stratification of ICU survivors that may be at risk of future cardiac events. Similarly, the association of high sensitivity troponin and LVSD aligns with data in the general populations that increased troponin values are associated with adverse cardiovascular outcomes.[148]

On exploring potential mechanisms, none of the participants with LVSD had localised scar to suggest a significant acute coronary syndrome. Instead, LV function was globally impaired, indicating a more diffuse process. Global native T1 values were elevated and ECV values were above local reference ranges. Whilst these values are not diagnostic of myocardial fibrosis, it may be that sepsis leads to long term cardiac remodelling and subtle fibrosis, predisposing to long-term cardiovascular dysfunction. There are numerous proposed mechanisms of chronic cardiovascular dysfunction following sepsis including ongoing chronic inflammation and neurohormonal changes which could help explain some of these results.[107] Indeed, the hypothesis that chronic inflammation causes chronic cardiovascular dysfunction is intriguing and will be explored further in the next chapter. Similarly, there are multiple features of intensive care admission with sepsis that could mechanistically exacerbate cardiac injury and dysfunction including: vasoactive medications, de-prescription of guideline-directed medical therapy, severity of illness and potentially injurious forms of organ support.[184] There were some associations with duration of organ support and LVSD, which support this hypothesis. Furthermore, there was a linear relationship between SOFA score on admission and LVEF (%) at follow-up which further supports this hypothesis.

The prospective nature of recruitment prior to ICU discharge, and its embedded nature within a wider biomarker study ensured we minimised so-called healthy user bias as much as possible, where participants who felt less able were less likely to attend if recruited at a later date. Nonetheless, as demonstrated in the previous chapter, the significant attrition rate although aligned with other ICU survivor populations may skew the results towards a lower prevalence of cardiac dysfunction. As demonstrated in Ch 4, participants who did not attend CMR follow-up had an even higher median value of NT-proBNP.

5.5.1 Limitations

There are limitations to the study. In its design, a key objective was to exclude patients with prior cardiovascular disease. Nonetheless, without key diagnostic tests before sepsis such as echocardiography or coronary angiography it is impossible to completely exclude participants who may have had a prior asymptomatic chronic heart failure or ischaemic heart disease before their sepsis admission. The high prevalence of LV dysfunction in survivors may have clinical significance in that many of these patients may not have had specific follow-up and the opportunity to have institution of guideline directed medical therapy, if appropriate.[264]

One further limitation is the timepoint around follow-up. This study was designed to pragmatically assess patients at a point in their recovery journey that aligns with local post ICU follow-up.[210 265] Despite similar follow-up times observed from point of hospital discharge, there is a much wider variation in length of hospital stay and as such this may unbalance the distribution of findings seen on CMR imaging.

Lastly, due to the number of participants any models are relatively vulnerable to outliers, unmeasured confounders and should be interpreted with caution. Nonetheless, efforts have been made to assess for limitations in predictive ability and ensure no excess contribution of outlier values.

5.6 Conclusion

The results presented in this chapter demonstrate a high prevalence (20.6%) of LVSD at 6-10 weeks following hospital discharge in a cohort of 34 ICU survivors without prior known heart failure or ischaemic heart disease who were admitted with sepsis. LVSD was associated with organ dysfunction and correlated with biomarkers of cardiovascular injury (hs-TnT) or dysfunction (NT-proBNP) at 6-10 weeks post-hospital discharge. The findings support the hypothesis that sepsis may be a non-traditional risk factor for chronic cardiovascular disease and ICU survivors of sepsis may be an at-risk cohort

Chapter 6 Biomarkers of cardiac dysfunction, injury and inflammation in ICU survivors of sepsis

6.1 Introduction

This chapter presents the biomarker analysis of study participants. It will provide a brief discussion of key biomarkers of cardiac dysfunction and inflammation utilised in the study, describing their rationale for inclusion. The chapter will then describe the methodology for obtaining samples and the approach to statistical analysis. Biomarkers of cardiac function and inflammation are presented and subsequently tabulated by presence of left ventricular systolic dysfunction (LVSD) on CMR at 6-10 weeks following hospital discharge. Associations between key biomarkers and clinically relevant outcomes are described. Finally, the chapter will discuss the interpretation of the findings in the context of the participant population and the broader implications for other ICU survivors of sepsis.

6.1.1 Biomarkers of cardiovascular dysfunction and injury

6.1.1.1 N-terminal pro-B-type natriuretic peptide (NT-proBNP)

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) have been cornerstones in the diagnosis and management of chronic heart failure for decades.[125 150 258] BNP is synthesised in ventricular myocardium and stored in small amounts within cytosolic granules. Stimulated predominantly by myocardial wall stress, the pre-hormone (proBNP) is released into the bloodstream where it is cleaved into the 32 amino acid, BNP and the biologically inactive 76 amino acid N-terminal fragment, NT-proBNP (Figure 6-1) in relatively equal amounts.[222] BNP exhibits a number of active neurohormonal effects by causing increased cGMP production, ultimately causing natriuresis and diuresis, peripheral vasodilatation and inhibition of the renin-angiotensin-aldosterone system (RAAS).[222] Whilst BNP has a half-life of around 20 minutes and is cleared by binding to natriuretic peptide receptors and subsequent proteolysis, NT-proBNP is renally excreted and has a half-life of approximately 120 minutes. As such, blood concentrations of NT-proBNP are typically much higher.[222]

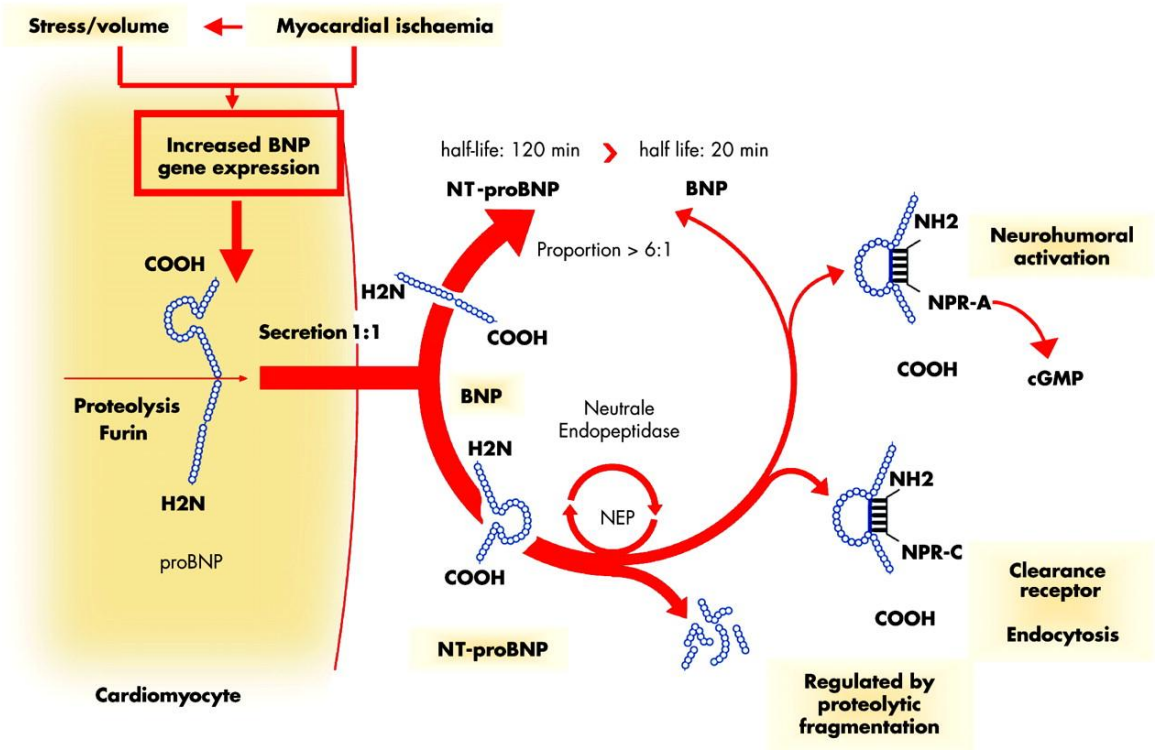

Figure 6-1 Illustration of BNP and NT-proBNP synthesis, release and receptor interaction

Upon release into circulation proBNP is cleaved into BNP and NT-proBNP in equimolar proportions. Interaction of BNP and the natriuretic peptide receptor type A (NPR-A) mediate the biological effects of BNP via an intracellular cGMP increase. Figure from Weber, M. and C. Hamm (2006).[222] Reproduced with permission from BMJ group.

In the diagnosis of chronic heart failure, The European Society of Cardiology (ESC) recommend a threshold of NT-proBNP >125pg/mL, beyond which further assessment is advised with echocardiography to evaluate and phenotype heart failure if present. In the UK, the national institute for clinical excellence (NICE) supports a higher threshold of >400pg/mL, with the cut-off supported by cost-benefit analysis. NICE also suggests that patients in the outpatient setting with NT-proBNP values >2000 pg/mL undergo echocardiography within 2 weeks, in keeping with longstanding evidence that higher NT-proBNP values confers a poorer prognosis in patients with heart failure.[150 266]

In acute decompensated heart failure (ADHF), increases in NT-proBNP are also associated with a greater risk of mortality, with the corresponding risk of a magnitude that is greater in comparison to patients with de-novo chronic heart failure presentations. Not only is the mortality risk higher in ADHF versus de-novo chronic heart failure, mortality risk increases in both groups with increasing NT-proBNP values.[267]

In patients with critical illness, NT-proBNP has been associated with an increased risk of mortality following discharge from intensive care, although can at times be non-specific and elevated in in patients without cardiac disease.[151 268]

Given the prognostic implications in patients with heart failure (both acute and chronic) and its association with mortality following critical illness, NT-proBNP serves as a key biomarker in evaluating myocardial stress in this study population.

6.1.1.2 High sensitivity troponin T (hs-TnT)

High-sensitivity troponin T (hs-TnT) is used to detect myocardial necrosis and has been widely adopted in the universal definitions of myocardial infarction.[144] Often rising above the 99th centile within hours of presentation, increases beyond this threshold - in persons with concomitant ischaemic changes on electrocardiography (ECG) or clinical features of an acute coronary syndrome - are likely to be due to myocardial infarction or necrosis.[269] Hs-TnT can also be elevated secondary to chronic myocardial injury, and as such it is often a significant change from baseline Hs-TnT values that is required to diagnose acute infarction. Nonetheless, its sensitivity and significant change in response to acute necrosis allows us to differentiate between acute and chronic injury.

Elevated troponin is common in patients with critical illness and sepsis.[146 270 271] Some of these elevations may reflect “type 2” myocardial infarctions where pre-existing coronary disease or other haemodynamic factors lead to oxygen supply-demand mismatch during periods of physiological stress.[144] There is also an increased risk of thrombotic events in sepsis. As such, classical ‘type I’ myocardial infarctions due to thrombus formation are relatively common.[272] It is perhaps unsurprising then, that regardless of the mechanism of injury by which myocardial injury occurs, raised troponin values are associated with increased mortality risk in critical illness populations.[114 273]

6.1.2 Biomarkers of renal dysfunction and cardiovascular events

Acute kidney injury (AKI) is common in critical illness and sepsis, and is associated with an increased risk of adverse cardiovascular events.[274] This risk has recently been demonstrated in Scottish populations who have survived

critical illness, where AKI was associated with an increased risk of myocardial infarction following discharge.[275]

The Kidney Disease Improving Global Outcomes (KDIGO) Work Group guidelines recommend estimation of glomerular filtration rate (eGFR) using biochemical markers such as creatinine or cystatin C to grade severity of chronic kidney disease.[225] Creatinine is a molecule produced predominately by skeletal muscle and filtered by the kidney. Increased levels may be reflective of acute kidney injury or chronic kidney disease depending on clinical presentation. However, there are multiple issues that limit the interpretation of creatinine as it is often significantly affected by muscle mass, which in turn is interrelated with many patient characteristics including age, sex and ethnicity.[225]

Cystatin C is an alternative renal biomarker which bears many similarities to creatinine in that it is filtered relatively unchanged by the kidney and can be used to estimate kidney function. However, rather than being produced by muscle, it is released by all nucleated cells and can be used to estimate kidney function independent of age, gender, ethnicity and muscle mass.[224] Cystatin C has shown to be more effective at predicting risk of fatal and non-fatal cardiovascular events, as well as all-cause mortality and is increasingly featured in international guidelines such as those produced by KDIGO.[217]

6.1.3 Biomarkers of inflammation and their role in heart failure pathophysiology

There are multiple biomarkers of inflammation that have been implicated in the pathogenesis of heart failure. The relationship between inflammation and evolution of chronic cardiovascular disease has been recognised for decades and is both complex and bi-directional.[276 277] Chronic risk factors such as obesity, diabetes or hypertension likely trigger low grade release of a chronic array of cytokines such as Tumour Necrosis Factor-alpha (TNF-α), high sensitivity C-Reactive protein (hs-CRP) and IL-1ß. Endovascular inflammation leads to a reduction in nitric oxide availability which in turn can lead to reactive oxygen species, stiffness of cardiomyocytes and myocardial collagen deposition.[107 277]

Ongoing activation of the innate immune system in heart failure leads to further chronic inflammation.[278] Toll-like receptors (TLRs) such as TLR4 expressed in abundance in cardiac myocytes, recognise specific damage-associated molecular proteins (DAMPs) and pathogen associated molecular proteins (PAMPs) which are derived from damaged host cells and pathogens.[278] The release of DAMPs and PAMPs may be induced by exogenous or endogenous stressors such as ischaemia and/or sepsis. This ultimately leads to an upregulation of pro-inflammatory cytokines such as TNF-α, Interleukin-1ß (IL-1ß), Interleukin-6 (IL-6) and Interleukin-10 (IL-10). In the short-term, this may be a cardio-protective response, but in the long-term it can lead to upregulation of inflammation, free radical mediated damage of vascular endothelium, alterations to RAAS signalling and further cardiomyocyte remodelling.[279] In animal models, these pathways have been associated with marked reductions in myocardial contractility, whilst blockade results in reduced measures of the inflammatory response.[280]

Many of these pathways have been targeted in clinical trials with little success, with some trials of high intensity blockade of cytokines such as TNF-α demonstrating harm.[113] However, there has been modest success in trials of IL1-ß blockade, where reductions in adverse cardiovascular events (myocardial infarction, stroke and cardiovascular death) were observed in patients with previous myocardial infarction and hs-CRP >2mg/L.[111] Specifically, significant reductions in hospitalisation for heart failure were observed in subgroup who achieved a hs-CRP <2mg/L during the trial period.[200]

These conflicting results demonstrate the complexity of the inflammatory response in heart failure and its pathogenesis. Nonetheless, the hypothesis that chronic low-grade inflammation plays a key role in chronic cardiovascular disease is compelling. Multiple large epidemiological studies demonstrate the relationship of markers of inflammation such as hs-CRP with adverse cardiovascular events.[226 281] There are clear associations with sepsis admission and long-term adverse cardiovascular events such as myocardial infarction, stroke and heart failure admission.[105] There is significant overlap in the conceptual framework that underpins the persistent inflammation and catabolism identified following sepsis and the inflammatory processes that contribute to chronic cardiovascular disease.[282]

Thus, whilst examining for objective evidence of cardiac dysfunction following sepsis, it is prudent to examine the associations with key cytokines associated with the pathogenesis of chronic cardiovascular dysfunction. In doing so, this chapter explores causal mechanisms of cardiovascular dysfunction identified in the study population, and the interrelated pathophysiological processes associated with sepsis, recovery and evolution of chronic cardiovascular disease.

6.2 Methods

The overall aims, structure of the study and methodologic approach has been described in detail in Chapter 3. In short, survivors of sepsis with no prior cardiac disease or immune dysfunction were recruited at the point of ICU discharge and followed up 6-10 weeks following discharge from hospital, where they underwent CMR imaging, biomarker analysis and completed a series of patient reported-outcome questionnaires. Associations of cardiovascular, renal and inflammatory biomarkers were explored to investigate the hypothesis that relationships between cardiovascular dysfunction and inflammation may persist during convalescence from critical illness.

6.2.1 Sample collection and laboratory protocol

After informed consent was obtained, the recruiting research fellow assigned participants with an anonymised study ID which could be used for the purposes of CMR imaging and biomarker analysis. Blood samples were collected at the time of recruitment (at the point of ICU discharge) and again at participants' follow-up visit (6-10 weeks post-hospital discharge) which occurred at the Clinical Research Facility[5] on the Queen Elizabeth University Hospital (QEUH) campus and adjacent to the imaging centre of excellence. The full laboratory protocol is included in Appendix 8.

At sample collection, research fellows collected blood in 2 x 4ml serum separation tubes (SST) and 2 x 4ml ethylenediaminetetraacetic acid (EDTA) tubes, ensuring samples were labelled with pre-prepared barcodes that indicated the study participant numbers allocated at recruitment. All samples

[5] Clinical Research Facility, Institute of Neurological Sciences, 1345 Govan Road, Glasgow, G51 4TF

were secured in pre-prepared envelopes and transferred to the NHS Greater Glasgow and Clyde Biorepository[6] where they were aliquoted into pre-labelled 1.5ml cryovials by biorepository staff on the day of collection. SST samples were centrifuged at 1500G at 4°C for 10 minutes prior to aliquoting. All samples were then stored in a -80°C freezer in labelled study boxes to ensure they could be batch analysed at a later date or stored for further analysis pending further ethical approval.

Samples subsequently underwent batch analysis at the Glasgow Biomarkers Research Unit (GlasBRU)[7] at the University of Glasgow.

6.2.2 Outcome measures

Samples were analysed for levels of key cardiovascular biomarkers, hs-TnT and NT-proBNP. NTproBNP was assessed as a continuous variable, and also by established thresholds (<125, 126-399 and >400pg/ml) given the importance of these thresholds in UK and international guidelines for diagnosis and management of chronic heart failure.[125 258]

On an exploratory basis, samples were tested for biomarkers of renal function associated with adverse cardiovascular outcomes: Cystatin-C and Creatinine; as well as Ca-125 which has been associated with venous congestion.[217 283] To explore the relationship between cardiac dysfunction and inflammation, samples were analysed for biomarkers of systemic inflammation and specific cytokines that have been implicated in heart failure and other cardiovascular diseases (Ferritin, hs-CRP, IL-1ß, IL-6, IL-8 , IL-10, TNF-α).[277]

Lastly, samples were analysed for Mid-Regional-pro Adenomedullin (MR-proADM), a compound initially discovered in patients with phaeochromocytoma that exerts vasodilatory and positively inotropic effects on the cardiovascular system.[284] It has been shown to independently predict adverse outcomes in both sepsis and heart failure.[218 285]

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[6] NHS Greater Glasgow and Clyde Biorepository, Level 3, Laboratory Medicine Building, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF

[7] Glasgow Biomarker Research Unit, British Heart Foundation Glasgow Cardiovascular Research Centre (GCRC), 126 University Place, Glasgow, G12 8TA

6.2.3 Statistical analysis

All statistical analyses were performed using R software (version 4.4.3, http://www.r-project.org) by the author of this thesis with support from an experienced statistician.

Data are presented as median (Q1, Q3) or proportion (%). Linear or logistic regression models are presented as ß values or odds ratios with 95% CI. Median values of all biomarkers are tabulated in summary tables, with values representative of the overall cohort at recruitment (at the time of ICU discharge) and follow-up (6-10 weeks post-hospital discharge) time-points. Median values across both time-points are shown using violin plots to describe trends and distribution of values in the population over time. Where biomarkers contained left-censored values beyond established laboratory cut-offs (e.g. IL-1B <0.8pg/mL), tobit regression was used to ensure accurate medians that took account of the left-censoring.[286]

To explore associations with biomarkers of left ventricular systolic dysfunction (LVSD), patient demographics and potential inflammatory mechanisms, values were tabulated by an 'LVSD group' and 'No LVSD' group and median values compared using Mann-Whitney U Test or Kruskall-Wallis tests as appropriate.

To further explore mechanistic associations with LVSD, univariate logistic regression models were constructed to explore its relationship with: biomarkers of cardiovascular dysfunction, renal function and inflammation. Where values of predictor variables demonstrated significant rightward skew such that regression model assumptions were likely to be violated, values were log transformed and reassessed for goodness of fit.

Given the association of NT-proBNP with LVSD and left ventricular ejection fraction (LVEF) in the previous chapter - and its key role in heart failure diagnosis and management – univariate linear regression models were constructed to explore the ability of key demographics, illness characteristics and biomarkers of cardiac dysfunction, renal impairment and inflammation study to predict NT-proBNP values at 6-10 weeks post-hospital discharge.

The distribution of NTproBNP values were visually inspected for normality and tested using the Shapiro-Wilk test.[287] Due to the inherent qualities of biomarkers in common clinical practice, the distribution of NT-proBNP at follow-up was anticipated to be non-parametric due to rightward skew.

Due to violations of overall goodness-of-fit, data were further interrogated by creation of Cullen-Frey plots to assess for skew and kurtosis that may later affect data modelling.[288] This confirmed significant right skew and extreme kurtosis, and as such 'raw' NT-proBNP values were subsequently log transformed for use as an outcome variable. This resulted in significant reductions in the Shapiro-Wilk test and significant reductions in skew and kurtosis. Univariate linear regression models were then constructed to assess the association between log transformed NT-proBNP values at follow-up visits and key participant demographics, illness characteristics, and other cardiovascular and inflammatory biomarkers. Lastly, logistic and cumulative regression models were constructed to evaluate the ability of key patient demographics or illness characteristics to predict key diagnostic NT-proBNP thresholds that are widely established in national and international guidelines (≤125, 126-400 and >400pg/mL, or ≤400 vs >400pg/mL).[125 258]

Given the limited size of the dataset (n=34) and significant skew of many of the other biomarkers, all models were plotted and visually inspected. Spearman or Pearson correlation coefficients were calculated as appropriate to explore the strength of correlation between continuous variables.

With all linear, logistic or cumulative regression models that demonstrated statistical significance, models were further validated by QQ plots of model residuals and overall goodness-of-fit diagnostics as described in Chapter 3.6. Simulated data was built based on the models and the cumulative density function calculated for residuals. Observed residuals are then scaled in comparison to distribution simulated residuals, such that the distribution of residuals can be assessed across quantiles, ensuring models were predictive across the full range of values. This model validation was undertaken using the 'DHARMa' package in R software (version 4.4.3) and is described in Chapter 3.[239]

6.3 Results

6.3.1 Overall biomarkers at recruitment and 6-10 weeks post hospital discharge

Overall values of cardiac, renal and inflammatory biomarkers for the study cohort as a whole are displayed in Table 6-1. Median values of biomarkers measured in the study are also depicted as violin plots in Figure 6-2 - Figure 6-6. Note the y axes in these plots are logarithmic, with many of the biomarkers exhibiting significant rightward skew, often with tails extending well above the median. Nonetheless, these plots allow overall trends in the distribution to be appreciated

At recruitment, median NT-proBNP values were 1446 pg/ml (306, 4115), hs-TnT 19 pg/ml (12, 57), Ca125 37.89u/ml (19.43, 57.37) and MR-proADM 0.56nmol/L (0.42, 0.78), all out with the population reference ranges. At 6-10 weeks post-hospital discharge (Figure 6-2, Figure 6-3), values of these biomarkers trended back to within normal reference ranges, NT-proBNP 111 pg/ml (44, 157), hs-TnT 7 pg/ml (6, 12), Ca-125 12 u/ml (8, 17) and MR-proADM 0.56 nmol/l (0.42, 0.78).

In terms of renal function, median values were within normal limits throughout the duration of the study for Creatinine 66 umol/l (49, 91) to 58 umol/l (50, 84), and Cystatin C values 0.78mg/l (0.54, 1.04) to 0.81mg/l (0.63, 1.12). The values and distribution of renal biomarkers across the study duration are depicted in Figure 6-4.

There were elevated values of hs-CRP (78.62mg/L (17.77, 147.94)), Procalcitonin (0.49ng/mL (0.19, 1.92)), TNF-α (20.45pg/mL (15.60, 30.90)), IL-1ß (1.56), IL-6 (25.1pg/mL (12.9, 66.7)) and IL-8 (15.35pg/mL (9.15, 26.80)) at recruitment. Values of hs-CRP (1.71mg/L (0.88, 5.85)) and TNF-α (15.9pg/mL (12, 21.2)) remained elevated above reference range at follow-up 6-10 weeks following hospital discharge (Figure 6-6). The remaining inflammatory biomarkers reduced to within normal range at follow-up.

Table 6-1 Overall biomarkers at recruitment and 6-10 weeks post-hospital discharge

Biomarker	Recruitment (ICU discharge)	6-10 weeks post-hospital discharge	Reference Range
Cardiovascular			
NT-proBNP pg/ml	1,446 (306, 4115)	111 (44, 157)	<125 [2,3]
hs TnT pg/ml	19.30 (12.17, 56.96)	7.13 (6.61, 12.31)	<14 [2,4]
Ca 125 u/ml	37.89 (19.43, 57.37)	11.79 (7.66, 16.86)	<35 [2]
MR-proADM nmol/L	1.14 (0.68, 1.83)	0.56 (0.42, 0.78)	<0.55 [2]
Biomarkers of renal function			
Creatinine umol/l	66 (49, 91)	58 (50, 84)	45-104 [2,5]
Cystatin C mg/l	0.78 (0.54, 1.04)	0.81 (0.63, 1.12)	0.61-0.95 [2]
Biomarkers of inflammation			
Ferritin ug/l	217.95 (113.2, 437.1)	42.4 (14.10, 12.50)	15-400 [2,5]
hs-CRP mg/l	78.62 (17.77, 147.94)	1.71 (0.88, 5.85)	<0.5 [2]
Procalcitonin ng/ml	0.49 (0.19, 1.92)	0.08 (0.06, 0.11)	<0.05 [6]
TNF-α pg/ml	20.45 (15.60, 30.90)	15.90 (12.00, 21.20)	7.78-12.2[6]
IL-1ß pg/ml	1.56 [7]	0.80 [7]	<0.8 [6]
IL-6 pg/ml	25.1 (12.9, 66.7)	4.68 (3.18, 8.02)	0.76-13. 6[6]
IL-8 pg/ml	15.35 (9.15, 26.80)	8.96 (6.20, 12.40)	6.7-16.2 [6]
IL-10 pg/ml	9.42 (5.97, 14.90)	3.91 (3.11, 4.72)	1.52-5.66 [6]

[1]Median (Q1, Q3), [2]Reference range provided by Roche. [3]Reference range supported by ESC guidelines[125]. [4]Reference range supported by multicenter evaluation of hsTnT assay[289]. [5]Reference range inclusive for both male and female values. . [6]Reference range provided by Biotechne® R&D Systems™. [7]Tobit regression median. Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1ß=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha.

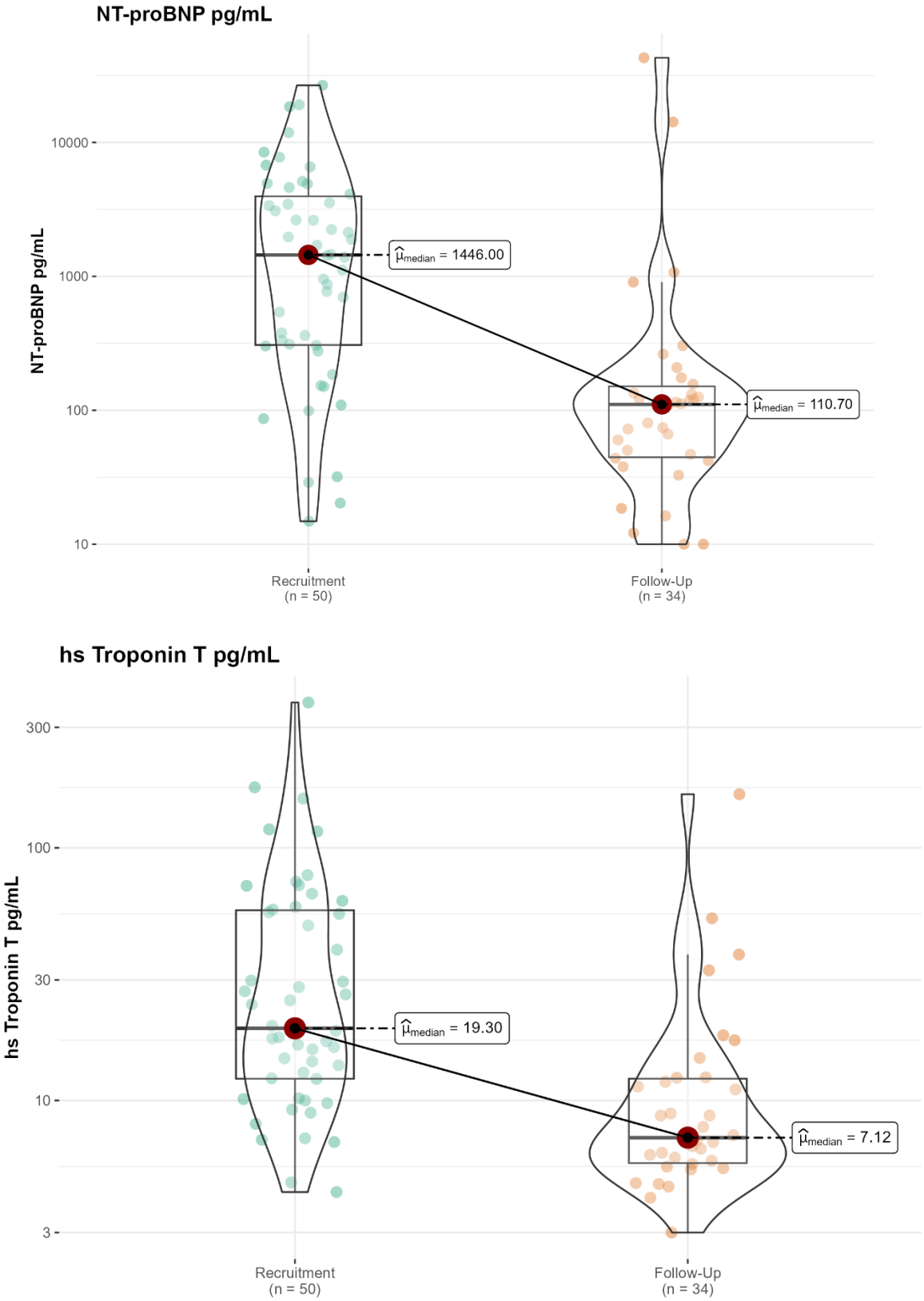


Figure 6-2 NTproBNP and hsTnT in study participants at ICU discharge and 6-10 weeks post-hospital discharge

Note y axes are logarithmic.

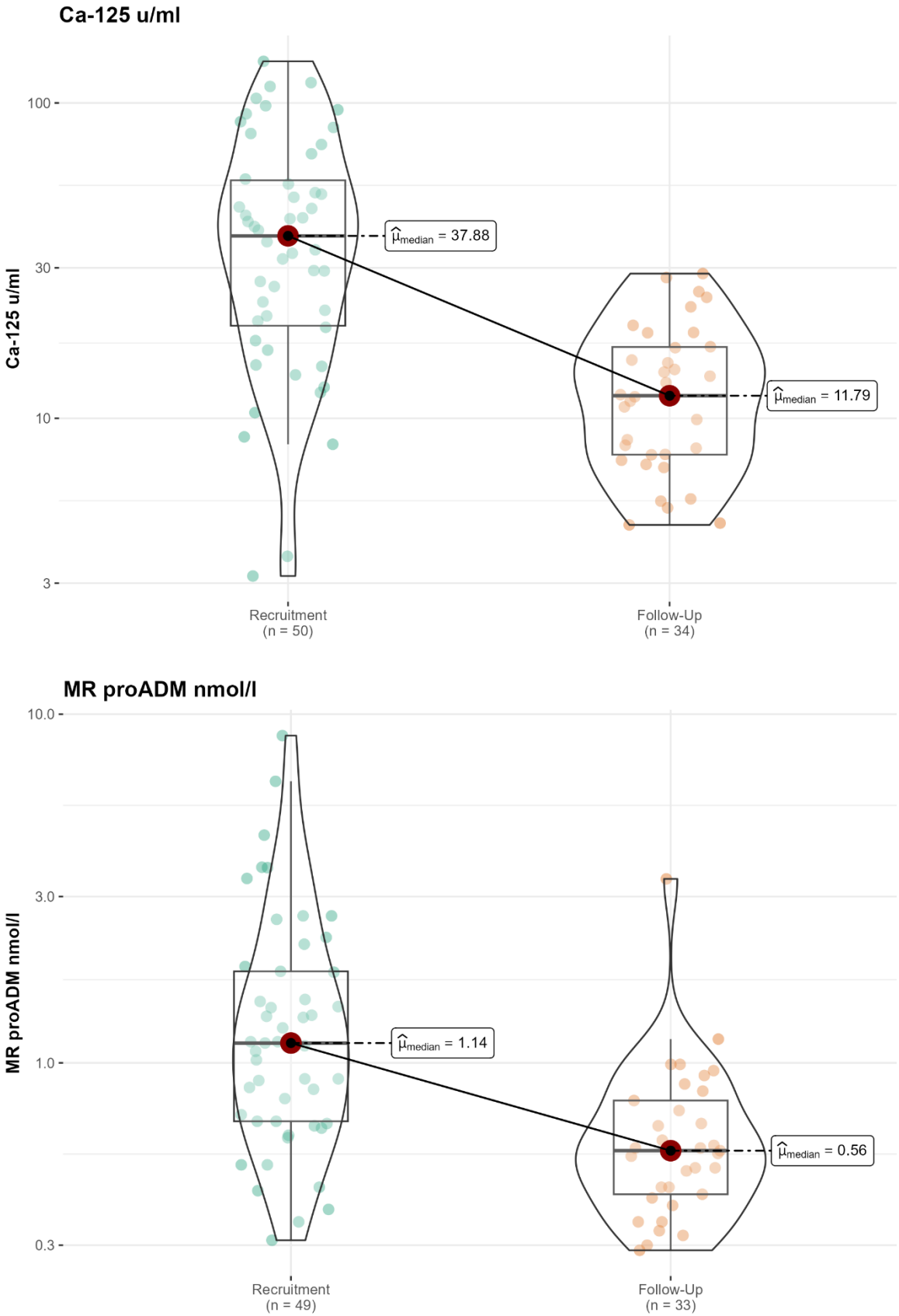


Figure 6-3 Ca-125 and MR-proADM in study participants at ICU discharge and 6-10 weeks post-hospital discharge

Note y axes are logarithmic

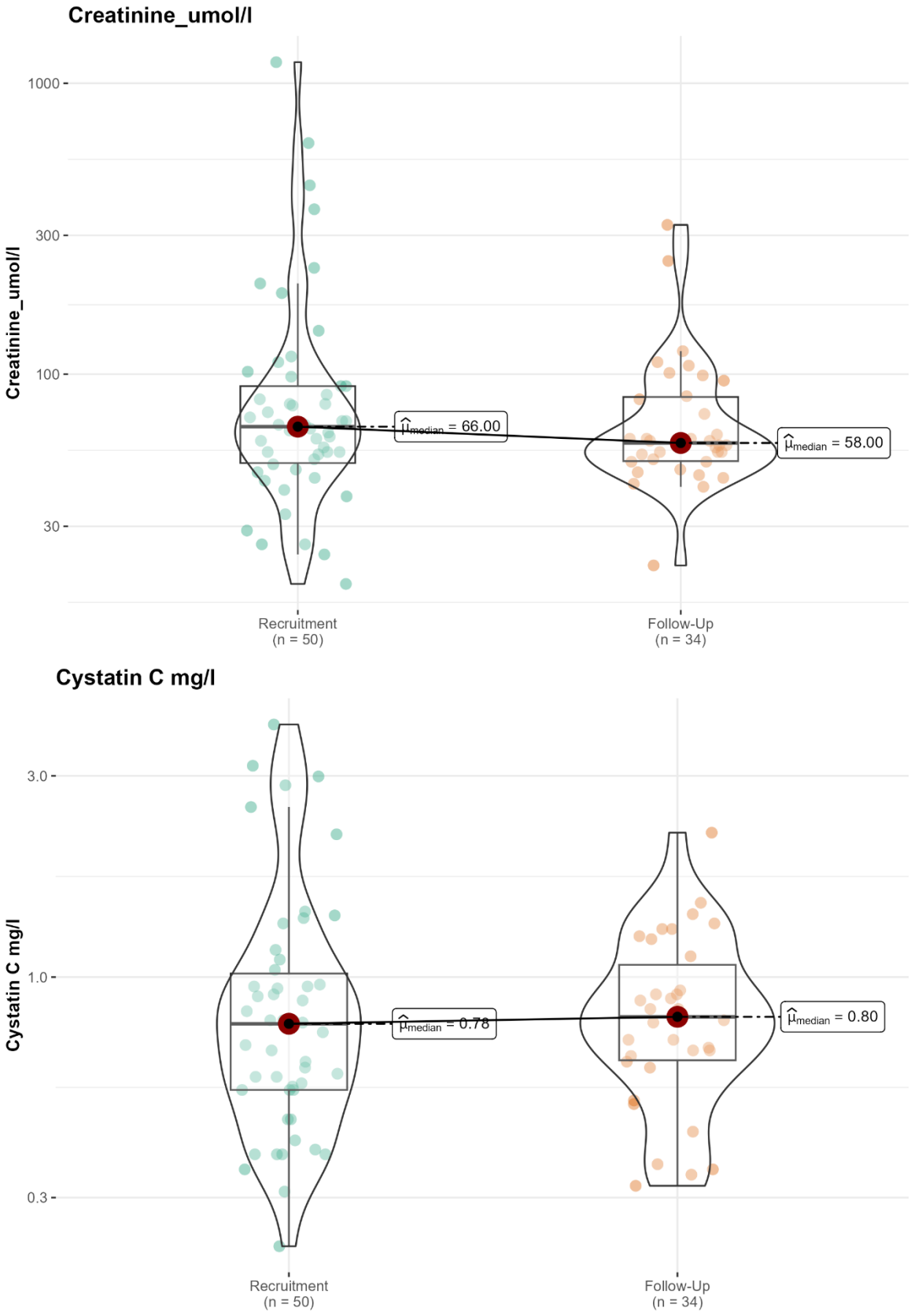


Figure 6-4 Creatinine and Cystatin-C in study participants at ICU discharge and 6-10 weeks post-hospital discharge

Note y axes are logarithmic

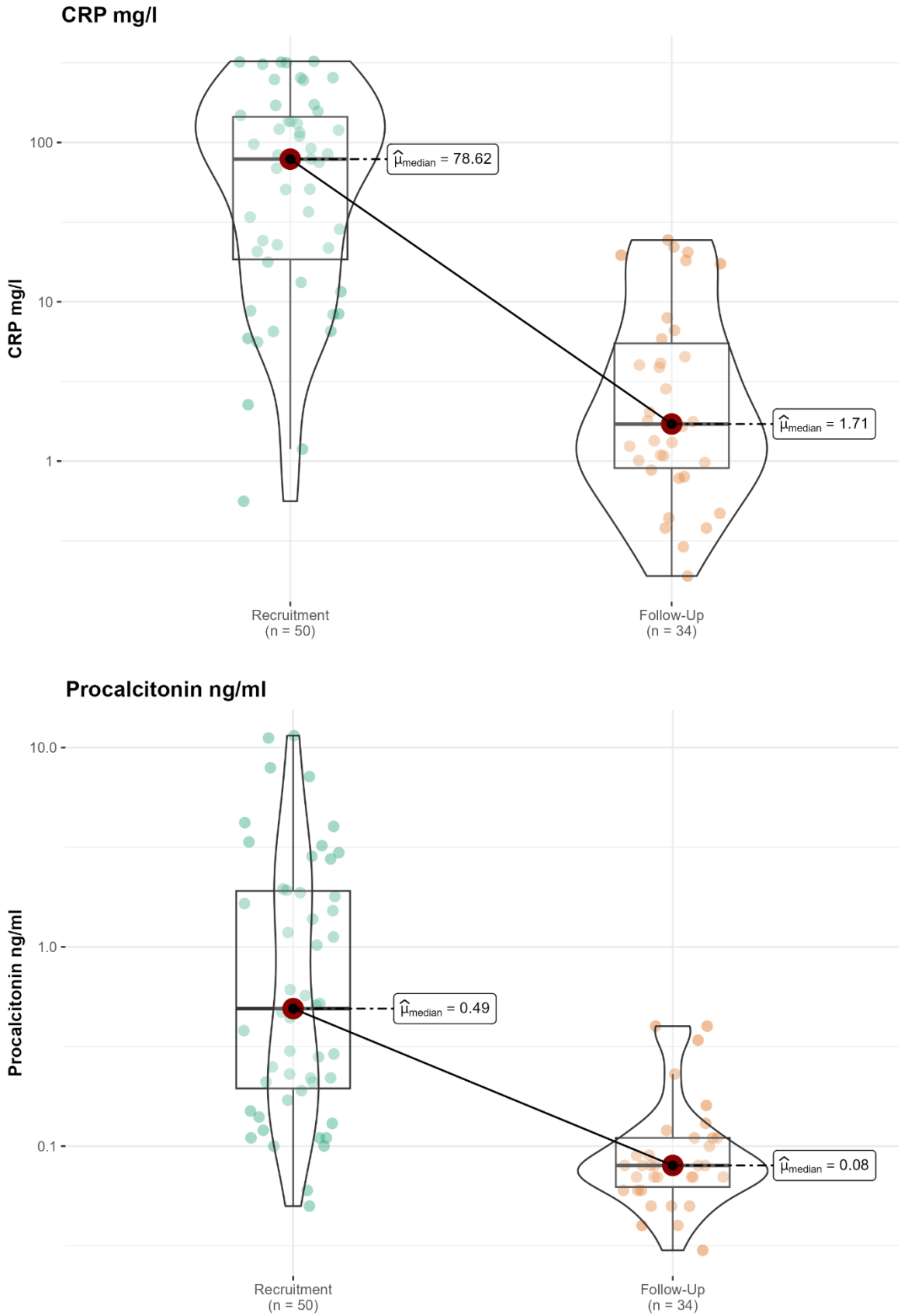


Figure 6-5 hs-CRP and Procalcitonin in study participants at ICU discharge and 6-10 weeks post-hospital discharge

Note y axes are logarithmic

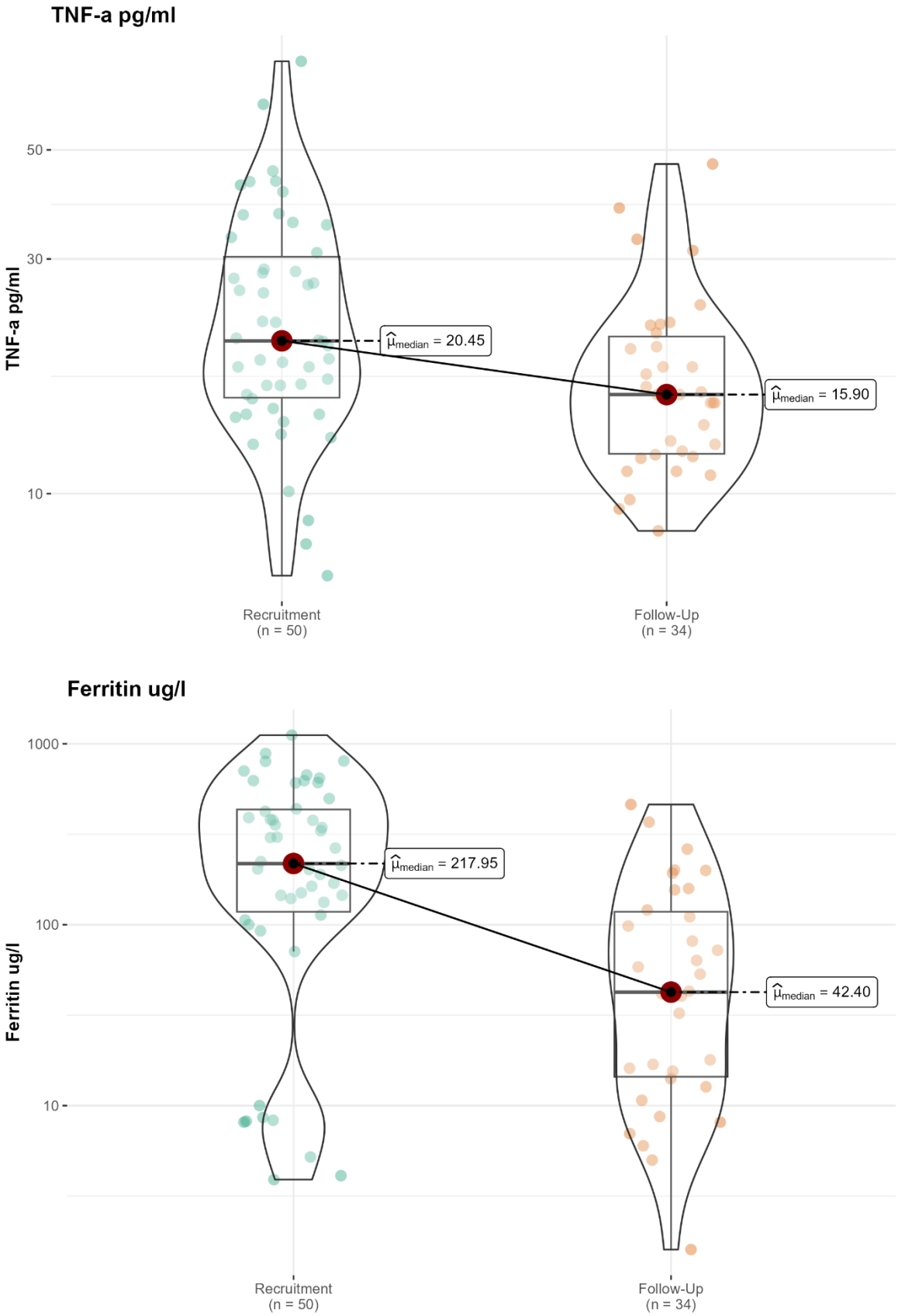


Figure 6-6 TNF-α and Ferritin in study participants at ICU discharge and 6-10 weeks post-hospital discharge

Note y axes are logarithmic

6.3.2 Biomarkers in participants with and without left ventricular systolic dysfunction

6.3.2.1 Biomarkers at ICU discharge in participants with and without LVSD

Table 6-2 Biomarkers of cardiac dysfunction, injury and inflammation of participants with and without LVSD at the point of ICU discharge displays biomarker values at the point of ICU discharge, tabulated by the presence of LVSD 6-10 weeks post-hospital discharge. There were notable differences in values of NT-proBNP (871pg/ml (110, 3087) vs 4908pg/ml (955, 8458) p = 0.073) , hs-TnT (16pg/ml (9, 56) vs 40pg/ml (14, 157) p = 0.2) and MR-proADM (0.97 nmol/L (0.62, 1.82) vs 1.37nmol/L (0.90, 3.64) p = 0.2) in those without vs those with LVSD, although these did not meet the threshold for statistical significance.

In both groups, NT-proBNP and hs-TnT were outwith reference ranges for normal endogenous values, as were median values of MR-proADM. Median values of Cystatin-C were also elevated above reference range (0.94mg/L (0.67. 2.85) in participants with LVSD. Median values of hs-CRP, TNF-α, IL-1ß, IL-6 and IL-10 were elevated above quoted reference ranges in both participants with LVSD and those without

6.3.2.2 Biomarkers at 6-10 weeks post-hospital discharge in participants with and without LVSD

Table 6-3 displays biomarker values at 6-10 weeks post-hospital discharge, tabulated by LVSD. Comparing participants without LVSD to those with LVSD at follow-up, there were significant differences in median values of NT-proBNP (74 vs 208pg/mL, p=0.024), MR-proADM (0.52 vs 0.95nmol/L, p=0.008), Cystatin C (0.71 vs 1.25mg/L, p=0.015), TNF-α (15 vs 20pg/mL, p=0.023) and IL-6 (3.8 vs 8.2pg/mL, p=0.003). With the exception of TNF-α, biomarkers of inflammation were within reference range in both participants those without and with LVSD. Cystatin C values were outwith the normal reference range in participants with LVSD at 6-10 weeks post-hospital discharge.

Table 6-2 Biomarkers of cardiac dysfunction, injury and inflammation of participants with and without LVSD at the point of ICU discharge

Biomarker	No LVSD N = 27[1]	LVSD N = 7[1]	p-value[2]	Reference Range
Cardiovascular biomarkers				
NT-proBNP pg/ml	871 (110, 3,087)	4,908 (955, 8,458)	0.073	<125 [3,4]
hs TnT pg/ml	16 (9, 56)	40 (14, 157)	0.151	<14 [3,5]
Ca-125 u/ml	32 (15, 50)	29 (14, 51)	>0.999	<35 [3]
MR-proADM nmol/L	0.97 (0.62, 1.82)	1.37 (0.90, 3.64)	0.179	<0.55 [3]
Renal biomarkers				
Creatinine umol/l	64 (47, 91)	79 (46, 446)	0.509	45-104 [3,6]
Cystatin C mg/l	0.63 (0.46, 1.34)	0.94 (0.67, 2.85)	0.186	0.61-0.95 [3]
Inflammatory biomarkers				
hsCRP mg/l	69 (9, 136)	37 (29, 310)	0.708	<5 [6,7]
Procalcitonin ng/ml	0.47 (0.15, 1.92)	1.18 (0.14, 3.22)	0.537	<0.05 [7]
Ferritin ug/l	190 (92, 381)	379 (133, 804)	0.478	<15-400 [7]
TNF-α pg/ml	19 (14, 33)	27 (17, 36)	0.427	7.78-12.2 [7]
IL-1ß pg/ml	2.00 (1.41, 3.71)	5.08 (1.85, 5.57)	0.174	<0.8 [7]
IL-6 pg/ml	21 (10, 47)	26 (9, 131)	0.427	0.76-13.6 [7]
IL-8 pg/ml	12 (8, 30)	15 (10, 34)	0.478	6.7-16.2 [7]
IL-10 pg/ml	8 (5, 14)	13 (8, 14)	0.338	1.52-5.66 [7]

[1]Median (Q1, Q3) [2]Wilcoxon rank sum exact test.), [3]Reference range provided by Roche. [4]Reference range supported by ESC guidelines[125]. [5]Reference range supported by multicenter evaluation of hsTnT assay[289]. [6]Reference range inclusive for both male and female values. .[7]Reference range provided by Biotechne® R&D Systems™. Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1ß=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha.

Table 6-3 Biomarkers of cardiac dysfunction, injury and inflammation of participants with and without LVSD at 6-10 weeks post-hospital discharge

Biomarker	No LVSD N = 27[1]	LVSD N = 7[1]	p-value[2]	Reference Range
Cardiovascular biomarkers				
NT proBNP pg/ml	**74 (38, 132)**	**208 (110, 14224)**	**0.024**	**<125** [3,4]
hs TnT pg/ml	7 (5, 11)	15 (6, 53)	0.066	<14 [3,5]
Ca-125 u/ml	12 (8, 17)	9 (6, 25)	0.967	<35 [3]
MR-proADM nmol/L	**0.52 (0.39, 0.66)**	**0.95 (0.56, 0.99)**	**0.008**	**<0.55** [3]
Renal biomarkers				
Creatinine umol/l	**57 (47, 62)**	**101 (56, 110)**	**0.024**	**45-104** [3,6]
Cystatin C mg/l	**0.71 (0.51, 0.91)**	**1.25 (0.84, 1.30)**	**0.015**	**0.61-0.95** [3]
Inflammatory Biomarkers				
hs-CRP mg/l	2 (1, 5)	2 (1, 20)	0.349	<5 [7]
Procalcitonin ng/ml	0.08 (0.06, 0.10)	0.11 (0.07, 0.23)	0.151	<0.05 [7]
Ferritin ug/l	42 (13, 81)	159 (16, 262)	0.081	15-400 [6,7]
TNF-a pg/ml	**15 (12, 18)**	**20 (18, 38)**	**0.023**	**7.78-12.2** [7]
IL-1β pg/ml	< LOD[8]	< LOD[8]	-	<0.8 [7]
IL-6 pg/ml	**3.8 (3.1, 7.8)**	**8.2 (7.7, 16.2)**	**0.003**	**0.76-13.6** [7]
IL-8 pg/ml	7.5 (5.9, 12.4)	9.6 (8.4, 21.4)	0.163	6.7-16.2 [7]
IL-10 pg/ml	3.87 (3.06, 4.81)	4.08 (3.55, 4.20)	0.551	1.52-5.66 [7]

[1]Median (Q1, Q3) [2]Wilcoxon rank sum exact test.), [3]Reference range provided by Roche. [4]Reference range supported by ESC guidelines[125]. [5]Reference range supported by multicenter evaluation of hsTnT assay[289]. [6]Reference range inclusive for both male and female values. .[7]Reference range provided by Biotechne® R&D Systems™. [8] >50% of values below the limit of detection and as such accurate medians could not be calculated. Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1β=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha.

Figure 6-7 - Figure 6-11 plot the distributions and median values for biomarkers of NT-proBNP, MR-proADM, Cystatin-C, TNF-α and IL-6 in participants with LVSD compared to those without, at 6-10 weeks post hospital discharge. Median values differ significantly between the two cohorts as outlined in Table 6-3, with median values of NT-proBNP (208pg/mL), Cystatin C (1.25mg/L), MR-proADM (0.95 nmol/L) and TNF-α (20pg/mL) above reference ranges for normal endogenous values in participants with LVSD at follow-up. The median value of TNF-α was also above the reference range in participants without LVSD (15.3pg/mL).

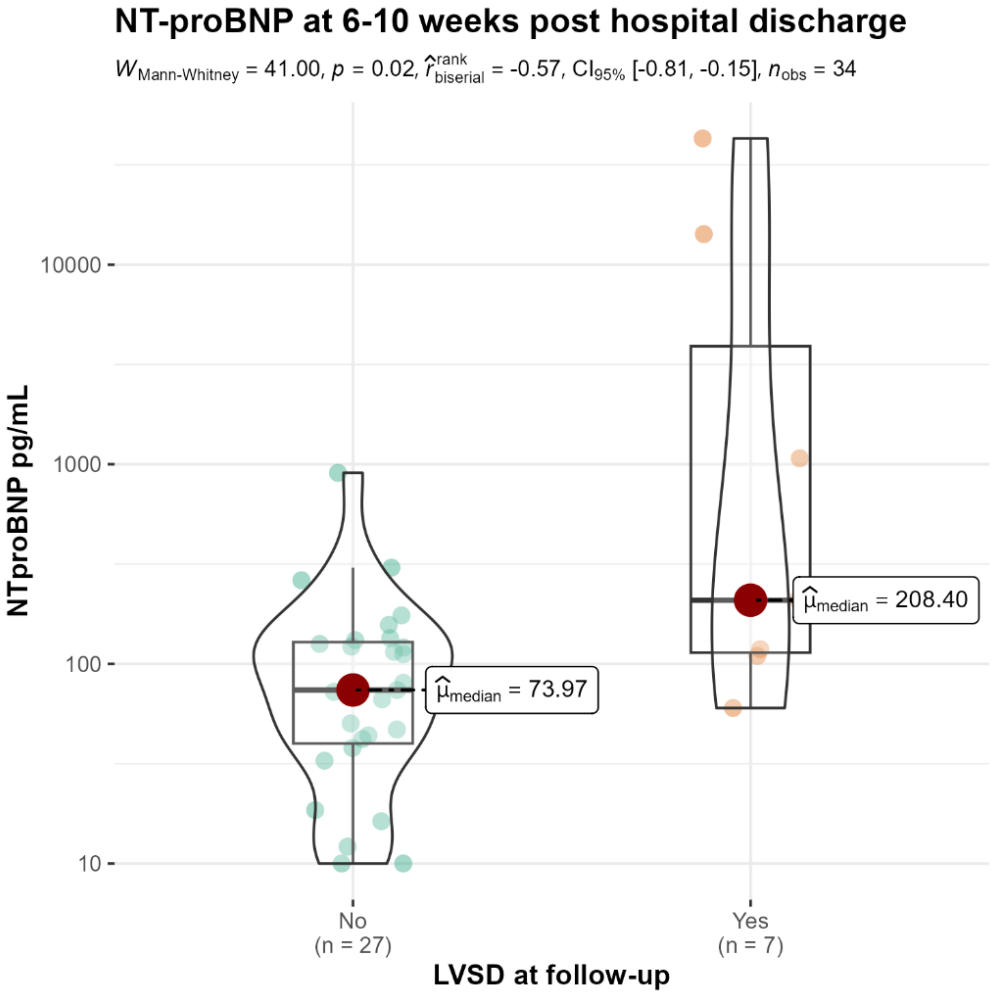


Figure 6-7 NT-proBNP values in study participants at 6-10 weeks following hospital discharge in participants with and without LVSD

Note y axes are logarithmic

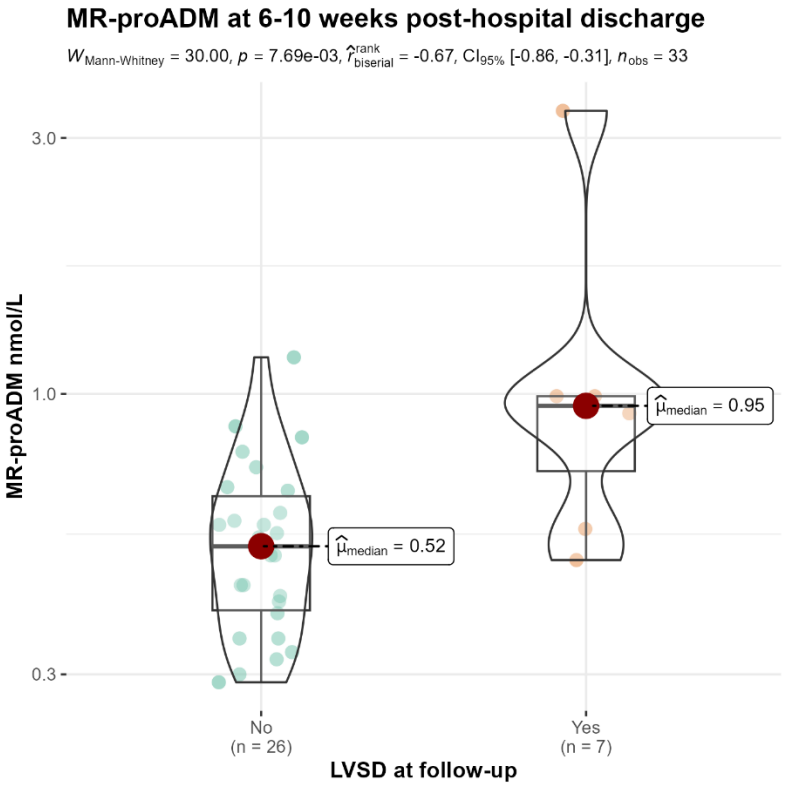


Figure 6-8 MR-proADM at 6-10 weeks post-hospital discharge in survivors with and without LVSD

Note y axes are logarithmic

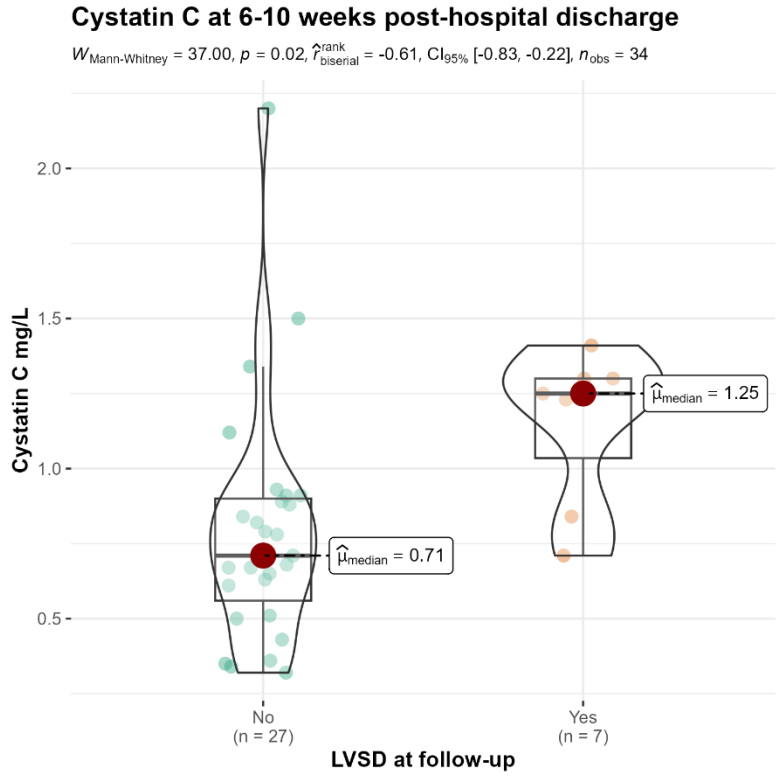


Figure 6-9 Cystatin C at 6-10 weeks post-hospital discharge in survivors with and without LVSD

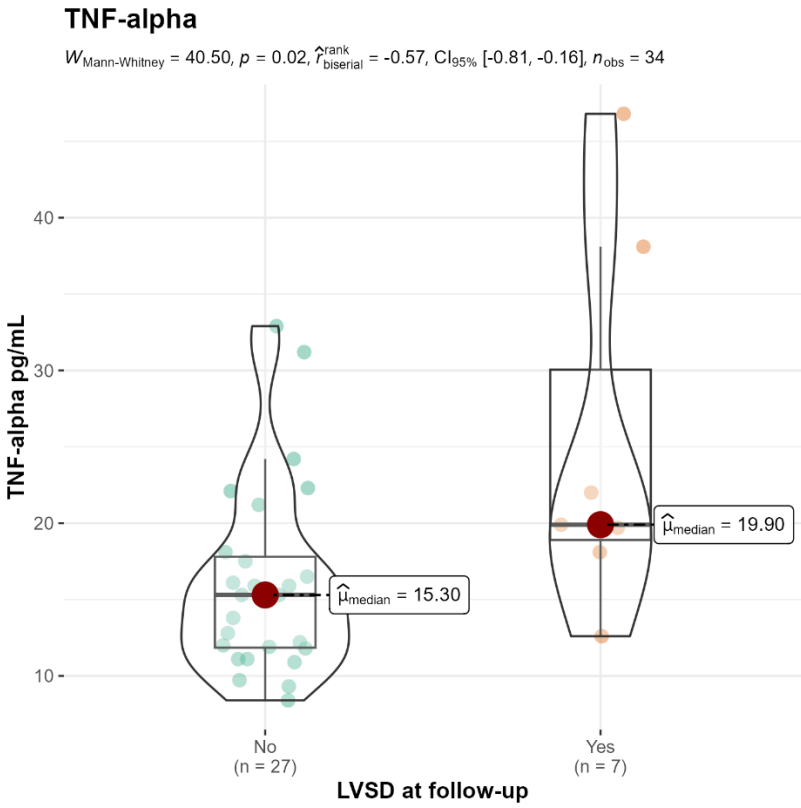


Figure 6-10 TNF at 6-10 weeks post-hospital discharge in participants with and without LVSD

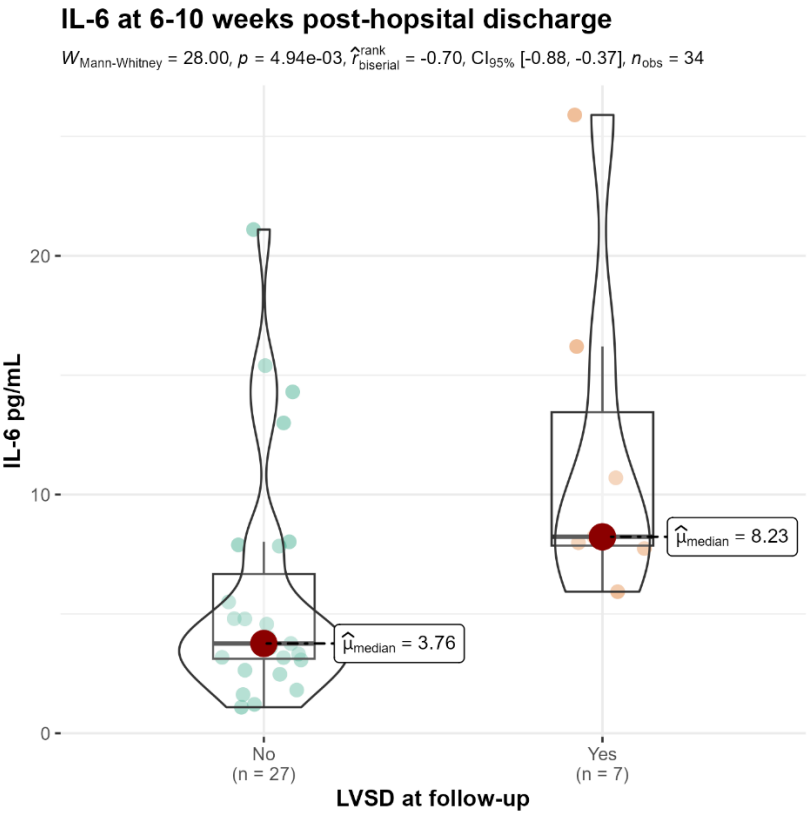


Figure 6-11 IL-6 at 6-10 weeks post-hospital discharge in participants with and without LVSD

6.3.3 Association of cardiac and inflammatory biomarkers and left ventricular systolic dysfunction

Table 6-4 displays univariate logistic regression models predicting the ability of biomarkers at recruitment to predict LVSD at follow-up. Although there were some biomarkers that demonstrated some promise (e.g. Cystatin-C), none of the recruitment biomarker models had odds ratios that achieved statistical significance.

Table 6-4 Univariate logistic regression analysis of biomarkers at point of recruitment and ability to predict LVSD

Biomarker	OR	95% CI	p-value
Cardiovascular biomarkers			
Log Recruitment NT-proBNP pg/ml	1.67	1.02, 3.29	0.077
Log Recruitment hs TnT pg/ml	1.73	0.82, 3.98	0.159
Recruitment Ca-125 u/ml	1.00	0.97, 1.02	0.918
Recruitment MR proADM nmol/L	1.22	0.78, 1.88	0.347
Renal biomarkers			
Recruitment Creatinine umol/l	1.00	1.00, 1.00	0.446
Recruitment Cystatin C mg/l	1.87	0.70, 5.02	0.197
Inflammatory biomarkers			
Recruitment hsCRP mg/l	1.00	0.99, 1.01	0.485
Recruitment Procalcitonin ng/ml	1.07	0.74, 1.45	0.661
Recruitment Ferritin ug/l	1.00	1.00, 1.01	0.183
Recruitment TNF-a pg/ml	1.01	0.95, 1.07	0.776
Recruitment IL-1B pg/ml	1.51	0.92, 2.71	0.117
Recruitment IL-6 pg/ml	1.01	0.99, 1.02	0.264
Recruitment IL-8 pg/ml	1.02	0.98, 1.06	0.345
Recruitment IL-10 pg/ml	0.99	0.89, 1.03	0.729

Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1ß=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha.

Table 6-5 demonstrates univariate logistic regression analysis of the ability of biomarkers at follow-up to predict presence of LVSD in the study cohort. Log NT-proBNP (OR 2.53 (1.33, 7.76) p=0.032), log hs-TnT (OR 3.37 (1.21, 7.76) p=0.037) and log MR-proADM (40.3 (3.13, 1943.38) p=0.022) were significantly associated with LVSD at 6-10 weeks following hospital discharge. In addition, the acute

phase inflammatory markers, Ferritin (OR 1.01 (1.00, 1.02) p=0.035), TNF-α (OR 1.13 (1.02, 1.28) p=0.032) and Interleukin-6 (OR 1.18 (1.03, 1.41) p=0.03) were also associated with LVSD.

Table 6-5 Univariate logistic regression analysis of biomarkers at 6-10 weeks post hospital discharge and ability to predict LVSD

Biomarker	OR	95% CI	p-value
Cardiovascular biomarkers			
Log Follow-up NT-proBNP pg/ml	**2.53**	**1.33, 7.76**	**0.032**
Log Follow-up hs TnT pg/ml	**3.37**	**1.21, 7.76**	**0.037**
Follow-up Ca-125 u/ml	1.03	0.90, 1.16	0.658
Log Follow-up MR proADM nmol/L	**40.3**	**3.13, 1943.38**	**0.022**
Renal biomarkers			
Follow-up Creatinine umol/l	1.01	1.00, 1.03	0.150
Follow-up Cystatin C mg/l	9.05	1.11, 134.2	0.061
Inflammatory biomarkers			
Follow-up Ferritin ug/l	**1.01**	**1.00, 1.02**	**0.035**
Follow-up hsCRP ng/ml	1.09	0.99, 1.22	0.085
Follow-up Procalcitonin ug/l	1.11	-0.21, 2.58	0.105
Follow-up TNF-a pg/ml	**1.13**	**1.02, 1.28**	**0.032**
Follow-up IL-1B pg/ml	-	-	-
Follow-up IL-6 pg/ml	**1.18**	**1.03, 1.41**	**0.032**
Follow-up IL-8 pg/ml	1.19	1.00, 1.46	0.061
Follow-up IL-10 pg/ml	0.99	0.65, 1.33	0.962

Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1ß=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha.

When further interrogated, all models of statistical significance demonstrated uniform residual distribution on QQ residual plots. However, the TNF-α model demonstrated significant heteroscedasticity when plotting scaled residuals against ranked model predictions, potentially indicating this model was unable to predict LVSD across the whole range of values.

6.3.4 Association of follow-up log NT-proBNP, patient demographics and illness characteristics

Table 6-6 displays univariate linear regression analyses exploring the association of patient and illness characteristics and log NT-proBNP 6-10 weeks post

discharge from hospital. Age (β 0.016 (-0.030, 0.063) p=0.499), Charlson comorbidity index (β 0.081 (-0.369, 0.530) p=0.727) and clinical frailty scale (β 0.209 (-0.247,0.666) p=0.375) were not associated with log NT-proBNP values at follow-up. However, multiple measures of illness severity including APACHE II (β 0.075 (0.006,0.145) p=0.041) and SOFA score (β 0.280 (0.139,0.422) p<0.001) demonstrated significant associations with follow-up values of log NT-proBNP. Furthermore, log NT-proBNP at 6-10 weeks post-hospital discharge was also significantly associated with ICU (β 0.06 (0.024, 0.097) p=0.003) and hospital length of stay (β=0.021 (0.009, 0.034) p=0.002).

Table 6-6 Patient and illness characteristics and their prediction of log NT-proBNP at 6-10 weeks post-hospital discharge

Characteristic	Beta	95% CI	p-value
Patient Characteristics			
Age (Years)	0.02	-0.03, 0.06	0.499
Charleson Comorbidity Index	0.08	-0.37, 0.53	0.727
Clinical Frailty Scale	0.21	-0.25, 0.67	0.375
Illness severity and characteristics			
APACHE II Score	**0.07**	**0.00, 0.14**	**0.045**
SOFA Score	**0.26**	**0.12, 0.39**	**<0.001**
Duration mechanical ventilation (days)	**0.06**	**0.01, 0.11**	**0.026**
Duration cardiovascular support (days)	**0.10**	**0.03, 0.16**	**0.008**
Duration of RRT (days)	**0.11**	**0.03, 0.19**	**0.019**
ICU length of stay (days)	**0.06**	**0.02, 0.10**	**0.003**
Hospital length of stay (days)	**0.02**	**0.01, 0.03**	**0.002**

Abbreviations: APACHE=Acute physiology and chronic health evaluation, ICU=Intensive care unit RRT=Renal replacement therapy, SOFA=Sequential organ failure evaluation

6.3.4.1 Illness severity scores

Figure 6-12 and Figure 6-13 display the association of illness severity scores with NT-proBNP at 6-10 weeks post-hospital discharge.

In addition to being significantly predictive of log NT-proBNP at follow-up, both APACHE II score and SOFA score demonstrated significant correlation with log NTpro-BNP, with moderate spearman correlation coefficients in both plots, APACHE II (r=0.35 ,p=0.045), SOFA score (r=0.55, p<0.001). However, in validation of the SOFA score model, plotting scaled residuals against simulated residuals demonstrated deviations in lower residual quantiles indicating lack of predictive ability across the whole model.

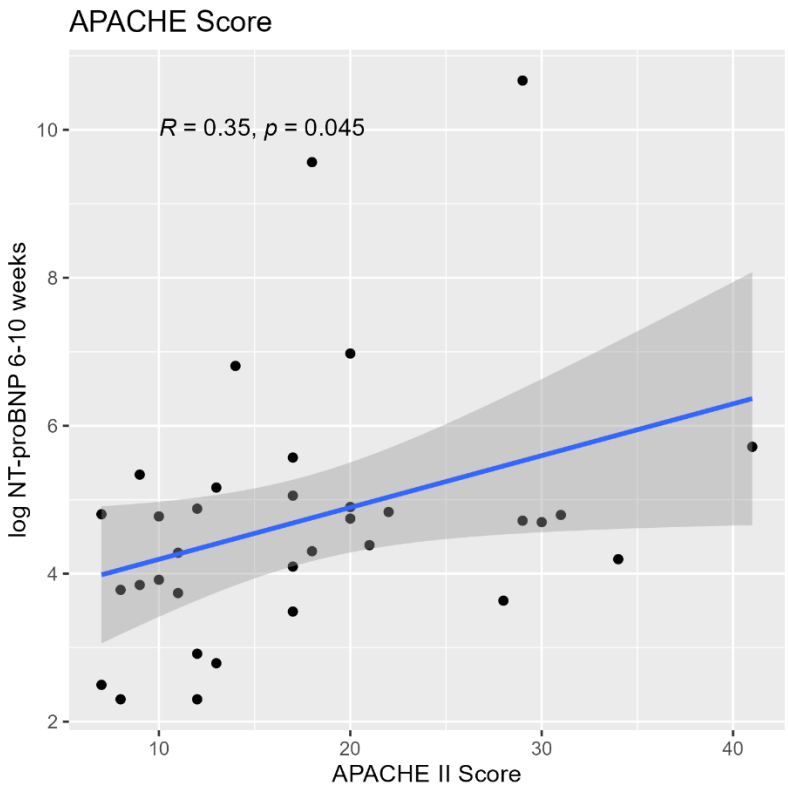


Figure 6-12 Association of APACHE II with log NT-proBNP values at 6-10 weeks post-hospital discharge

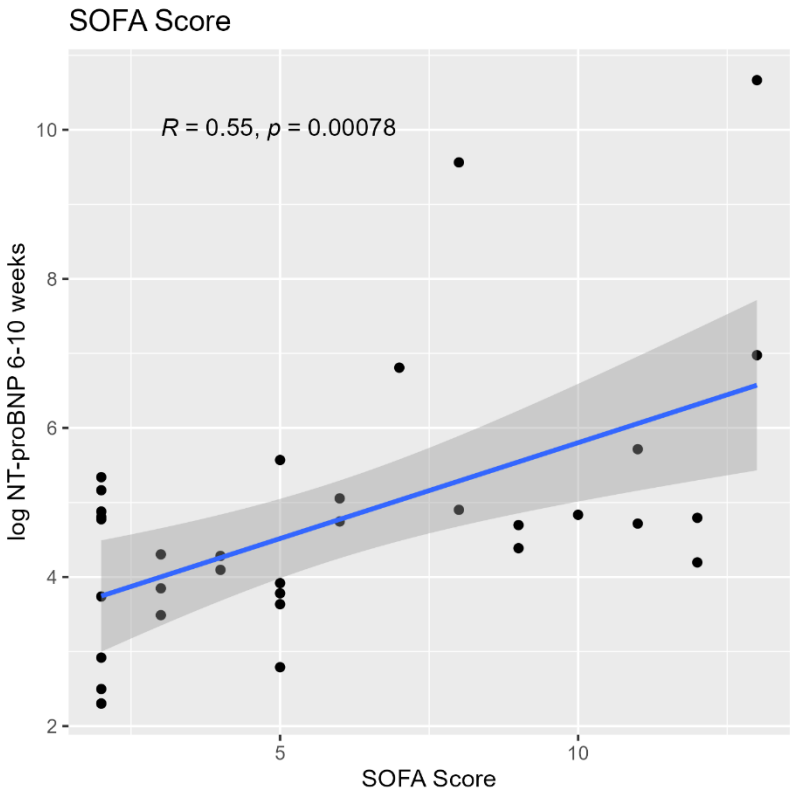


Figure 6-13 Association of SOFA score on admission with log NT-proBNP values at 6-10 weeks post-hospital discharge

6.3.4.2 Duration of organ support

Similar results were generated when exploring association with duration of organ support. Although duration of mechanical ventilation (Figure 6-14) and CV support (Figure 6-15) demonstrated significant predictive ability for log NT-proBNP, visual inspection identified outliers that were likely to impact the model.

6.3.4.3 Length of stay

Despite clear outliers on visual inspection of ICU (Figure 6-16) and hospital (Figure 6-17) LOS, there were no significant violations of overall goodness of fit testing or across different quantiles of scaled residuals, indicating model integrity across the range of observed values. Similarly, models retained predictive value when participants with extended ICU or hospital LOS were removed from the analysis.

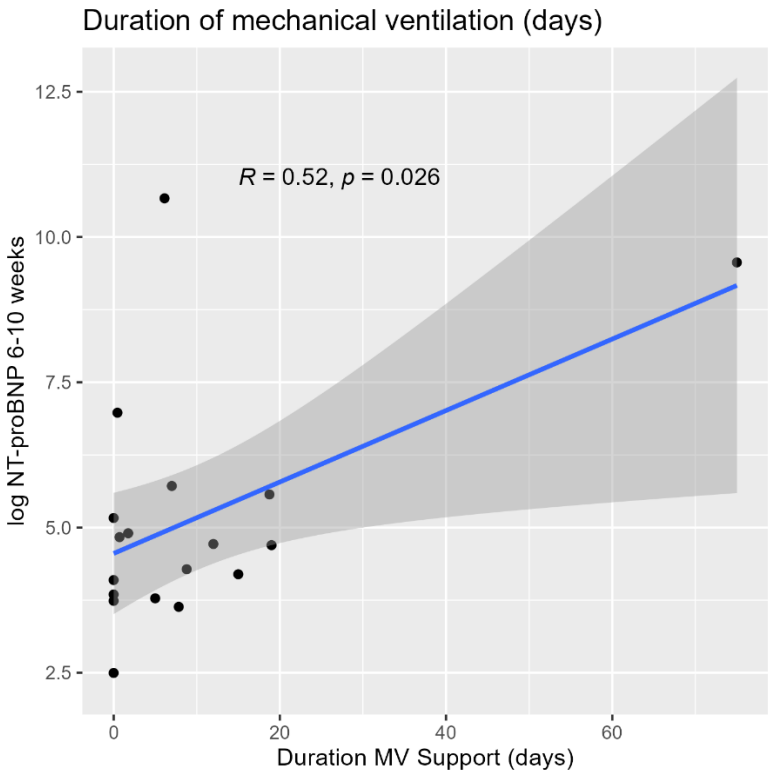


Figure 6-14 Association of duration of mechanical ventilation (days) and log NT-proBNP values at 6-10 weeks post-hospital discharge

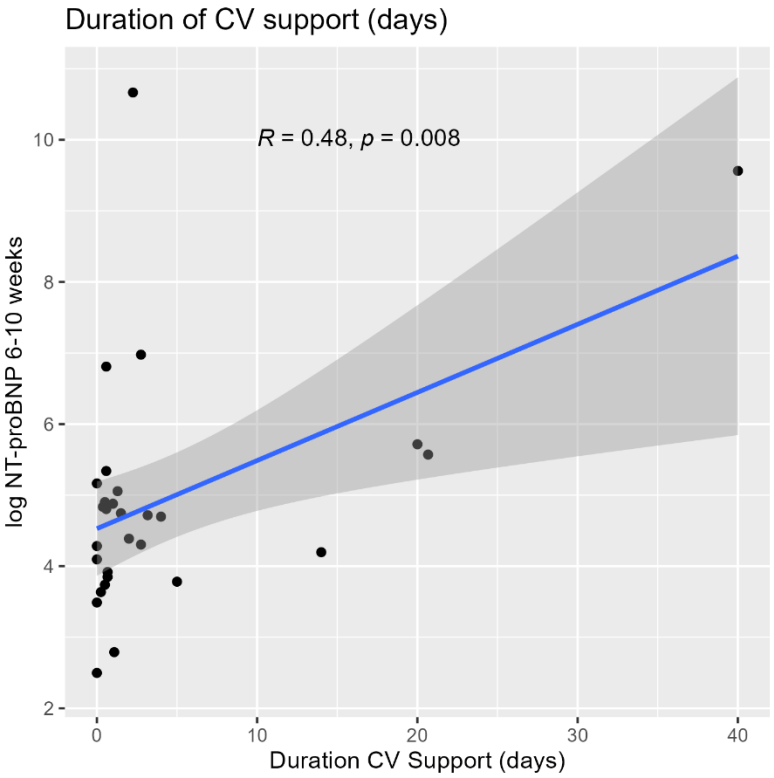


Figure 6-15 Association of duration of cardiovascular support (days) and log NT-proBNP values at 6-10 weeks post-hospital discharge

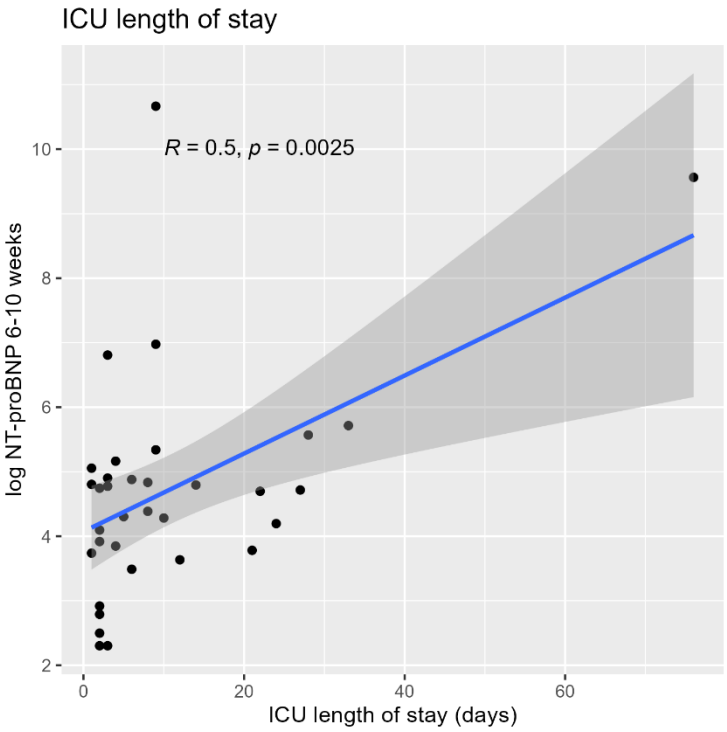


Figure 6-16 Association of ICU length of stay with log NT-proBNP values at 6-10 weeks post-hospital discharge

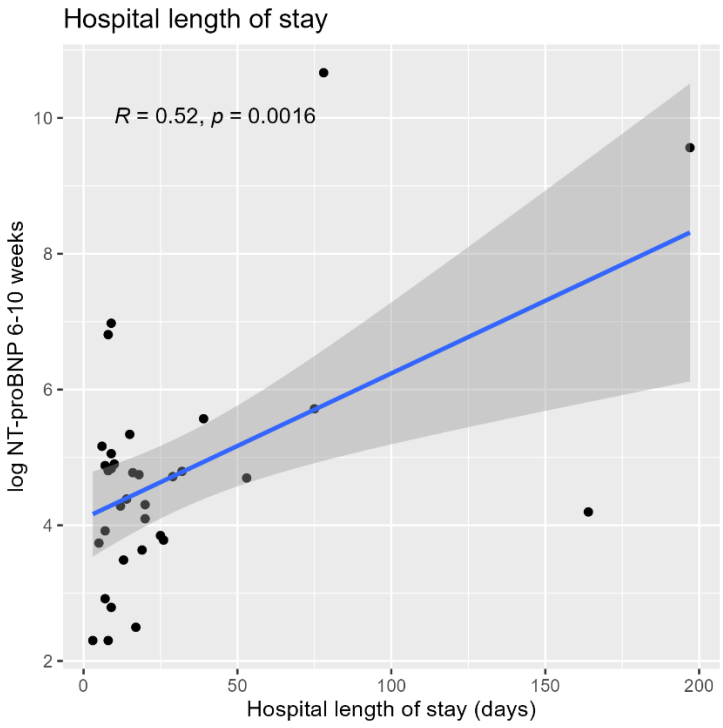


Figure 6-17 Association of hospital length of stay with log NT-proBNP values at 6-10 weeks post-hospital discharge

6.3.5 Association of log NT-proBNP at 6-10 weeks post-hospital discharge with biomarkers of cardiovascular dysfunction, renal function and inflammation

6.3.5.1 Recruitment biomarkers

Table 6-7 displays univariate linear regression models exploring the association between biomarkers at the point of recruitment (ICU discharge) and log NT-proBNP at 6-10 weeks post-hospital discharge.

Table 6-7 Univariate linear regression analysis of biomarkers at point of recruitment and ability to predict log NT-proBNP at follow-up

Biomarker	Beta	95% CI	p-value
Cardiovascular biomarkers			
log Recruitment NT-proBNP pg/ml	**0.50**	**0.25, 0.74**	**<0.001**
log Recruitment hs TnT pg/ml	**0.79**	**0.31, 1.27**	**0.003**
Recruitment Ca-125 u/ml	**0.02**	**0.00, 0.03**	**0.076**
Recruitment MR-pro ADM nmol/L	**0.51**	**0.22, 0.80**	**0.002**
Renal biomarkers			
Recruitment Creatinine umol/l	**0.00**	**0.00, 0.01**	**0.024**
Recruitment Cystatin C mg/l	**1.01**	**0.33, 1.68**	**0.006**
Inflammatory biomarkers			
Recruitment hsCRP mg/l	0.00	0.00, 0.01	0.174
Recruitment Procalcitonin g/ml	0.14	-0.10, 0.38	0.265
Recruitment TNF-a pg/ml	0.02	-0.02, 0.06	0.348
Recruitment IL-1B pg/ml	-	-	-
Recruitment IL-6 pg/ml	0.01	0.00, 0.02	0.055
Recruitment IL-8 pg/ml	0.04	0.01, 0.07	0.005
Recruitment IL-10 pg/ml	0.00	-0.03, 0.04	0.808

Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1β=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha

There are significant relationships between log NT-proBNP at 6-10 weeks following hospital-discharge and values of log NT-proBNP at recruitment (β=0.50 (0.25, 0.74) p<0.001) and log hs-TnT (β=0.79 (0.31, 1.27) p=0.003) (Figure 6-18 - Figure 6-19).

Ca-125 (β 0.02 (0.00, 0.03) p=0.076), MR-proADM (β 0.51 (0.22, 0.80) p=0.002) and Cystatin C (β=1.01 (0.33, 1.68) p=0.006) also demonstrated ability to predict NT-proBNP values at 6-10 weeks post-hospital discharge.

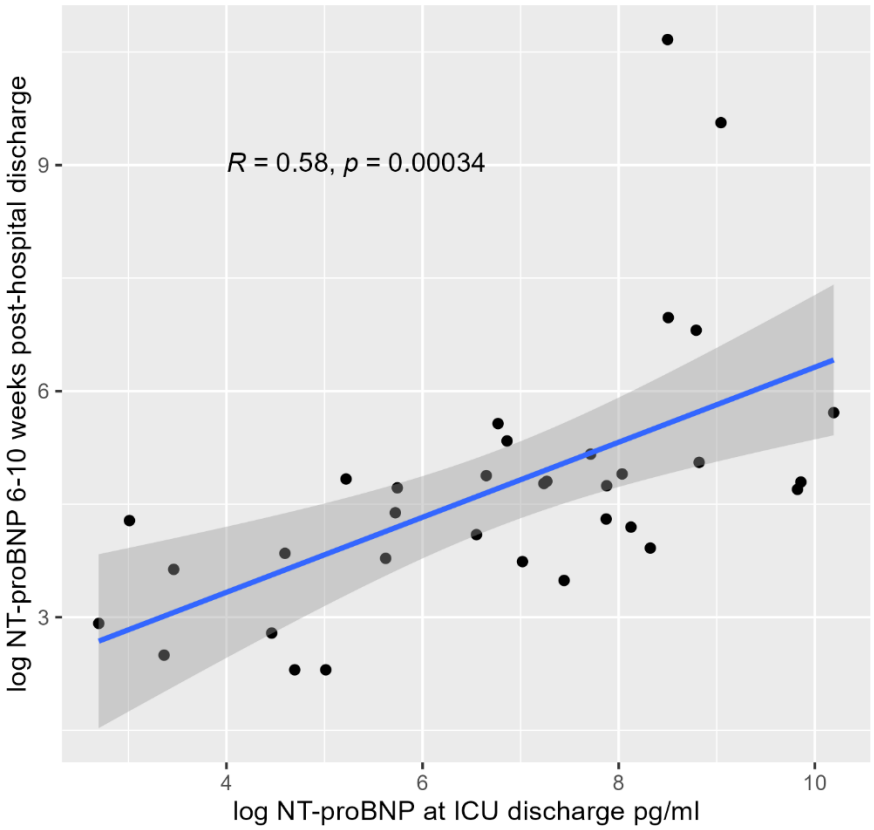


Figure 6-18 Association of log NT-proBNP at ICU discharge and log NT-proBNP at 6-10 weeks post-hospital discharge

Log NT-proBNP demonstrated significant ability to predict log NT-proBNP at follow up.

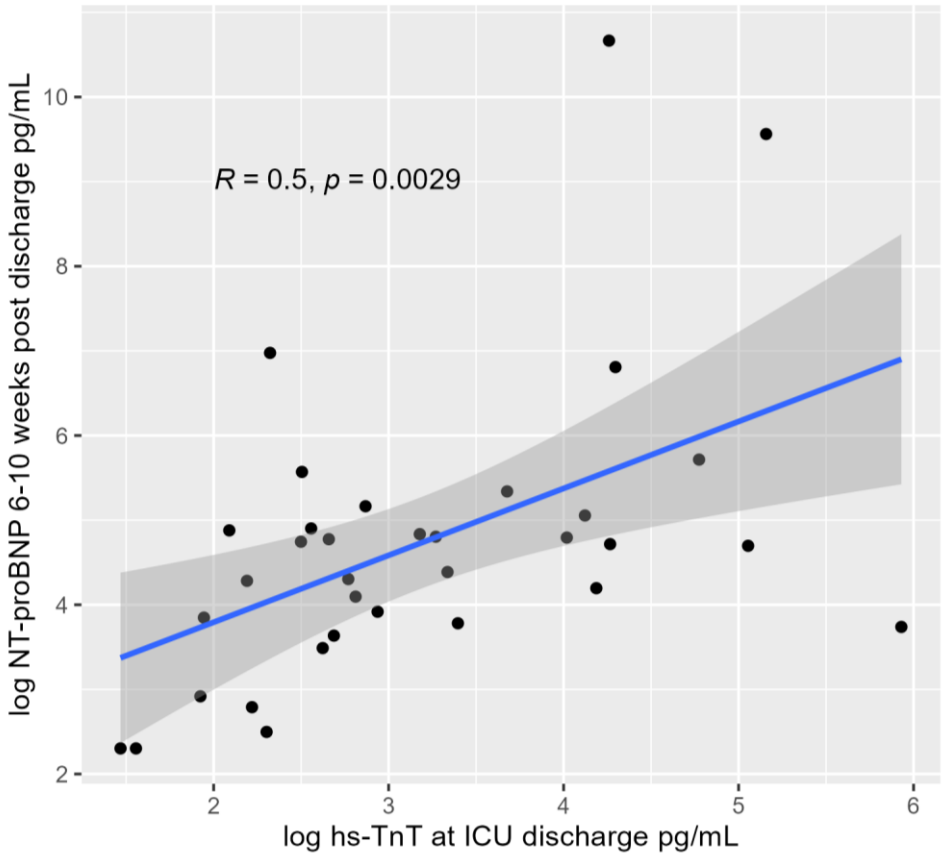


Figure 6-19 Association of log NT-proBNP at ICU discharge and hs-TnT at 6-10 weeks post-hospital discharge

6.3.5.2 Follow-up biomarkers

There were multiple observed associations with log NT-proBNP and biomarkers of cardiovascular dysfunction, renal dysfunction and inflammation at 6-10 weeks post-hospital discharge. However, despite statistical significance, many of these associations were modest and on further validation, although they did not violate overall goodness of fit testing, residuals deviated depending on quantile of residuals assessed.

Hs-TnT demonstrated significant ability to predict log NT-proBNP at follow-up (ß 0.04 (0.03, 0.06) p<0.001). Despite apparent outliers on visual inspection (Figure 6-20), the model met overall goodness of fit testing and was consistent across quantiles of residuals.

Table 6-8 Univariate linear regression analysis of biomarkers at 6-10 weeks post-hospital discharge and prediction of follow-up log NT-proBNP

Biomarker	Beta	95% CI	p-value
Cardiovascular biomarkers			
Follow-up hs TnT pg/ml	**0.04**	**0.03, 0.06**	**<0.001**
Follow-up Ca-125 u/ml	**0.10**	**0.01, 0.18**	**0.028**
log Follow-up MR proADM nmol/L	**2.52**	**1.77, 3.27**	**<0.001**
Renal biomarkers			
Follow-Up Creatinine umol/l	**0.02**	**0.01, 0.03**	**<0.001**
Follow-up Cystatin C mg/l	**2.48**	**1.24, 3.73**	**<0.001**
Inflammatory biomarkers			
Follow-up ferritin ug/l	**0.01**	**0.00, 0.01**	**0.006**
Follow-up hsCRP mg/l umol/l	0.06	-0.02, 0.14	0.14
log Follow-up Procalcitonin ng/ml	**9.67**	**4.11, 15.23**	**0.002**
Follow-up TNF-a pg/ml	**0.14**	**0.08, 0.19**	**<0.001**
Follow-up IL-1B mg/ml	**-**	**-**	**-**
Follow-up IL-6 pg/ml	**0.19**	**0.10, 0.27**	**<0.001**
Follow-up IL-8 pg/ml	**0.18**	**0.07, 0.29**	**0.003**
Follow-up IL-10 pg/ml	0.16	-0.06, 0.38	0.17

Ca125=Cancer Antigen 125. hs-CRP= High-sensitivity C-reactive protein. Hs-TnT= High Sensitivity Troponin T. IL-1ß=Interleukin-1 beta, IL-6=Interleukin-6. IL-8=Interleukin-8. IL-10=Interleukin-10. MR-proADM= Mid-regional proadrenomedullin (MR-proADM), NT-proBNP= N-terminal pro-B-type natriuretic peptide. TNF-α= Tumour necrosis factor-alpha

Of the remaining follow-up biomarkers, only Cystatin C and Procalcitonin demonstrated ability to predict log BNP at 6-10 week follow-up reliably across a range of values. In these models, Spearman correlations were significant, Cystatin C ($r=0.57$, $p<0.001$), and Procalcitonin ($r=0.52$, $p=0.002$).

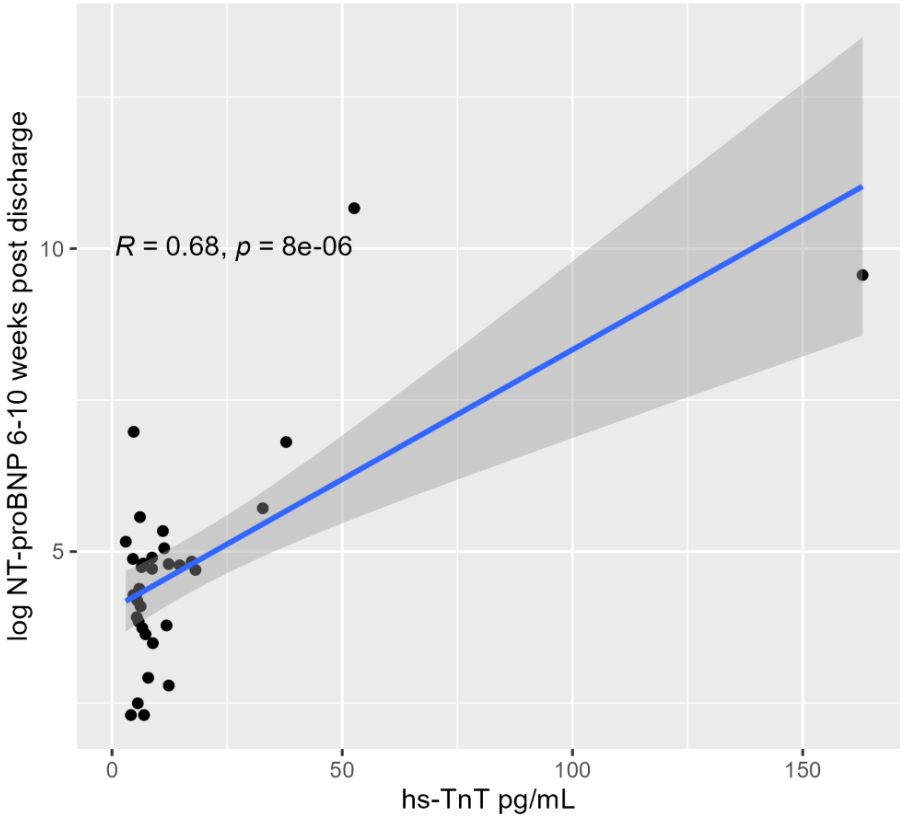


Figure 6-20 Association of hs-TnT values with log NT-proBNP values at 6-10 weeks post-hospital discharge

6.3.6 NTproBNP thresholds and recruitment NT-proBNP values

Figure 6-21 demonstrates the median values of NTproBNP at recruitment, categorised by established thresholds in heart failure diagnosis at 6-10 weeks post-hospital discharge. Participants in higher categories of NT-proBNP at follow-up had significant differences in median values of NTproBNP at ICU discharge (505.25 vs 1596.25 vs 5754.50pg/ml, p=0.019). A univariate cumulative regression model demonstrated significant ability of log NTproBNP values at ICU discharge predict follow up categories of NT-proBNP threshold at 6-10 weeks post-hospital discharge, (OR 1.80 (1.42, 2.29) p =0.016).

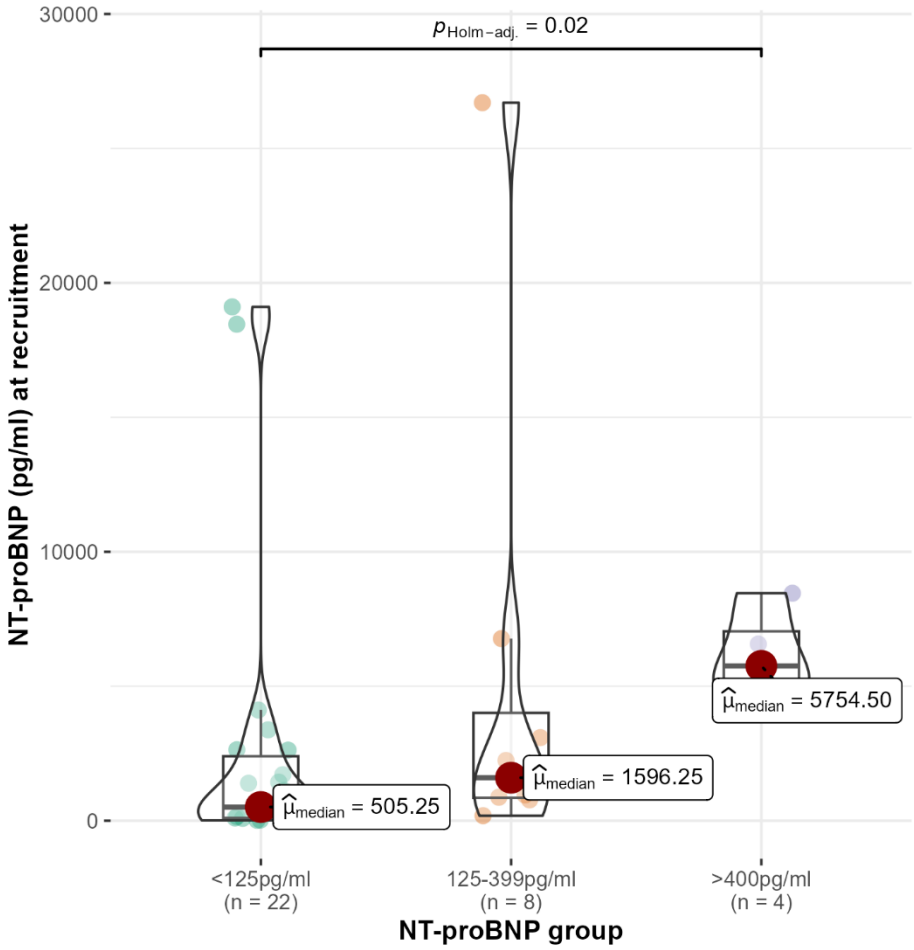


Figure 6-21 Median NT-proBNP values at recruitment by NT-proBNP threshold at 6-10 weeks post hospital discharge. (N-terminal brain-natriuretic peptide, NT-proBNP)

6.3.7 Association of established NT-proBNP thresholds and patient or illness characteristics and left ventricular systolic dysfunction

Univariate logistic regression modelling demonstrated NT-proBNP values >400 were predicted by SOFA Score (OR 1.49 (1.09, 2.42) p=0.035). Furthermore, cumulative regression analysis also demonstrated SOFA score was significantly associated with progression through ordinal BNP thresholds used in clinical practice i.e. ≤125, 126-400 and >400 pg/ml (OR 1.24 (1.02, 1.53) p=0.037). Median SOFA score on admission differed significantly (p=0.040) in patients with higher NT-proBNP values at 6-10 weeks following discharge from hospital. Neither a single threshold of NT-proBNP ≥400pg/ml, nor NT-proBNP thresholds of <125, 126-400 or >400pg/ml were associated with any other patient demographic or illness characteristics including age, sex, frailty, comorbidity index, hypertension, diabetes, APACHE II, duration of organ support or LOS.

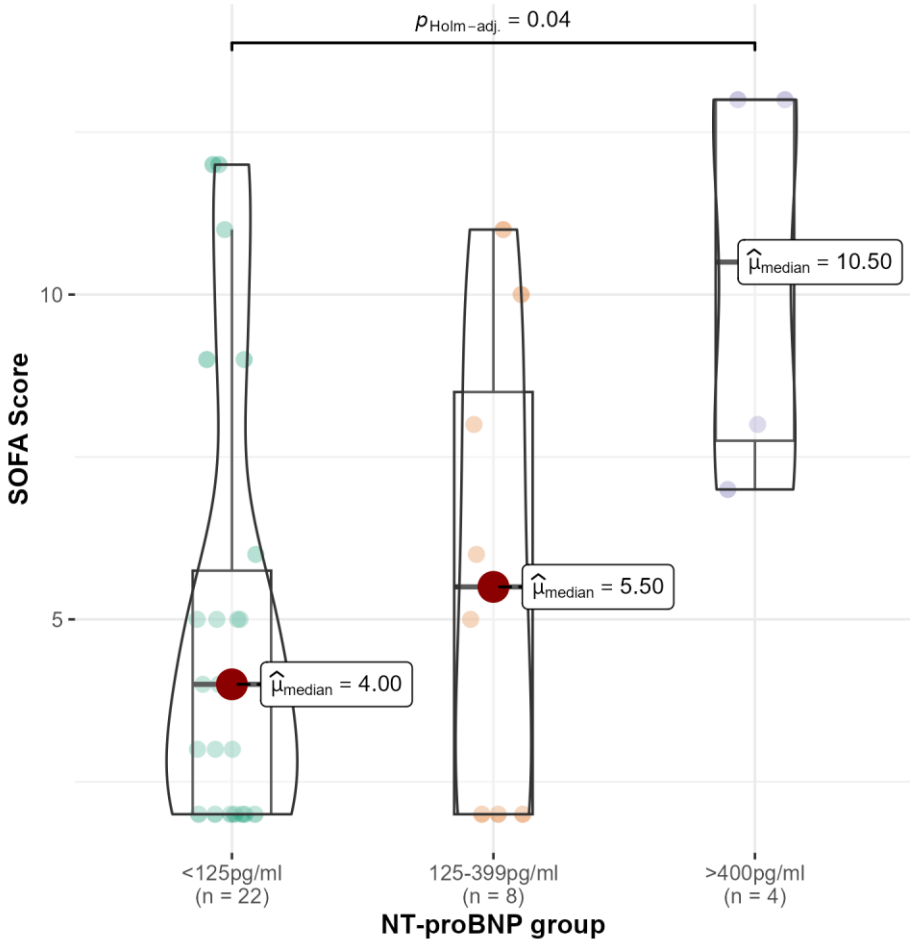


Figure 6-22 Median SOFA score on admission grouped by category of NT-proBNP 6-10 weeks post hospital discharge

6.4 Discussion

This chapter explores cardiac, renal and inflammatory biomarkers at recruitment and 6-10 weeks post-hospital discharge and explores their relationship with CMR findings at the same follow-up timepoint. The results demonstrate marked rises in NT-proBNP, well above reference range, across the study cohort on discharge from ICU. At follow-up, values remained high in participants with LVSD, and at thresholds supporting investigation with cardiovascular imaging in other populations.[125 243]

Study participants also had abnormal median values of cardiac injury and inflammation at recruitment. Many of these biomarkers fell back within reference ranges in the majority of patients at follow-up. However, for key biomarkers such as NT-proBNP, hs-TnT and Cystatin C, median values remained significantly different in patients who had LVSD, and within clinically significant ranges. The cohort of participants with LVSD also had differences in median

values of the inflammatory biomarkers, TNF-α and IL-6. These findings demonstrate a number of key points.

It is clear that across the whole study population, the majority of patients demonstrated biochemical evidence of significant myocardial strain and dysfunction immediately following an ICU admission with sepsis. These values were particularly high in patients with LVSD at follow-up, and at levels that have been associated with an increased mortality risk in other populations (e.g. de-novo or acute decompensated heart failure).[266 267] In participants with LVSD, the significant differences in biomarker profiles are supportive of myocardial wall stretch, cardiomyocyte injury (hs-TnT) and persistent inflammation.

NT-proBNP is not only associated with adverse cardiovascular outcomes, but has also predicted mortality in patients with critical illness following ICU discharge.[119] The high values in this study at discharge are consistent with other critical illness datasets, supporting their validity. Given the diagnostic and prognostic utility of NT-proBNP in other settings,[263 290] it is intriguing to consider whether NT-proBNP could be used as a prognostic marker for long-term cardiovascular outcomes in patients with critical illness, either on discharge from ICU or at a later stage during convalescence. Although not statistically significant, the markedly elevated values in participants who had LVSD (median 4908pg/ml) appear clinically important. Future adequately powered research should investigate this relationship further.

There are of course many other causes of abnormal NT-proBNP values beyond cardiac dysfunction, including critical illness and sepsis in their own right.[291 292] However, in this analysis NT-proBNP values at 6-10 weeks differed not only in terms of statistical significance, but median values of those with LVSD were within a clinically significant threshold.[125] This supports the hypothesis that in ICU survivors with signs and symptoms of heart failure, NT-proBNP may have utility when used in a similar manner to patients in the general population in diagnosing chronic heart failure. Furthermore, when stratified into conventional NT-proBNP thresholds used in NICE or ESC, increasing NT-proBNP was significantly associated with the presence of LVSD. Future work is required to explore whether this hypothesis is supported controlling for other clinically important variables.

From a mechanistic perspective, the study demonstrates a number of associations. NTproBNP values at follow-up were consistently associated with severity of illness scores, duration of cardiovascular or ventilatory support and also hospital and ICU LOS. Whilst these models are exploratory in nature, it supports the hypothesis that prolonged admissions with severe critical illness may be associated with cardiovascular injury and strain, for which there may be long term consequences. There are multiple interrelated and interdependent factors at play during intensive care admission, for example pre-existing co-morbidity, factors related to precipitating pathogens, disease trajectory and of course specific treatments required.[41 184] Specifically, ICU admission with severe illness often involves treatments that confer significant cardiovascular and haemodynamic stress, for example: vasoactive medications that increase myocardial contractility and systemic vascular resistance; the haemodynamic effects of prolonged mechanical ventilation; or indeed the cessation of drugs to avoid acute complications that in the long term are beneficial for chronic cardiovascular disease such as angiotensin converting enzyme (ACE) inhibitors or Sodium-Glucose Transport-2 (SGLT2) inhibitors.[184] Many patients are also noted to have septic cardiomyopathy in ICU.[100] Whilst these conditions are traditionally thought to have resolved, there are scant real-world data to support this hypothesis.[162 293] The data in this chapter support the mechanistic association between severe illness and biochemical CMR evidence of myocardial dysfunction and injury that persists weeks beyond discharge from hospital.

Biomarkers of inflammation and renal dysfunction were associated with both LVSD and increased values of NT-proBNP. There is much evidence examining the role of inflammation in the pathogenesis of chronic heart failure and an evolving body of literature that describes mechanisms of persistent inflammation following critical illness and the potential role in chronic cardiovascular disease.[82 107] The data in this chapter is in keeping with other studies that demonstrate increased inflammatory biomarkers in some cohorts of patients persisting following discharge, and support the possible underlying mechanistic association with chronic cardiac dysfunction with persisting inflammation following sepsis admission.[110]

Lastly, the data in this chapter support the need for ongoing mechanistic work to examine an apparent association between biomarkers of cardiovascular

dysfunction, renal disease, inflammation and imaging findings. Data could be used to evaluate for more detailed models and planning of further mechanistic work, observational studies and clinical trials.

6.4.1 Limitations

There are limitations to this area of the study. As with the previous chapter, the relatively small sample size (n=34) limits statistical power and ability to conduct multivariate analysis and determine any definitive associations. Similarly, because of the inherent skew and non-normal distribution of biomarkers used in clinical practice, models must be interpreted with caution with regard to their generalisability. Nonetheless, significant efforts were undertaken to ensure any models presented were predictive across the whole dataset, with goodness of fit testing and comparisons of scaled residuals against predicted data, so that meaningful conclusions could be drawn as far as the data allows.

As with the previous chapter, it may be that findings were confounded by participants with a prior burden of unidentified cardiovascular disease. Nonetheless, these patients would still have likely been admitted to ICU on the basis of other clinical factors. This still presents us with the problem of large numbers of survivors who may have acquired a meaningful risk of (if not established) cardiovascular disease following admission. As such, there is much work to do to find out how we might better identify these patients and improve their future recovery trajectory.

6.5 Conclusion

This chapter demonstrates that participants without prior known cardiovascular disease had biochemical evidence of cardiovascular and renal dysfunction that was associated with LVSD on follow-up imaging. Biomarkers of cardiovascular dysfunction were associated with biochemical evidence of inflammation, severity of illness and hospital LOS. Conventional clinical thresholds for raised NT-proBNP also conferred a higher risk of LVSD and this may be of utility in this population of patients to help stratify those at risk of adverse cardiovascular outcomes.

Chapter 7 Patient-reported outcome measures in ICU survivors of sepsis

7.1 Introduction

This chapter presents results of patient-reported outcome measures (PROMs) collected at 6-10 weeks post-hospital discharge in participants who were admitted to intensive care with sepsis. It also describes their relationship with patient demographics, illness characteristics, CMR findings and biomarkers of cardiovascular dysfunction and inflammation.

The chapter will outline PROMs utilised in the study and the rationale for their inclusion. It will go on to describe the methodology involved in their collection and analysis. It will present a descriptive summary of the study cohort at 6-10 weeks post-hospital discharge

7.1.1 Patient important outcomes

In 2024, the James Lind alliance reported their 'top 10' research priorities for sepsis research, integrating the views of patients, relatives and health professionals from multiple disciplines.[97] They identified the long-term consequences of sepsis as a research priority, aligning with prior literature that highlights 'patient important outcomes' as a priority for inclusion in critical care research.[294]

The concept of patient important outcomes has been prevalent in other fields of research for some time. The evolution of Post Intensive Care Syndrome (PICS) as a concept, and the heterogenous array of impairments it encompasses, has highlighted the need for a focus on understanding these outcomes and their underlying drivers.[294 295] Even in the last decade, a systematic review evaluating the prevalence of patient important outcomes in critical care trials demonstrated that beyond mortality, only 10% of articles published across an entire year of randomised controlled trials reported any other patient-important outcomes (for example physical function, quality of life measures or cognitive function), highlighting the need for better inclusion.

These findings also pose questions regarding what is indeed considered a patient important outcome. In a well-conducted qualitative analysis of interviews with critical care survivors of acute respiratory failure (ARF), domains such as physical function, cognitive function, mental health and return to work emerged as consistent themes reported by patients, families and researchers.[296] These findings served as the basis for the researchers to convene an international panel comprising of patients, caregivers and clinicians to participate in a modified Delphi process with the aim of identifying a core-outcome set and a core outcome *measurement* set for survivors of acute respiratory failure after critical care admission.[294 296] The panel identified: survival, health-related quality of life (HRQoL), mental health, pain, cognition, physical function, muscle or nerve function, and pulmonary function as key domains for assessment.

Consensus for inclusion of outcome measures in the core set required that - a priori - 70% of respondents deemed the outcome measure as 'critical'. In addition, if >15% of respondents indicated the measure was 'not important', then these were not included, ensuring that if minority stakeholder groups consistently rated outcome measures as unimportant then this was adequately accounted for. Recommended core outcome measures for survivors of ARF included: EQ-5D (3L or 5L version) for measurement of HRQoL, and/or the Short-Form-36. The hospital anxiety and depression scale (HADS) was recommended for assessment of mental health issues. Other PROMs which were reported for consideration (although did not reach consensus) were the Montreal-cognitive assessment (MOCA), the 6-minute walk test (6-MWT) and grip-strength testing.[55 297 298]

Whilst findings represent outcome sets for survivors of ARF as a distinct cohort, there is clear overlap between the problems often experienced by survivors of ARF on discharge and recovery and those who had other critical illness syndromes (such as sepsis). Thus, the outcome measures achieved here by consensus were judged to be important in measuring patient important outcomes in this study.[2 5 30 31 299]

7.1.2 Euro-QoL 5D-5L Descriptive System

The Euro-QoL 5D-5L (EQ-5D-5L) was first introduced by the EuroQol group as an outcome measure of HRQoL in 2009. The EQ-5D-5L comprises of two main components, the health utility score (HUS) and the visual analogue scale (VAS). The HUS assesses 5 domains: Mobility; self-care; usual activities; pain or discomfort; and anxiety or depression. The tool is displayed in Appendix 9.

Participants are asked to best rate the degree of problems they have in each domain, with all domains stratified by the levels: Unable/no problems (1); mild (2); moderate (3); severe (4) and unable/extreme problems (5).[300] For example, for the mobility domain, participants are asked to best rate their mobility by choosing one of the following statements: "I have no problems in walking about" (1), "I have slight problems walking about", "I have moderate problems walking about" (3), "I have severe problems walking about"(4), or "I am unable to walk about"(5). Thus, across the 5 domains, participants may report a score in the form of '33434', which in this case would indicate a degree of moderate or severe impairments across every domain.

Measurement of these impairments have a clear floor and ceiling, with participants rating themselves as having 'no problems' or being 'unable' to undertake activities. However, categories in between (i.e. mild/ moderate/ severe) are self-reported, not quantifiable or directly comparable on their own. To overcome this, values obtained in each level can be converted into a 'value-set' which allows the generation of an overall score for 'health-utility states' (HUS). The HUS scores at '1', indicating of full health and '0' a state equivalent to death. Values less than '0' are possible and conceptualised as health states 'worse than death'.[301] Whilst there is a published value-set for the EQ-5D-5L for the UK population, the National Institute for Clinical Excellence (NICE) have raised concerns about the quality and reliability collected in the valuation study upon which these values are based. As such, NICE currently recommend the 'crosswalk' method, published by van Hout et al to create value sets in the UK, mapping EQ-5D-5L values back onto prior validated EQ-5D-3L measures. As such, these values have been used in this thesis.[301-303]

The EQ-5D-5L also has a 'visual analogue scale' (VAS), where users are asked to self-rate their health on a scale of 0-100 on day of completion, 0 being the worst health and 100 being the best health. For the EQ-5D-5L summary measures, the minimally clinically important difference[8] is determined to be 0.08 and 8 for health-utility state and visual analogue scales respectively.[305 306]

7.1.3 Hospital anxiety and depression score

The hospital anxiety and depression score (HADS) was used to explore mental health outcomes in this study, in-keeping with the suggested core outcome set described above. It is a 14 item questionnaire asking participants their level of agreement with statements that correlate with anxiety or depressive symptoms Appendix 10.[307]

The 7 items that correlate with anxiety form the subscale HADS-A, whereas the 7 items correlating with depressive symptoms form the HADS-D score, with each item having 4 levels, 0, 1, 2 and 3. Thus, scores for HADS-A and HADS-D can maximally score 21 in each subscale. Generally, scores ≥8 are considered as cut-offs as a screening tools for anxiety or depression, with scores ≥15 indicating severe symptoms.[308 309]

7.1.4 Duke activity status index

The Duke Activity Status Index (DASI) was developed in 1989 and was designed and validated as a patient reported measure of functional capacity, correlating with peak oxygen capacity on exercise testing.[310] It is a 12 item questionnaire asking participants to indicate 'Yes' or 'No' with regard to their ability to undertake various activities, e.g. Is the patient able to "run a short distance?". Each item correlates to a numerical score, each with different weightings which are totalled following completion of the questionnaire. The maximum possible score is 58.2.

DASI has been shown to correlate with HRQoL and adverse cardiovascular events in the heart failure population[311] and with formal exercise testing in the chronic obstructive pulmonary disease (COPD) population.[312] DASI at peri-operative

[8] The minimal clinically important difference (MCID) is defined as the smallest benefit of value to patients.[304]

assessment has been associated with death, myocardial injury and moderate to severe complications in patients undergoing non-cardiac surgery.[313] In general, a DASI score of ≥34 has been associated with lower rates of death or myocardial injury in peri-operative populations. In patients with chronic heart failure, DASI scores <40 have a predicted two-fold increased risk of all-cause mortality.[314]

DASI is included to explore the relationship between functional capacity and key characteristics related to sepsis admission and follow-up.

7.1.5 Short-Form-36 Vitality domain

Fatigue is a common symptom in survivors of critical illness and a suggested core outcome domain.[297] This thesis utilises the vitality domain of the Short-form-36 (SF-36), a score used to evaluate HRQoL by asking questions related to physical functioning; emotional well-being; role limitations due to physical or emotional problems; energy and fatigue; social functioning; pain and general health.[232]

In a recent meta-analysis, the vitality domain has been demonstrated to capture fatigue in survivors of critical with scores reaching a nadir within 1 month of discharge.[233] Whilst the SF-36 is not recommended as a *core* outcome measure, this thesis uses SF-36 vitality domain to augment EQ-5D-5L scores as an extended assessment of HRQoL Appendix 11.

7.1.6 MRC Dyspnoea Scale

The MRC dyspnoea scale has been studied extensively in respiratory populations. It is a 5 level ordinal scale, ranging from 0 (dyspnoea only with strenuous exercise) to 4 (too dyspnoeic to leave the house or breathless when dressing).[315] It has been integrated into the body mass, airflow obstruction, dyspnoea and exercise capacity (BODE) index, a measure for estimating mortality in populations with airways disease and is recommended in international guidelines for management of chronic obstructive lung disease.[316] [317] Given pulmonary function has been identified as a core outcome following critical illness, it is prudent to include a specific outcome measure for breathlessness Appendix 12.[297]

7.2 Methods

7.2.1 Study design

The study design has been outlined in detail in Chapter 3. Survivors of an ICU admission with sepsis with no prior known cardiovascular disease or immune dysfunction were followed up 6-10 weeks following discharge from hospital where they underwent CMR imaging, biomarker analysis and completed a series of PROMs.

Recruitment took place in two general ICUs in the West of Scotland. All follow-up appointments for participants in the CMR imaging arm of the study, took place in the Clinical Research Facility of the Queen Elizabeth University Hospital campus and were conducted by research fellows.

The relationship between exercise capacity, HRQoL, CMR findings and cardiac, renal and inflammatory biomarkers was explored. Key objectives were to:

- Describe patient-reported outcome measures in ICU survivors of sepsis.
- Explore the association with left ventricular systolic dysfunction (LVSD) and measures of exercise capacity or HRQoL at 6-10 weeks following hospital discharge
- Explore associations with biomarkers of cardiovascular and renal dysfunction or inflammation and PROMs in ICU survivors of sepsis.
- Explore whether patient demographics, illness characteristics or biomarkers during ICU admission with sepsis can predict exercise capacity or HRQoL in the study population.
- Explore whether there is a burden of anxiety or depression at 6-10 weeks post hospital discharge and whether this is associated with exercise capacity and HRQoL

7.2.2 Outcome measures

The outcome measures recorded were as follows:

- Duke Activity Status Index (DASI)[310]
- MRC Dyspnoea Scale[315]
- EuroQoL EQ-5D-5L Scale[300]
- Hospital anxiety and depression score (HADS)[307]
- Short Form-36 (Fatigue Domain)[318]

Research fellows ensured that participant answers were entirely self-reported, and assisting participants only should they require clarification regarding conceptual understanding of components of the PROMs or further explain wording.

The association of demographics, illness characteristics, CMR findings and biomarkers with PROMs was explored by modelling the predictive ability of select variables to predict DASI scores and the overall summary measures of EQ-5D-5L (overall health-utility state and visual analogue scores).

7.2.3 Statistical analysis

Data are presented as medians (Q1, Q3) for continuous variables, or proportions n(%) for categorical variables. Median values and proportions of the overall cohort were tabulated to characterise overall degree of exercise capacity and HRQoL. To explore the relationship with LVSD, exercise capacity and HRQoL, median values and proportions were tabulated by LVSD. Wilcoxon rank sum tests, Kruskall-Wallis or Fisher's exact tests were used to compare medians as appropriate, depending on whether the variables were compared between binary or multiple groups and whether outcomes were categorical or continuous.

Univariate linear regression models were constructed to explore the relationship of patient demographics, illness severity, key CMR findings and PROMs. Due to

the sample-size, linear regression models were likely to be vulnerable to outliers in the data. Thus, DASI and EQ-5D-5L summary measures were plotted and their distribution visually inspected. If data were not normally distributed or had significant skew, overall 'goodness of fit tests' were conducted: Kolmogorov-Smirnov, Cramer-von Mises and Anderson-Darling tests and Cullen-Frey plots were constructed to assess alternative distributions. If variables demonstrated evidence of significant deviation from normality, they were transformed and reassessed with further goodness of fit testing, with the more normally distributed transformation selected as the outcome variable for linear regression.

On an exploratory basis, multivariable linear models were constructed to explore whether clinical frailty score (CFS) predicted DASI, EQ-5D-5L HUS and EQ-5D-5L VAS when accounting for presence of LVSD and follow-up values of NT-proBNP. These were generated post-hoc to explore the interaction between key cardiovascular outcomes explored in this thesis and established determinants of functional trajectory following admission. Regression models are presented as β values or odds ratios (β/OR, CI95%, p).

Lastly, regression models were validated by assessment of QQ plot residuals and plotting quantiles of model residuals against simulated residuals to ensure model fit across their range. All statistical analyses were undertaken with R software (version 4.4.3, http://www.r-project.org) and conducted by the author of this thesis, supported by an experienced statistician.

7.3 Results

7.3.1 Overall summary of patient-reported outcome measures

Table 7-1 presents overall summary values of PROMs across the cohort who attended follow-up (n=34). Figure 7-1 depicts a graphical illustration of the degree of impairments at follow-up reported by participants across EQ-5D-5L domains.

Median DASI score was 21 (14, 37). Using EQ-5D-5L, the proportions of participants who reported any level of impairment in each domain was as follows: mobility 16/34 (47%), self-care 14/34 (41%), usual activities 22/34 (65%), pain and discomfort 20/34 (59%), and anxiety/depression 22/34 (65%). The median overall health state and visual analogue scales were 0.79 (0.38, 0.94) and 63 (45, 85) respectively. Median SF-36 vitality scores were 43 (21-61).

Table 7-1 Patient-reported outcome measures in ICU survivors of sepsis

Patient-reported outcome measure	N = 34
DASI Score, Median (IQR)	21 (14 – 37)
MRC Dyspnoea Scale, Median (IQR)	2.50 (2.00 – 4.00)
EQ-5D-5L Score (% with impairment at any level)	
EQ-5D-5L Mobility, n (%)	16 (47)
EQ-5D-5L Self-Care, n (%)	14 (41)
EQ-5D-5L Usual Activities, n (%)	22 (65)
EQ-5D-5L Pain/Discomfort, n (%)	20 (59)
EQ-5D-5L Anxiety Depression, n (%)	22 (65)
EQ 5D 5L Overall Health State, Median (IQR)	0.74 (0.22 – 0.88)
EQ 5D 5L Visual Analogue Scale, Median (IQR)	63 (45 – 85)
Hospital anxiety and depression score (HADS)	
HADS Anxiety Score, Median (IQR)	6.0 (3.0 – 14.0)
HADS Depression Score, Median (IQR)	4.0 (1.0 – 11.0)
SF-36 Energy and Fatigue Domain, Median (IQR)	43 (21 – 61)

Abbreviations: DASI=Duke activity status index, EQ-5D-5L= EuroQol 5-level 5-dimension, HADS=Hospital anxiety and depression scale, IQR=Interquartile range, MRC=Medical research council, SF-36=Short form 36.

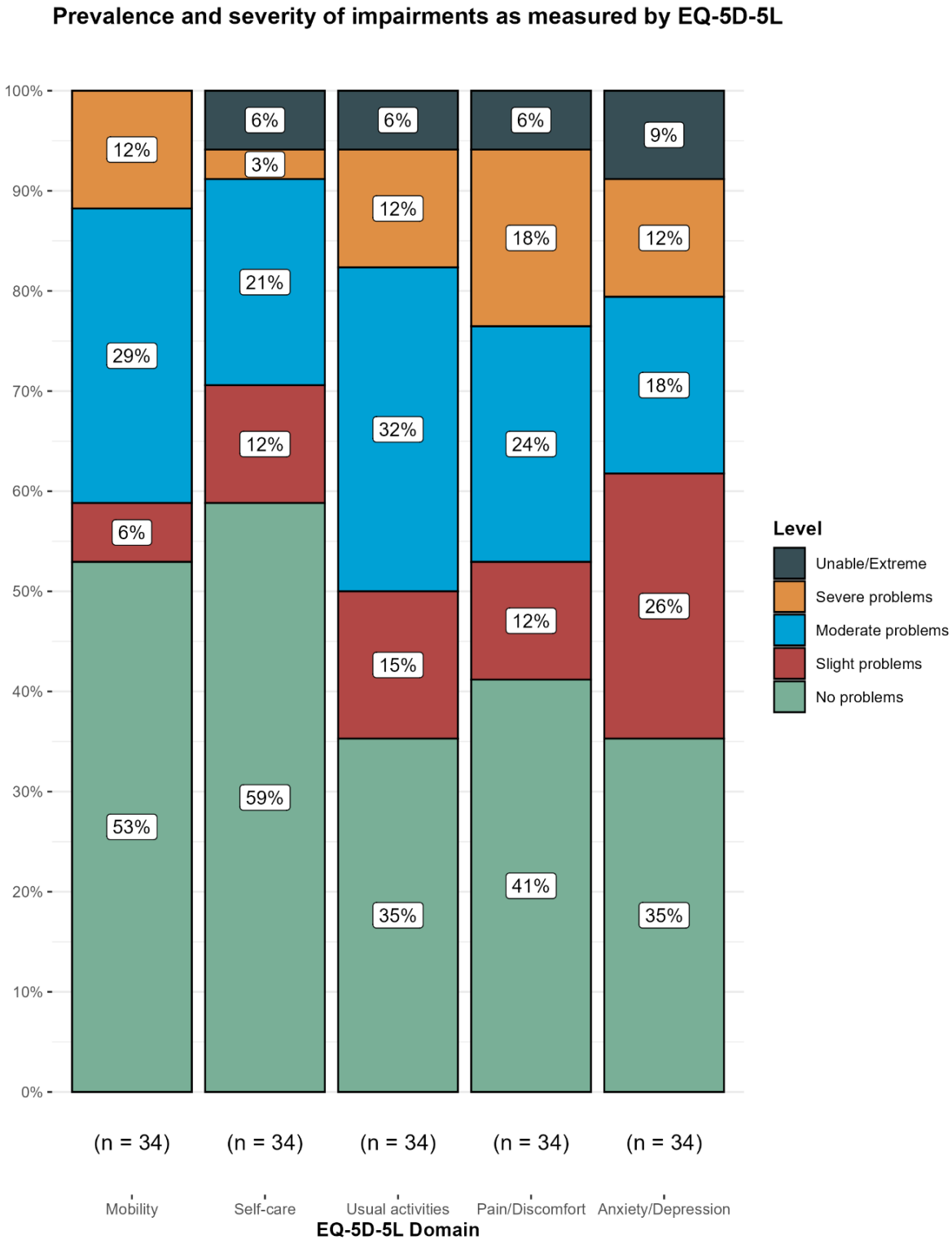


Figure 7-1 Overall prevalence and severity of impairments as measured by EQ-5D-5L in ICU survivors of sepsis

The bar chart displays the 5 domains of EQ-5D-5L, with the distribution of impairments for each domain mapped by level scores across the study cohort. No problems (teal), slight problems (red), moderate problems (blue), severe problems (yellow) and unable/extreme problems (grey).

7.3.2 Patient-reported outcome measures by presence of left ventricular systolic dysfunction

Table 7-2 displays PROMs, tabulated by presence of LVSD. Patients with LVSD had lower median DASI scores (14.48 (1.00, 24.20) vs 21.45 (16.20, 36.70), p=0.25), higher MRC dypsnoea scores (4 (2, 5) vs 2 (2, 4), p=0.11), lower median EQ-5D-5L visual analogue score (55 (25, 65) vs 70 (52, 90), p = 0.069 and overall health state (0.36 (0.12, 0.86) vs 0.80 (0.42, 0.94), p = 0.15). Patients with LVSD also had lower scores in the SF-36 vitality domain (21.25 (11 – 55.75) vs 45.75 (21.25, 60.50) p = 0.36). Despite a consistent trend of reduced exercise capacity and HRQoL, none of these differences were statistically significant.

Patients with LVSD had higher proportions of impairment in every domain of EQ-5D-5L (Figure 7-2). This was particularly marked in the self-care domain, where there was a significant difference in the distribution, with 3 (57%) participants reporting moderate impairments or above, compared with 6 (22%) in the group without LVSD (p = 0.024).

Table 7-2 Patient-reported outcome measures in ICU survivors of sepsis tabulated by presence of left ventricular systolic dysfunction

Patient-reported outcome measure	No LVSD N = 27	LVSD N = 7	p-value[1]
DASI Score, Median (IQR)	21.45 (16.20 – 6.70)	14.48 (10.00 – 24.20)	0.343
MRC Dyspnoea Scale, Median (IQR)	2 (2 – 4)	4 (2 – 5)	0.111
EQ-5D-5L Score (Any level of impairment)			
EQ-5D-5L Mobility, n (%)	12 (44)	4 (57)	0.681
EQ-5D-5L Self-Care, n (%)	10 (37)	4 (57)	0.410
EQ-5D-5L Usual Activities, n (%)	17 (63)	5 (71)	>0.999
EQ-5D-5L Pain/Discomfort, n (%)	14 (52)	6 (86)	0.198
EQ-5D-5L Anxiety Depression, n (%)	17 (63)	5 (71)	>0.999
EQ 5D 5L Visual Analogue Scale, Median (IQR)	70 (52 – 90)	55 (25 – 65)	0.069
EQ 5D 5L Overall Health State, Median (IQR)	0.77 (0.42 – 0.94)	0.22 (0.12 – 0.86)	0.146
Hospital anxiety and depression scores			
HADS Anxiety Score, Median (IQR)	6(3 – 15)	9 (6 – 14)	0.454
HADS Depression Score, Median (IQR)	4 (1 – 11)	5 (2 – 11)	0.549
SF-36 Energy and Fatigue Domain, Median (IQR)	45.75 (21.25 – 0.50)	21.25 (11 – 55.75)	0.359

[1]Wilcoxon rank sum test; Fisher's exact test. Abbreviations: DASI=Duke activity status index, EQ-5D-5L= EuroQol 5-level 5-dimension, HADS=Hospital anxiety and depression scale, IQR=Interquartile range, MRC=Medical research council, SF-36=Short form 36.

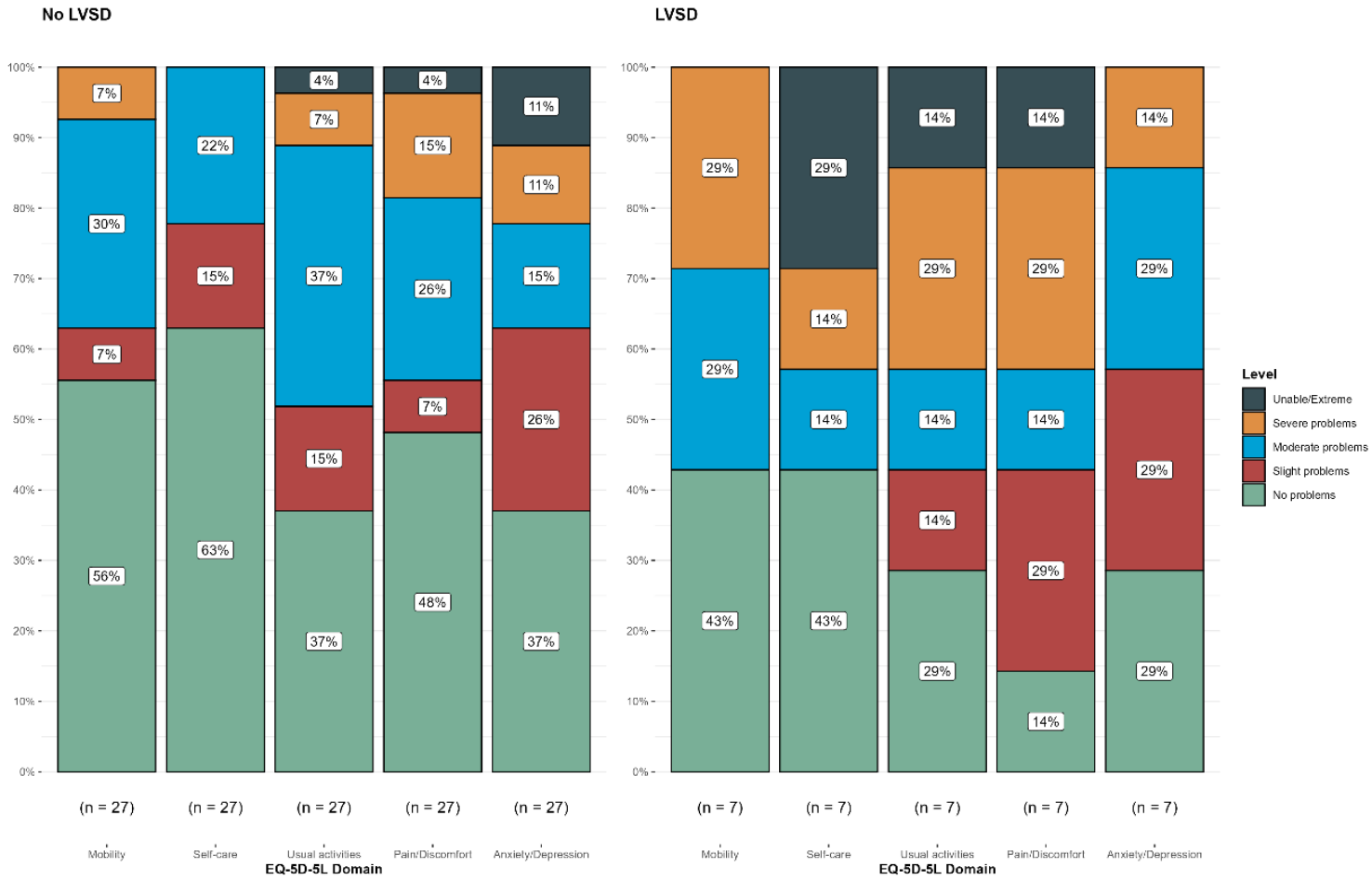


Figure 7-2 Overall prevalence and severity of impairments as measured by EQ-5D-5L in ICU survivors of sepsis with and without left ventricular systolic dysfunction

EQ-5D-5L impairments are mapped by presence of no LVSD (left) and LVSD (right) The distribution of impairments for each EQ-5D-5L domain is mapped by level scores across the study cohort. No problems (teal), slight problems (red), moderate problems (blue), severe problems (yellow) and unable/extreme problems (grey).

7.3.3 Univariate regression analysis of log DASI scores in participants at follow-up

Table 7-3 displays univariate linear regression analysis of patient characteristics, CMR findings and biomarkers at recruitment and at 6-10 weeks post hospital discharge and their ability to predict log DASI scores.

Only clinical frailty score at admission to intensive care demonstrated a significant ability to predict log DASI scores at 6-10 weeks following hospital discharge (ß -0.026 (-0.43,-0.09) p=0.005), indicating a significant decrease in logDASI score for every successive stage in frailty. Figure 7-3 displays median DASI scores by category of frailty on admission to intensive care, demonstrating the general trend towards progressively lower scores depending on degree of frailty. ($X^2_{(KW)}$.8.27, p = 0.07).

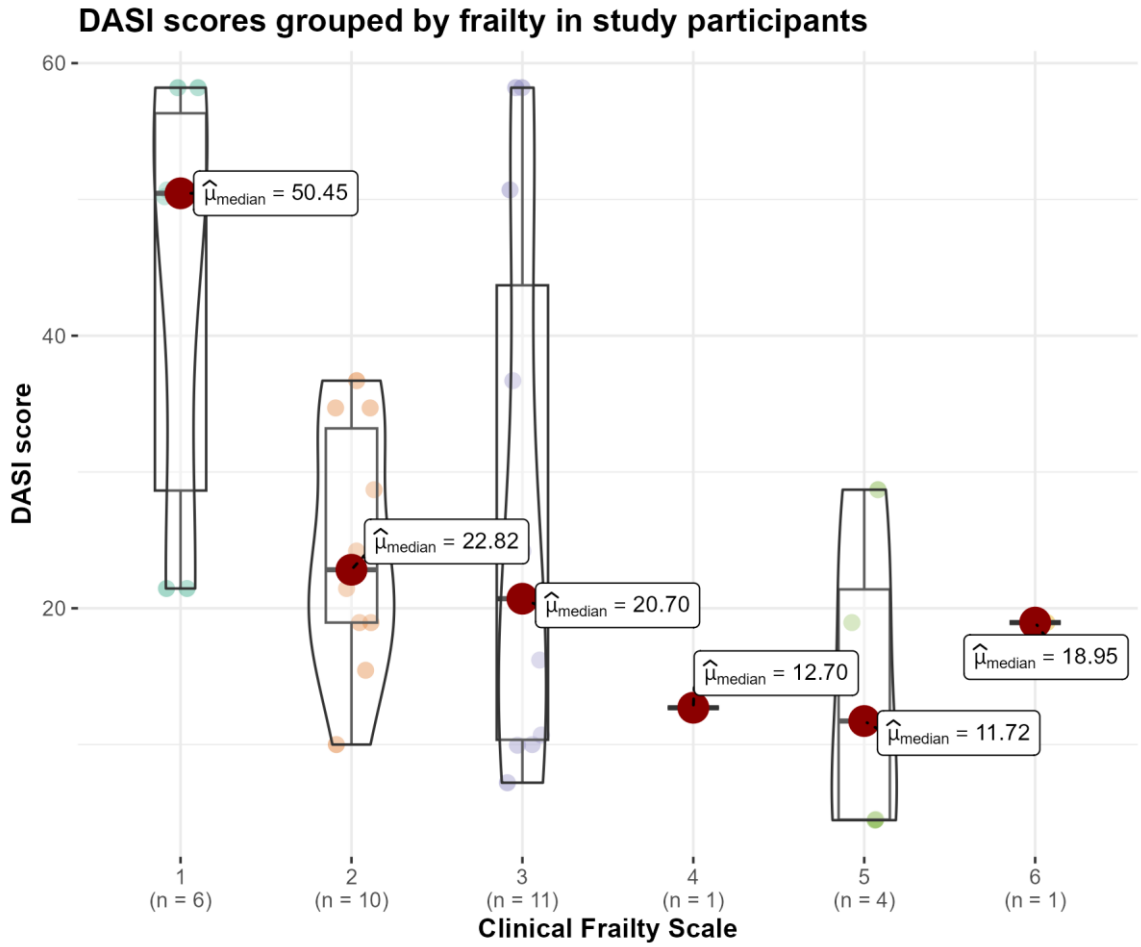


Figure 7-3 Median DASI scores at 6-10 weeks post-hospital discharge, by clinical frailty scale on admission to ICU

Table 7-3 Univariate linear regression analysis of patient demographics, illness characteristics, CMR findings and biomarkers with log DASI scores in ICU survivors of sepsis at 6-10 weeks post-hospital discharge

Characteristic	Beta	95% CI	p-value
Patient characteristics			
Age	-0.01	-0.03, 0.01	0.581
Clinical frailty scale	**-0.26**	**-0.43, -0.09**	**0.005**
Charleson comorbidity index	-0.05	-0.25, 0.15	0.626
Illness and hospital characteristics			
APACHE II score	-0.02	-0.04, 0.01	0.283
SOFA Score	-0.02	-0.09, 0.05	0.603
ICU length of stay (days)	-0.01	-0.03, 0.00	0.131
Hospital length of stay (days)	0.00	-0.01, 0.00	0.262
CMR at 6-10 weeks post-hospital discharge			
Left ventricular ejection fraction (LVEF%)	0.00	-0.02, 0.03	0.726
LVSD (Yes vs No)	-0.35	-0.97, 0.27	0.256
Biomarkers at point of ICU discharge			
log hs-TnT pg/mL	-0.13	-0.37, 0.10	0.256
log NT-proBNP pg/mL	-0.08	-0.21, 0.04	0.188
MR-proADM nmol/L	-0.02	-0.17, 0.13	0.801
Cystatin C umol/L	-0.09	-0.43, 0.24	0.563
hs-CRP mg/L	0.00	0.00, 0.00	0.297
TNF-α pg/mL	0.00	-0.02, 0.02	0.829
IL-6 pg/mL	0.00	-0.01, 0.00	0.442
Biomarkers at 6-10 weeks post-hospital discharge			
log hs-TnT pg/mL	-0.21	-0.53, 0.11	0.196
log NT-proBNP pg/mL	-0.10	-0.24, 0.05	0.188
log NT-proBNP pg/mL	-0.22	-0.70, 0.26	0.365
MR-proADM nmol/L	-0.65	-1.40, 0.11	0.091
Cystatin C mg/L	-0.02	-0.05, 0.02	0.326
hsCRP mg/L	-0.02	-0.05, 0.01	0.237
TNF-α pg/mL	-0.03	-0.08, 0.01	0.155
IL-6 pg/mL	-0.21	-0.53, 0.11	0.196

Abbreviations= APACHE=Acute physiology and chronic health evaluation, hs-CRP=High sensitivity C-reactive protein, hs-TnT=High sensitivity Troponin T, ICU=Intensive care unit, IL-6=Interleukin 6, MR-proADM=Midregional pro-adrenomedullin, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TNF-α=Tumour necrosis factor alpha, SOFA=Sequential organ failure assessment

7.3.4 Univariate regression analysis of EQ-5D-5L overall health-utility score at follow-up

Table 7-1 displays univariate linear regression analysis of patient characteristics, CMR findings and biomarkers and their ability to predict EQ-5D-5L overall health utility score. There were no statistically significant associations demonstrated with univariate modelling. Although clinical frailty score demonstrated a similar stepwise trend in reduced scores, this was not statistically significant.

Figure 7-4 demonstrates the trend in EQ-5D-5L overall health state scores with increasing frailty score.

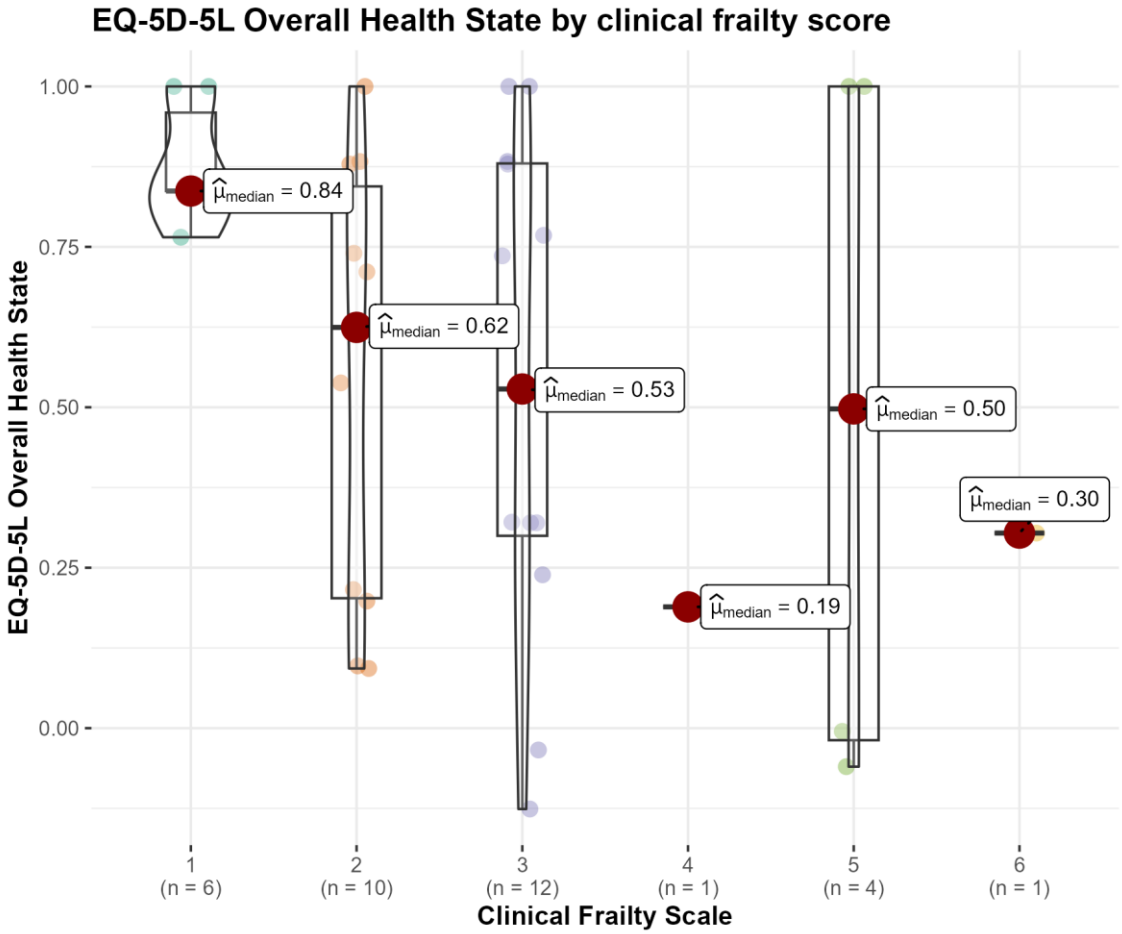


Figure 7-4 Median EQ-5D-5L overall health state scores at 6-10 weeks post-hospital discharge, by clinical frailty scale on admission to ICU

Table 7-4 Table 7 5 Univariate linear regression analysis of patient demographics, illness characteristics, CMR findings and biomarkers with EQ-5D-5L health utility score in ICU survivors of sepsis at 6-10 weeks post-hospital discharge

Characteristic	Beta	95% CI	p-value
Patient characteristics			
Age	0.00	-0.01, 0.01	0.749
Clinical frailty scale	-0.09	-0.19, 0.01	0.070
Charleson comorbidity index	0.03	-0.07, 0.13	0.552
Illness and hospital characteristics			
APACHE II score	-0.01	-0.02, 0.01	0.365
SOFA Score	0.00	-0.04, 0.03	0.902
ICU length of stay (days)	-0.01	-0.02, 0.00	0.144
Hospital length of stay (days)	0.00	0.00, 0.00	0.260
CMR at 6-10 weeks post-hospital discharge			
Left ventricular ejection fraction (LVEF%)	0.00	-0.01, 0.02	0.567
LVSD (Yes vs No)	-0.23	-0.56, 0.09	0.153
Biomarkers at point of ICU discharge			
log hs-TnT pg/mL	-0.05	-0.17, 0.08	0.445
log NT-proBNP pg/mL	-0.04	-0.11, 0.03	0.243
MR-proADM nmol/L	-0.03	-0.10, 0.05	0.472
Cystatin C umol/L	-0.11	-0.27, 0.06	0.208
hs-CRP mg/L	0.00	0.00, 0.00	0.141
TNF-α pg/mL	0.00	-0.01, 0.01	0.863
IL-6 pg/mL	0.00	0.00, 0.00	0.073
Biomarkers at 6-10 weeks post-hospital discharge			
log hs-TnT pg/mL	-0.10	-0.27, 0.06	0.218
log NT-proBNP pg/mL	-0.04	-0.12, 0.03	0.259
log NT-proBNP pg/mL	-0.19	-0.44, 0.07	0.142
MR-proADM nmol/L	-0.10	-0.44, 0.24	0.548
Cystatin C mg/L	-0.01	-0.03, 0.01	0.391
hsCRP mg/L	-0.01	-0.02, 0.01	0.421
TNF-α pg/mL	-0.02	-0.04, 0.01	0.136
IL-6 pg/mL	-0.10	-0.27, 0.06	0.218

Abbreviations= APACHE=Acute physiology and chronic health evaluation, hs-CRP=High sensitivity C-reactive protein, hs-TnT=High sensitivity Troponin T, ICU=Intensive care unit, IL-6=Interleukin 6, MR-proADM=Midregional pro-adrenomedullin, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TNF-α=Tumour necrosis factor alpha, SOFA=Sequential organ failure assessment

7.3.5 Univariate analysis of EQ-5D-5L visual analogue scores in participants at follow-up

Figure 7-5 displays univariate regression of patient and illness characteristics, biomarkers and CMR findings with patient reported visual analogue scores. CFS was, again, the only significant predictor of EQ-5D-5L visual analogue score (β=-6.24 (-12.3, -0.78) p = 0.044).

There was a downward trend in median EQ-5D-5L VAS for every progressive category of CFS (Figure 7-5), albeit these differences were not statistically significant ($X^2_{(KW)}$.7.5, p = 0.19).

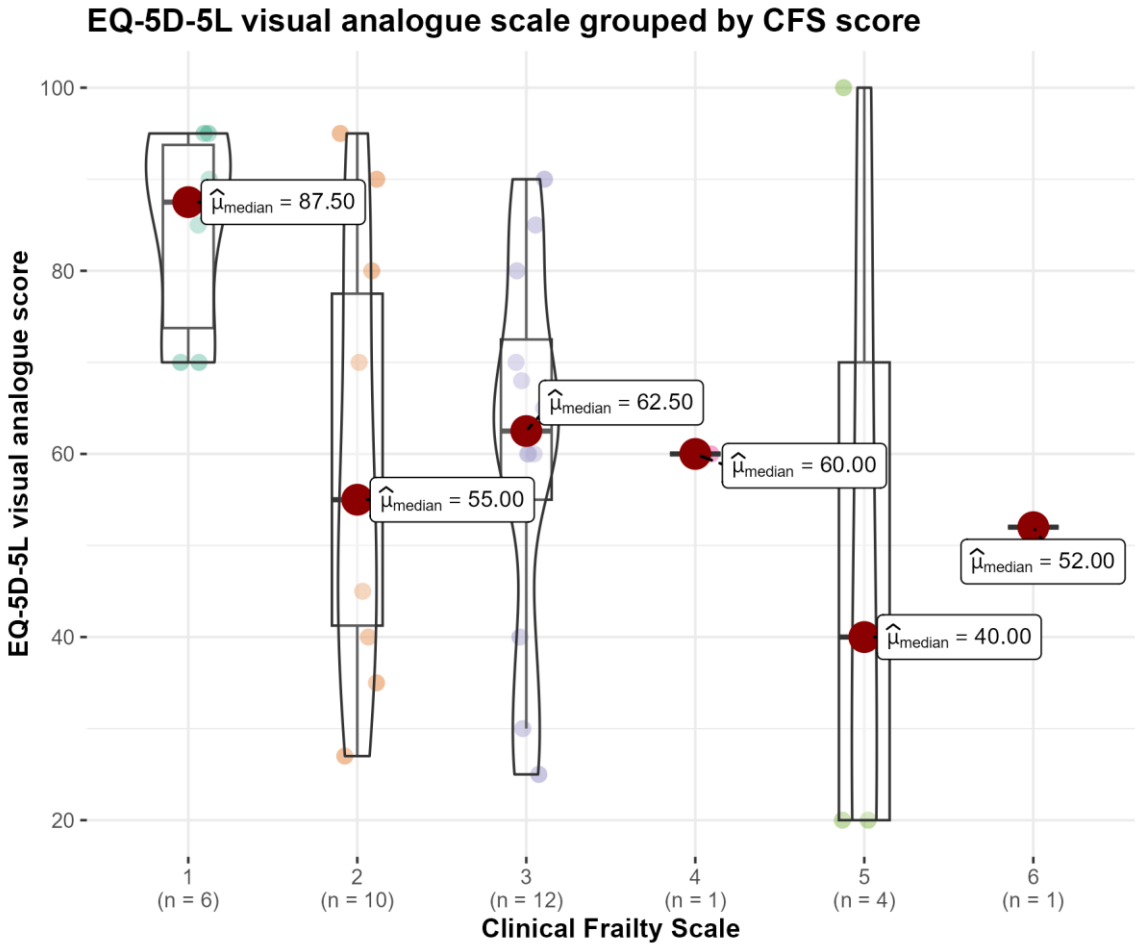


Figure 7-5 Median EQ-5D-5L visual analogue scores at 6-10 weeks post-hospital discharge, by clinical frailty scale on admission to ICU

Table 7-5 Univariate linear regression analysis of patient demographics, illness characteristics, CMR findings and biomarkers with EQ-5D-5L visual analogue score in ICU survivors of sepsis at 6-10 weeks post-hospital discharge

Characteristic	Beta	95% CI	p-value
Patient characteristics			
Age	0.16	-0.50, 0.81	0.627
Clinical frailty scale	**-6.24**	**-12.30, -0.18**	**0.044**
Charleson comorbidity index	-0.42	-6.72, 5.88	0.894
Illness and hospital characteristics			
APACHE II score	-0.15	-1.13, 0.83	0.752
SOFA Score	0.08	-2.19, 2.35	0.945
ICU length of stay (days)	-0.52	-1.07, 0.04	0.067
Hospital length of stay (days)	-0.13	-0.32, 0.06	0.182
CMR at 6-10 weeks post-hospital discharge			
Left ventricular ejection fraction (LVEF%)	0.56	-0.29, 1.4	0.187
LVSD (Yes vs No)	-19.00	-38, 0.87	0.060
Biomarkers at point of ICU discharge			
log hs-TnT pg/mL	-2.57	-10.24, 5.10	0.500
log NT-proBNP pg/mL	-2.15	-6.25, 1.95	0.293
MR-proADM nmol/L	-1.59	-6.36, 3.19	0.502
Cystatin C umol/L	-5.08	-15.54, 5.38	0.330
hs-CRP mg/L	-0.04	-0.12, 0.04	0.324
TNF-a pg/mL	0.04	-0.54, 0.63	0.880
IL-6 pg/mL	-0.08	-0.22, 0.05	0.201
Biomarkers 6-10 weeks post-hospital discharge			
log hs-TnT pg/mL	-8.98	-18.90, 0.93	0.074
log NT-proBNP pg/mL	-2.49	-7.26, 2.27	0.295
log NT-proBNP pg/mL	-10.01	-25.98, 5.97	0.211
MR-proADM nmol/L	-16.52	-36.82, 3.79	0.107
Cystatin C mg/L	-0.19	-1.34, 0.96	0.742
Hs-CRP mg/L	-0.53	-1.52, 0.45	0.279
TNF-a pg/mL	-1.13	-2.53, 0.27	0.109
IL-6 pg/mL	-8.98	-18.90, 0.93	0.074

Abbreviations= APACHE=Acute physiology and chronic health evaluation, hs-CRP=High sensitivity C-reactive protein, hs-TnT=High sensitivity Troponin T, ICU=Intensive care unit, IL-6=Interleukin 6, MR-proADM=Midregional pro-adrenomedullin, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TNF-α=Tumour necrosis factor alpha, SOFA=Sequential organ failure assessment

7.3.6 Multivariate regression analysis of clinical frailty score and patient-reported outcome measures

Table 7-6 displays univariate and multivariate regression analysis of clinical frailty scale and its ability to predict patient reported exercise capacity, health state and overall perception of health as measured by logDASI scores and EQ-5D-5L, adjusting for presence of LVSD and NT-proBNP at 6-10 weeks post-hospital discharge. Despite imaging and biochemical findings, CFS remained independently predictive of logDASI score (β -0.24 (-0.42, -0.010) p=0.010).

7.4 Discussion

These results demonstrate that in a cohort of ICU survivors of sepsis, without prior ischaemic heart disease or heart failure, exercise capacity was reduced in the majority of participants as measured by DASI score. HRQoL measures were also reduced as measured by EQ-5D-5L. In every domain of EQ-5D-5L, at least 40% of participants reported 'slight' impairment or above.

Overall, the cohort had a high prevalence of impairments across all HRQoL domains. The impairments observed in the cohort with LVSD were often more severe across all domains albeit scores did not achieve statistical significance. The study was not powered to detect differences in HRQoL or exercise capacity measures and as such any findings or extrapolation should be interpreted with caution. Nonetheless, the overall outcomes are of a similar range to those observed in other studies utilising EQ-5D-5L in critical illness populations, supporting the need for further investigation in this population.[209 319-321]

Survivors with LVSD had marked reductions in exercise capacity as measured by median DASI scores. Even in survivors with no LVSD, median DASI scores were at levels associated with significant functional impairment associated with an increased risk of all-cause mortality in peri-operative or heart failure populations.[313 314] EQ-5D-5L scores were also reduced in terms of HUS and VAS across the study population and more marked in participants who had LVSD at follow-up.

Table 7-6 Multivariate regression analysis of clinical frailty scale and its ability to predict logDASI scores, EQ-5D-5L overall health state and EQ-5D-5L visual analogue scores, accounting for LVSD and NT-proBNP on follow-up

Regression model	logDASI			EQ-5D-5L HUS			EQ-5D-5L VAS		
	Beta	**95% CI**	**p-value**	**Beta**	**95% CI**	**p-value**	**Beta**	**95% CI**	**p-value**
Unadjusted analysis									
Clinical Frailty Scale	**-0.26**	**-0.43, -0.09**	**0.005**	-0.09	-0.19, 0.01	0.070	**- 6.24**	**-12.30, -0.18**	**0.044**
Adjusted for LVSD									
Clinical Frailty Scale	**-0.25**	**-0.42, -0.07**	**0.009**	-0.08	-0.18, 0.02	0.124	- 5.18	-11.28, 0.92	0.093
LVSD (Yes/No)	-0.17	-0.74, 0.41	0.558	-0.18	-0.50, 0.15	0.281	-14.93	-34.47, 4.61	0.129
Adjusted for LVSD and NTproBNP									
Clinical Frailty Scale	**-0.24**	**-0.42, -0.06**	**0.010**	-0.08	-0.18, 0.03	0.133	- 5.18	-11.39, 1.03	0.099
LVSD (Yes/No)	0.00	-0.71, 0.70	0.996	-0.14	-0.53, 0.26	0.480	-15.07	-38.61, 8.47	0.201
log NTproBNP[1]	-0.07	-0.23, 0.10	0.409	-0.02	-0.11, 0.07	0.712	0.06	- 5.37, 5.49	0.982

[1]NT-proBNP values at 6-10 weeks post hospital discharge. Abbreviation: CI = Confidence Interval, DASI=Duke activity status index, EQ-5D-5L=EuroQol 5 dimension 5 level, HUS=Health utility score, LVSD=Left ventricular systolic dysfunction, NT-proBNP=N-terminal pro-B-type natriuretic peptideVAS=Visual analogue scale

HADS median anxiety scores reflected clinically significant symptomatology in study participants. Whilst these rates were higher in participants with LVSD they were not statistically significant. Severity of depressive symptoms in all survivors were below thresholds considered for investigating for depressive disorders.

Despite the differences in function and exercise capacity between those with and without LVSD, the strongest independent predictor of outcomes at follow-up was CFS at admission. Even when accounting for NT-proBNP and presence of LVSD, incremental progression in CFS was independently predictive of DASI score at follow-up. This is perhaps not surprising and reflects the known importance of prior frailty and function in determining overall patient trajectory following critical illness.[6 322 323] Given the study population reflect those who managed to attend follow-up post critical illness, it may be that participants had a reduced overall burden of frailty in comparison to all of those who were initially recruited, with more favourable physical and psychological outcomes than is reflective of the general ICU survivor population. Future research is needed to greater understand the impact of frailty on long-term outcomes following critical illness and the interplay between frailty and acquisition of additional comorbidities following ICU admission.

Despite the significance of frailty in this study, the reduction in exercise capacity and HRQoL measures in participants with new LVSD suggests that further research may further elucidate a group with significantly poorer patient-important outcomes. If this was the case, then LVSD may represent a discrete, acquired comorbidity following intensive care with a potentially modifiable disease trajectory. This is an attractive premise, as rather than viewing PICS as a collection of interrelated functional and psychological impairments that occur as a direct consequence of critical illness in general, we could move towards viewing these impairments as symptoms of discrete comorbidities acquired due to the idiosyncratic consequences of individual patient journeys. These comorbidities may be acquired due to sequelae of the index illness, treatments required or due to a complex interaction of illness and treatment factors with underlying patient characteristics. This hypothesis allows us to focus on identifying specific diseases with an established evidence base, in this particular case, chronic heart failure.

There is significant overlap with symptoms of chronic heart failure and the spectrum of symptoms experienced in PICS.[2 125] It is too simplistic to suggest that symptoms of left ventricular dysfunction are the main driver of functional impairment in PICS, however it is compelling to consider cardiac dysfunction as one of several potential drivers of functional impairment, reduced exercise tolerance and reduced HRQoL. If this were the case, there is potentially a subpopulation of sepsis or critical illness survivors that may be amenable to disease modifying therapies that reduce the risk of rehospitalisation or functional decline. Further prospective studies are required to delineate the association between discrete comorbidities that occur following critical illness and the degree to which their symptoms are associated with functional impairments.

This study has limitations. The nature of PROMs are such that they are not objective measures of exercise capacity or other physical functions, in comparison to cardiopulmonary exercise testing or grip strength, for example. It may be that more objective measures capture a differing prevalence or burden of symptoms and impairment in this population. However, the measures used in this study are part of a core outcome measure set developed in survivors of ARF. DASI has been shown to correlate with other measures of physical capacity and EQ-5D-5L has been validated as a tool for measuring quality of life in multiple populations including critical illness.[310 320 324 325] When the study was conceived, it was felt that further exercise testing, in addition to a relatively lengthy imaging study along with patient interview may be too arduous for participants with significant psychological and physical impairments following prolonged hospital admission. The attrition rate, although common in other critical care literature may suggest that more arduous objective tests, beyond what was already proposed, may have been a step too far for some of our participants. Lastly, the study was not powered to detect differences in the outcome measure scales utilised and as such there is a risk the data may not detect clearer differences in the study population.

7.5 Conclusion

This study demonstrates a reduced exercise capacity and reduced HRQoL measures in a cohort of 34 survivors of sepsis, without prior known heart failure

or ischaemic heart disease. Survivors with LVSD had lower median measures of HRQoL, exercise capacity and fatigue as measured by EQ-5D-5L, DASI and the SF-36 vitality domain, although these were not statistically significant. Clinical frailty score on admission to ICU was the only patient demographic predictive of reduced measures of exercise capacity or HRQoL at follow-up. Further studies of LVSD following critical illness are required to further characterise the relationship between LVSD and physical impairments following recovery.

Chapter 8 Discussion

8.1 Introduction

In the following chapter, the findings of this thesis are summarised and strengths and limitations of the work are discussed. The chapter will consider the prevalence of LVSD observed in the study cohort, potential driving mechanisms, and the implications for recovery and quality of life following an admission to the ICU. Finally, the chapter will consider future directions for the study of cardiovascular disease and multimorbidity acquired following critical illness.

8.2 Summary of thesis findings

The primary results and findings from this thesis are as follows.

8.2.1 Scoping review of cardiovascular dysfunction following admission with sepsis

Chapter 2 presents a scoping review of the literature pertaining to cardiovascular dysfunction following hospital admission with sepsis. It demonstrates that whilst there are many studies exploring the relationship between sepsis admission and adverse cardiovascular outcomes, almost all of these data explore *incident* cardiovascular outcomes in the follow-up period. Furthermore, whilst studies explore a wide range of differing adverse cardiovascular outcomes, less than half the identified literature examined objective methods of cardiovascular assessment, for example cardiac imaging or biomarker analysis. No studies were found that prospectively investigated cardiovascular function or dysfunction during recovery using objective measures of cardiovascular dysfunction, for example imaging or biomarkers.

As such, the scoping review identified gaps in the existing literature. The full extent to which patient demographics or illness characteristics might increase the risk of post-critical illness cardiovascular disease are unclear. Consequently, there is little to guide future to research to stratify the risk of cardiovascular disease following admission. Although there are many data exploring and quantifying the risk of adverse cardiovascular events following sepsis admission, there are few data exploring underlying mechanisms, with only one study

identified that explored mechanistic observations following the participants' index illness.

The scoping review highlights a need for further research in this area. The subsequent chapters in this thesis begin to address these gaps.

8.2.2 Study cohort and participant demographics

Chapter 4 demonstrates key demographic data of patients recruited to a prospective, multi-centre, multimodal cohort study aimed at characterising cardiovascular function in ICU survivors of sepsis. To the author's knowledge, it is the first study to prospectively recruit ICU survivors and undertake cardiovascular imaging, in combination with biomarker analysis and PROMS following admission.

It outlines evidence supporting the feasibility of this methodology in ICU survivors and demonstrates how it could potentially be used for larger observational cohort studies or even randomised controlled trials in similar cohorts. It also demonstrates recruitment and study retention rates that are similar to other studies in other populations.[30 31] The demographics of the overall population are demonstrably similar to other large cohort studies of ICU survivors of sepsis.[64 241]

For participants that met criteria for follow-up imaging outlined in the study protocol, CMR scanning was well tolerated by patients who attended and could be used to create detailed assessments of cardiovascular function which were subsequently compared with biomarkers and patient reported outcomes.

The chapter presents key feasibility data that can be used to plan further investigations of cardiovascular dysfunction in ICU survivors of sepsis, or indeed other discrete comorbidities that can be investigated using similar methodology.

8.2.3 CMR findings in ICU survivors of sepsis

Chapter 5 characterises cardiovascular function using CMR imaging in ICU survivors of sepsis. In the study population, seven (20.6%) of participants had LVSD 6-10 weeks following hospital discharge, a prevalence comparable to other

populations with traditional cardiovascular risk factors such as diabetes or hypertension.[260 261] To the authors knowledge, this is the first study to prospectively characterise cardiac function in this population using this modality.

Acute LV dysfunction whilst in ICU was predictive of LVSD 6-10 weeks post hospital discharge. LVEF, used to define LVSD in this study, was associated with severity of illness as measured by SOFA score. In addition, LVEF was associated with duration of cardiovascular support, ICU LOS and NT-proBNP at both ICU discharge and 6-10 weeks post-hospital discharge.

Participants with LVSD predominantly had global LV dysfunction, with no regional component or evidence of myocardial scar on LGE contrast sequences, suggesting a more diffuse process rather than infarction. There were modest elevations in myocardial ECV, perhaps indicating some mild oedema or subtle remodelling. Participants with LVSD also had a high prevalence of RVSD.

8.2.4 Biomarkers of cardiovascular dysfunction and inflammation

Chapter 6 analysed the biomarkers which were obtained in this study population. In particular, it focussed on biomarkers of cardiovascular dysfunction, inflammation and renal dysfunction. Perhaps most striking, are the marked elevations in NT-proBNP across the study cohort. The study demonstrates that in a cohort of ICU survivors of sepsis with no prior diagnosis of heart failure or coronary artery disease, that NT-proBNP values are markedly elevated at the point of ICU discharge, a time where patients would be considered fit for a lower acuity environment with little or minimal requirement for ongoing organ support and monitoring. Participants also had elevated biomarkers of hs-TnT, a biomarker of myocardial injury.

In comparison to those without, participants with LVSD had significant differences in NT-proBNP at 6-10 weeks post hospital discharge, with median values beyond the threshold required to support a chronic heart failure diagnosis. These participants also had markedly higher values of NT-proBNP on discharge from ICU, albeit this was not statistically significant.

At 6-10 weeks following hospital discharge, participants with LVSD had significantly increased values of NT-proBNP, MR-proADM, Cystatin-C and the inflammatory biomarkers TNF-α and IL-6. These biomarkers were all predictive of LVSD on univariate logistic regression modelling.

Similar to LVEF in the previous chapter, NT-proBNP values at follow-up were predicted by severity of illness scores (APACHE II and SOFA) as well as ICU LOS and duration of cardiovascular support. NT-proBNP values could also be predicted by biomarkers of renal dysfunction (cystatin-C) and the inflammatory biomarkers, TNF-α, IL-6, IL-8 and procalcitonin. These findings support the hypothesis that persisting inflammation in sepsis survivors is associated with long-term cardiovascular dysfunction.

8.2.5 Exercise capacity and health related quality-of-life in ICU survivors of sepsis

Chapter 7 found that this study cohort had reduced exercise capacity and high levels of impairment across all domains of EQ-5D-5L. There were reductions in exercise capacity, overall health utility scores and participants self-perceived health ratings as measured by EQ-5D-5L visual analogue scores. Reductions were particularly evident in participants with LVSD, albeit not statistically significant.

Participants with LVSD had reduced exercise capacity and lower ratings in terms of health related quality of life. Although these differences were not significant, the study was not powered to detect these differences. Similarly, CMR findings or biomarkers of cardiovascular dysfunction were not significantly predictive of patient reported outcome measures in the study cohort. Clinical frailty score at admission was the only participant characteristic associated with DASI score or HRQOL measured at 6-10 weeks post hospital discharge. For DASI scores, this relationship was independent of NTproBNP values or presence of LVSD at follow up.

These findings demonstrate the overall importance of prior functional status in determining overall trajectory following critical care admission. Although there

were no significant differences in overall HRQOL in participants with LVSD, the study was not powered to detect these differences. Nonetheless, LVSD was negatively associated with DASI and both EQ-5D-5L HUS and VAS, almost crossing the threshold for statistical significance for the latter. Further exploration in future work is required to further characterise the impact of LVSD acquired following ICU admission with sepsis on exercise capacity and HRQOL .

8.3 Clinical implications of the work as a whole

Although implications have been discussed in each chapter, it is worth considering the work as a whole, before discussing limitations of the thesis.

8.3.1 Cardiac dysfunction in survivors of sepsis

In this study of 50 ICU survivors of sepsis without prior heart failure or coronary artery disease, 34 went on to undergo follow-up investigations 6-10 weeks following discharge. Of these, seven (20.6%) had LVSD on CMR imaging.

It is increasingly recognised that adverse cardiovascular outcomes following admission with sepsis are common. A recent systematic review identified that following sepsis, hazard ratios of myocardial infarction, stroke and congestive heart failure are 1.77 (95%CI 1.26, 2.48), 1.67 (95%CI 1.37, 2.05) and 1.65 (95%CI 1.46, 1.86) respectively compared to non-sepsis controls, with the risk persisting at least 5 years following discharge.[105] Furthermore, admission with congestive heart failure is one of the most common reasons for hospital readmission following sepsis, accounting for readmission in 3-5% of patients following discharge from hospital.[106 326] To the authors knowledge, this is the first study which may provide objective evidence of cardiovascular function following discharge explaining why these adverse cardiovascular events may occur.

The high prevalence of LVSD is an important finding. LVSD represents an objective diagnosis, with treatment options available that may improve the recovery trajectory. However, it is important to highlight that LVSD on its own is not synonymous with a diagnosis of heart failure. Rather, heart failure as defined by current ESC guidelines, is a ‘clinical syndrome characterized by cardinal symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be

accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema), due to structural and/or functional abnormality of the heart that result in elevated intracardiac pressures and /or inadequate cardiac output at rest and/or during exercise'.[125]

In contrast to the ESC definition, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of heart failure set out a staged definition of heart failure, with a focus on development and progression of disease.[149] The term 'Stage B Heart Failure (HF)' has been defined as patients with no symptoms or signs of HF and one of: evidence of structural heart disease (e.g. left or right systolic dysfunction); evidence of increased filling pressures by invasive methods or on imaging; or patients with risk factors *and* increased levels of BNP or persistently elevated troponin.[149] Stage B heart failure has been recognised in various populations as a risk factor for disease progression to so called Stage C or D heart failure, with definitions that are much more aligned with ESC criteria.[125 149 264 327 328]

Although the risk of symptomatic heart failure is established for those with asymptomatic LVSD, much of the evidence for pharmacological treatment is in groups with LVEF<40%. Studies to examine the benefits of treating those with moderately reduced ejection fraction have been limited, with much of the focus on treatment of underlying cardiovascular risk factors or treatment of associated conditions, e.g. coronary vascular disease or valvulopathies.[149]

Regardless of whether sepsis survivors develop asymptomatic LVSD or meet criteria for a diagnosis of chronic heart failure, the findings of this study begin to fill a significant gap in the literature between the acute cardiac dysfunction commonly seen during sepsis admission and the increased risk of cardiovascular events that follow.[105 189] The large proportion of participants with LVSD observed in this study support the hypothesis that chronic cardiovascular disease is prevalent in ICU survivors, and may be amenable to disease modifying treatment.

This subsequently raises the question as to whether there are any predictive factors by which we can better identify those at risk in the population. In this thesis, sepsis survivors who had LVSD had median NT-proBNP values >125 pg/mL,

i.e. above a clinical threshold supportive of a chronic heart failure diagnosis in international guidelines in patients with associated symptoms and functional cardiac abnormalities.[125 149] Similarly, NT-proBNP values >400pg/mL were significantly predictive of LVSD in the study population. Furthermore, NT-proBNP and hs-TnT was associated with LVEF. All of these findings highlight that the use of NT-proBNP in combination with symptom burden in ICU survivors of sepsis could be used to identify patients at risk of heart failure on follow-up. Future research should further explore the utility of NT-proBNP in identifying chronic heart failure in this population.

Fatigue and breathlessness are common symptoms following intensive care admission and may be attributed to the general consequences of critical illness.[2 5 40 296 297] Similarly, although NT-proBNP is primarily used as a biomarker in heart failure, it is known to be associated with other heart conditions and has been associated with other factors such as increasing age or conditions such as cirrhosis.[222 243] It is not surprising that, despite breathlessness or fatigue being core heart failure symptoms, suspicion of new onset heart failure following ICU admission may be easily overlooked or attributed to PICS in general, even in the presence of abnormal biomarkers of cardiovascular dysfunction. The findings of this study provides a foundation for exploring the use of NT-proBNP for assessing risk of heart failure in ICU survivors.

There were also some associations with LVSD and factors relating to illness severity or characteristics. For example, LVSD during admission was associated with LVSD at follow-up. Furthermore, secondary outcomes such as NT-proBNP and LVEF at 6-10 weeks post-hospital discharge were associated with NT-proBNP on ICU discharge, illness severity scores, duration of cardiovascular support and ICU LOS. Whilst these findings should be interpreted with caution, they provide potential predictors of LVSD at follow-up that if confirmed in larger studies – could potentially be used to identify at risk participants before leaving the ICU.

These findings also bring into question the concept of so-called ‘septic cardiomyopathy’. This condition, thought to be in part due to protective mechanisms activated during sepsis is traditionally considered to be reversible in nature, with little or no long-term consequence.[162] The findings of this study challenge this hypothesis. Participants who had acute LVSD were at significant

risk of LVSD at follow-up. Whilst septic cardiomyopathy refers to a condition thought to be aetiologically distinct from MI or other types of myocardial injury, the paucity of data that examining objective measures of cardiac function following ICU means further study is required to examine whether this is indeed the cause or whether ICU survivors may yet be at risk of cardiovascular disease following admission.

8.3.2 Mechanisms of cardiovascular disease following sepsis

The above brings us to consider potential mechanisms of LVSD following sepsis. There are multiple potential reasons why survivors of sepsis might be at risk of LVSD, heart failure or other adverse cardiovascular outcomes following admission, outlined in Figure 8-1.

In terms of factors during related to admission, LVSD identified during the index illness was associated with its persistence 6-10 weeks following discharge. Furthermore, LVEF was related to severity of illness as measured by SOFA score, duration of cardiovascular support and ICU LOS. Overall, this implies that severity of illness and the degree of support may have long term implications for LV function.

Cardiovascular support provided in the ICU is not a benign intervention. Beyond the direct consequences of exposure to procedures such as central venous catheter insertion, multiple ICU trials comparing blood pressure targets or different vasoactive medications have demonstrated that the vasoactive agents (e.g. noradrenaline or vasopressin) commonly used for haemodynamic support are associated with higher rates of complications such as arrythmia, acute myocardial infarction, acute kidney injury and tissue ischaemia.[329-331] Similarly, there are multiple injurious mechanisms by which interventions such as mechanical ventilatory support might be associated with worse outcomes.[332] The data in this thesis support the hypothesis that continued and persistent exposure to the supportive interventions in intensive care may be injurious to the cardiovascular system and have long-term consequences. This is further supported by data in the literature demonstrating biomarkers, such as troponin and NT-proBNP, are associated with adverse outcomes and mortality following discharge from intensive care.[114 151]

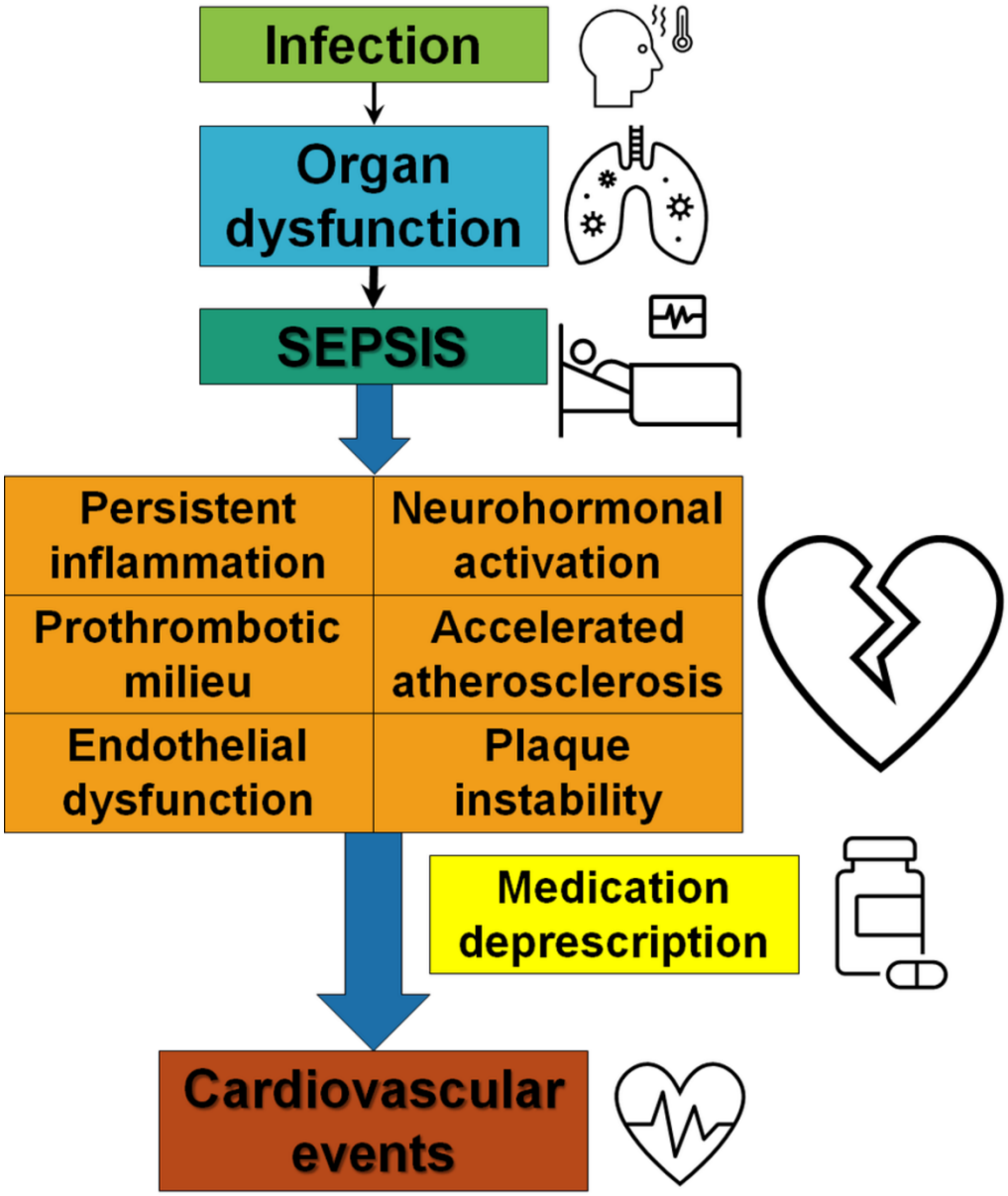


Figure 8-1 Conceptual model describing potential pathways by which sepsis during hospitalization may be associated with risk of cardiovascular events.

There are multiple factors during index illness and during convalescence that may contribute to this acquired risk. From Jentzer et al.[184] CC-BY licence.

Patient characteristics may further contribute to the long-term risk of cardiovascular disease following a critical care admission. Whilst the study in this thesis made effort to exclude patients with underlying coronary artery disease or prior heart failure, it was not possible to completely exclude this as a confounding factor in the study population. It is physiologically plausible that groups of patients with prior asymptomatic coronary artery disease for example, were subjected during sepsis to periods of hypoperfusion or vasoconstriction with vasoactive therapies. In populations at risk of myocardial ischaemia, these

pathophysiological states or interventions may further compound the risk of type 2 myocardial infarction (MI). Patients with type 2 MI have been estimated to have a risk of adverse cardiovascular events of around 30% following the myocardial injury. Compared to patients with Type 1 MI, they have markedly increased risk of mortality, albeit often driven by non-cardiovascular death.[333]

It is not clear whether this acquired cardiovascular risk occurs de-novo as a consequence of sepsis, or whether it is a consequence of the interaction of prior cardiovascular risk and the physiological stress of sepsis and associated treatments. Regardless, this population of patients has multiple plausible aetiological reasons by which they may sustain myocardial injury and be at risk of further heart failure events in the future. This is supported in this thesis by abnormal values of cardiac injury (hs-TnT) and of NT-proBNP on discharge from ICU and their association with LVSD.

Additionally, patients with type 2 MI are less frequently prescribed secondary prevention to reduce risk of further coronary events.[333] There are many reasons why these medicines (e.g. renin angiotensin system inhibitors (RASi) or beta blockers) would not be prescribed or withheld during admission with sepsis (e.g. ongoing hypotension or AKI). Whilst not conclusive, there is some observational evidence that initiation of RASi medication is associated with a lower risk of adverse cardiovascular events following sepsis admission.[171] Whilst not explored in this thesis, it is another consideration that demonstrates there are complex interrelated factors likely to increase long-term cardiovascular risk.

As outlined in chapter 6, there are multiple mechanisms by which inflammation has been associated with the pathogenesis of heart failure.[107 277] In the study population, there was evidence of persistent inflammation with abnormal levels of TNF-α and procalcitonin at follow-up. TNF-α demonstrated some ability to predict LVSD at follow-up, whilst procalcitonin demonstrated a consistent ability to predict NT-proBNP. There was also a relationship between LVSD and MR-proADM, an endogenous hormone with vasodilatory properties used as a biomarker of endothelial dysfunction, further supporting the concept of chronic endothelial dysfunction following sepsis. The data presented in this thesis demonstrates persistently abnormal levels of inflammatory biomarkers following sepsis, and is consistent with other studies in the field.[110 334] Nonetheless,

further work is required to delineate the relationship between inflammation and cardiovascular dysfunction following admission with sepsis.

Putting together all of the above, the data in this thesis support the model initially postulated following the scoping review, where acquired risk of chronic cardiovascular disease results from a complex interplay between an individuals' prior cardiovascular risk, the acute consequences of sepsis and required treatments, and the long-term effects of cardiovascular injury and chronic inflammation following discharge (Figure 8-2). The resulting interplay between these factors suggest an admission with sepsis may contribute to the significant acceleration of cardiovascular disease in someone without prior risk, or perhaps the acute inflammation or physiological stress might precipitate a cardiovascular event in someone already at high risk. This might manifest as abnormal biomarkers of cardiac injury on follow-up, LVSD on imaging, or indeed an established new diagnosis of heart failure. There are participants that represent this full spectrum across the study population.

8.3.3 Post-intensive care syndrome

The findings have implications for the study of PICS. The term "post-intensive care syndrome" was devised following a two-day conference organised by Needham et al in 2012 to increase awareness of the long-term impacts of critical illness.[36] Over the past decade or so, research into the consequences of critical illness and PICS has rapidly expanded and in 2019 a further conference was convened by Mikkelsen et al to help clarify recommendations on which groups were at most risk of PICS and associated impairments.[335] Whilst there were clear recommendations regarding at-risk groups (e.g. frailty, duration of delirium, sepsis, acute-respiratory distress syndrome) there is a lack of clarity regarding what might mediate some of these impairments.

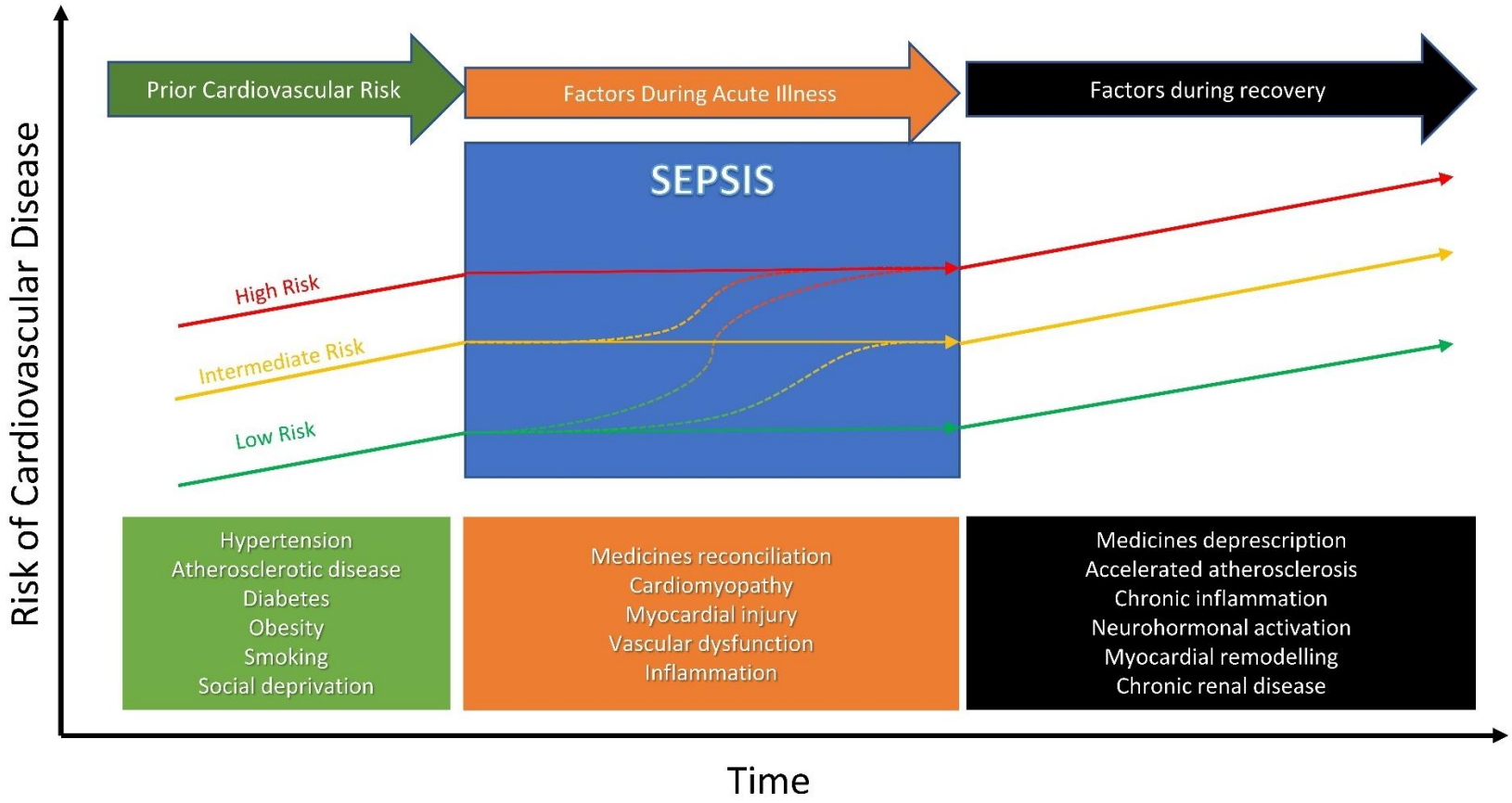


Figure 8-2 A proposed model of acquired cardiovascular risk of sepsis

There is a complex interplay between patient risk factors, illness characteristics and treatment factors, and factors during recovery that might determine a patient's overall risk of cardiovascular disease following admission with sepsis. The proposed prior risk is conceptual in nature, but may be related to factors such as age, index of social deprivation or presence of cardiovascular risk factors e.g. hypertension. Factors during acute illness may represent exposure to vasoactive drugs or periods of hypotension causing myocardial injury. Factors during recovery may relate to cessation of medicines that would reduce overall risk of cardiovascular events, or persistent inflammation contributing to pathogenesis of chronic disease.

This in part stems from the broad heterogeneity of ICU survivors as a cohort. Over two thirds of intensive care survivors will experience impairments in physical function, cognitive function and only around half will return to employment within a year of admission.[2 4] However, there are often distinct groups of patients within this broad cohort. One way of describing these is to differentiate between patients without comorbidity, those with multimorbidity and those with multimorbidity *and* frailty.[336] The foremost group - sometimes termed the 'big hit' group - may sustain significant physiological insult, but likely go on to recover, whereas others with prior multimorbidity develop a so-called 'slow-burn' in declining recovery trajectory following admission. Others with frailty and multimorbidity may experience 'relapsing recurrences' .[336] This conceptual framework demonstrates how frailty and dependence prior to admission interacts with other patient characteristics and the idiosyncratic consequences of individual illness, leading to variable trajectories in recovery (Figure 8-3).[6 41]

It is unsurprising then, that despite the clear identification of PICS as a significant public health issue, there is a lack of clarity regarding how best to design services to address the needs of ICU survivors. Many RCTs of interventions that attempt to address this have failed to show meaningful differences in patient outcomes, although there is evidence that some structured complex multi-disciplinary interventions can improve HRQoL.[209 337-344] Aiming to further address the needs of ICU survivors, the 'GRACE' roundtable was set up in June 2024, involving multiple relevant stakeholders including healthcare professionals, patients and families with the aim of identifying a further research agenda for post-ICU recovery research.[345]

Broadly, the roundtable recognised that the conceptual model supported by Needham's original Delphi consensus is likely too broad when considering the full range of disease pathways that lead to critical illness recovery, and that moving forward the literature should move towards a 'precision-recovery' approach to identify specific cohorts at risk of discrete comorbidities, allowing enrichment of studies in the area and hopefully improved outcomes for ICU survivors.[345]

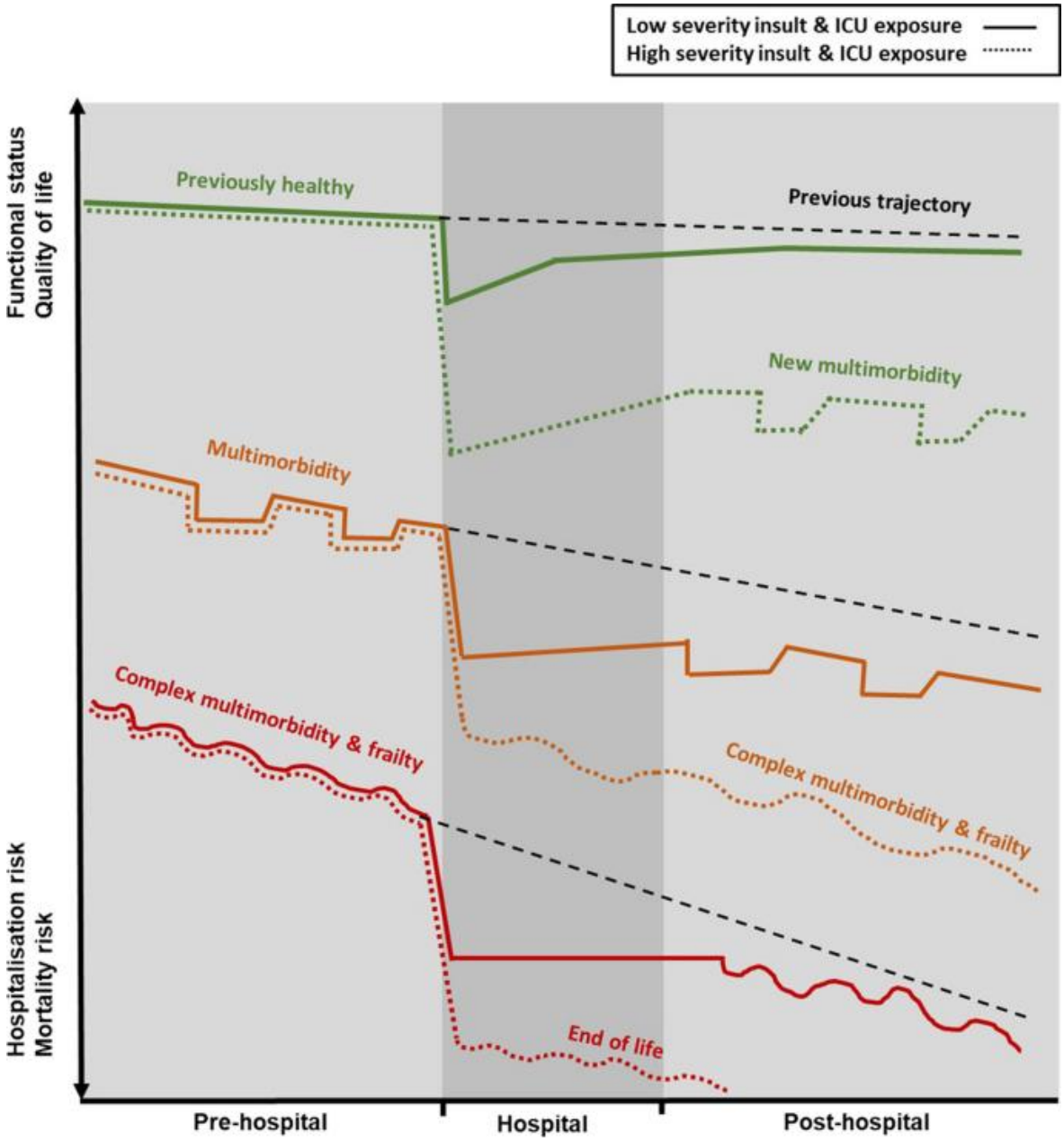


Figure 8-3 Recovery trajectories following critical illness

There are distinct recovery trajectrories postulated depending on prior burden of multimorbidity and frailty. The black hashed line represents functional decline that would have occurred had critical illness not have occurred. For indiciduals with no prior muitimorbidity, they are often liukely to recover following the 'big hit' of critical illness. Patients with multimorbidity or associated frailty often have significant functional decline following discharge. Note the altered recovery trajectory of those that qcquire new nultimorbidity, with a reduced ability to recover to previous functioal state. From Stewart et al[346]

The work in this thesis supports this approach. Whilst PICS has clearly brought the field forward in terms of identifying the needs of survivors, the literature is required to evolve. PICS was never intended as a diagnosis, but rather a

syndrome or ‘co-occurrence’ of discrete symptoms and impairments.[2 36] The work in this thesis supports the view that it may also be helpful to view recovery through the lens of post-critical illness acquired morbidity. Whilst not all symptoms will be attributable to a particular disease, identification of discrete co-morbidities can lead to more precise and targeted interventions, reducing the risk of adverse events.

It has already been outlined in this thesis that it is too simplistic to view comorbidities such chronic cardiovascular diseases as the sole drivers of post-intensive care multimorbidity, even at an individual patient level. However, this thesis supports the hypothesis that there are discrete populations of patients who develop specific comorbidities and impairments that may be amenable to treatments that reduce risk of hospital readmission or even improve recovery trajectory and HRQoL.

8.4 Strengths and limitations

The work in this thesis has several strengths. To the authors’ knowledge, it is the first study to follow up ICU survivors of sepsis utilising a combination of gold-standard cardiovascular imaging, biomarkers and patient reported outcome measures.

There have been other studies that have utilised CMR imaging, but have done so by inviting participants who were retrospectively identified, potentially encouraging healthy-user bias.[347] Another study prospectively recruited patients, but only utilised imaging in the follow-up period undertaken as part of usual care, potentially leading to selection bias where participants who received cardiac imaging were more likely to have abnormal findings by virtue of meeting clinical criteria to require cardiac imaging.[189] Nonetheless, this study found a similar prevalence of LVSD in the cohort imaged.

The study outlined in this thesis prospectively offered all eligible survivors cardiac imaging provided they did not have prior heart failure, known coronary artery disease or endogenous or exogenous immune dysfunction. As such, the study aims to mitigate and minimise any selection or healthy-user bias as much as possible. In doing so, the study has also allowed the generation of key

feasibility data regarding recruitment and retention in a Scottish cohort of ICU survivors which could be used in planning of further work.

A further key strengths include our approach to imaging; CMR imaging was reported by an accredited cardiovascular radiologist who was not part of the participants clinical team, the study utilises gold-standard imaging and generates reliable indices of cardiac function in the population described. Where parametric mapping was employed, reliability analyses were undertaken to further ensure validity of the reported results. The study has also cross-referenced values against local and national published reference ranges, ensuring the data are interpreted on comparable terms with other populations.

One of the key strengths of the data is the ability to explore association between objective imaging, biomarker analyses and patient reported outcome measures. This has allowed the study to generate a multidimensional characterisation of cardiac function which can be used to explore the relationship of cardiovascular pathology to participant demographics and illness characteristics, as well as underlying mechanisms and the implications for the study of post-critical illness multimorbidity and other functional impairments.

Many of the variables utilised in univariate modelling had nonparametric distributions and were prone to effects of outliers. Where presented, efforts have been made to ensure that any relationships of statistical significance were been assessed with goodness of fit testing against simulated models, both globally and across residual quantiles to ensure overreaching conclusions have not been drawn.

The thesis also has significant limitations. The sample size provides limited statistical power to explore key mechanistic outcomes or build multivariable models. As such, the thesis predominately focuses on univariate analyses, has limited ability to deal with confounding, and should be considered exploratory in nature. This exploratory nature was intrinsic to the study's design, with feasibility of the protocol a key component. This study will serve as a skeleton on which to build other research questions in this population utilising similar methodology, and provide further confidence in the degree to which participants can be recruited and retained.

This study is also vulnerable to selection bias. Ethical and logistical considerations led us to exclude patients with on-going delirium at the point of ICU discharge from taking part in the study. Delirium is prevalent in intensive care and is often associated with poorer outcomes.[57] Excluding this subgroup of patients may mean that the study cohort is representative of a population with less multimorbidity or less prone to acquire impairments following critical illness. Similarly, despite attempts to exclude underlying cardiac pathology such as coronary artery disease or heart failure, it is possible that the population included recruits with prior undiagnosed cardiovascular disease. Nonetheless, this is perhaps reflective of standard clinical practice and it remains important to understand the extent to which all ICU survivors are at risk of cardiovascular disease - even if the propensity to develop cardiovascular morbidity following critical illness is greater than known prior to admission.

Lastly, whilst this is a multi-centre study, both recruiting sites are in the West of Scotland and serve populations that are predominately from regions with a lower index of social deprivation. Social deprivation has been established as being associated with a higher degree of adverse cardiovascular outcomes and this may play some role in the high prevalence of LVSD observed.[348]

8.5 Future directions for research

This thesis demonstrates that in ICU survivors of sepsis who have no known prior heart failure or ischaemic heart disease, there was a high prevalence of LVSD. Future work is required to delineate and quantify this risk and further stratify what groups may be at most risk.

Whilst the scoping review identified multiple observational studies exploring the relationship between sepsis and incident cardiovascular outcomes, none of these studies involved UK cohorts and few focused on European cohorts. Despite an understandable focus on incident outcomes, there are few available data to explore other causative mechanisms that may further help us understand the pathogenesis of chronic cardiovascular disease following critical illness.

Further observational work is required to understand the risk of chronic cardiovascular disease following critical illness in Scottish or UK populations, the

risk of developing key cardiovascular risk factors following admission (e.g. hypertension and diabetes) and the impact of cessation or initiation of cardiovascular therapies which may impact the long-term incidence of cardiovascular outcomes in this population. In combination with the feasibility data in this study, this will contribute to a more nuanced understanding of the risks and pathogenesis of cardiovascular comorbidity to support the development of future prospective work.

The thesis presents other opportunities for prospective study. With greater resource we would have been able to further characterise the burden of cardiovascular disease using other imaging modalities such as CT-Coronary Angiography (CTCA), or by following up participants at multiple time points e.g. 1 year post discharge. Further modalities of observation would have helped delineate burden of coronary disease and the association with CMR findings. Further time-points in the study would help identify if recorded LVEF represents a nadir from which patients improve and get better, or whether LVSD persists or even declines following admission.

Whilst patient reported outcome measures allow exploration of key patient-important outcomes, it would have been helpful to explore other objective measures of functional capacity, e.g. cardio-pulmonary exercise testing or 6 minute-walk tests. When the study was conceived, there was uncertainty regarding the intensity of investigation for which participants would be willing to undergo following what were often traumatic intensive care admissions. Future work could incorporate these objective measures to add further dimensions to functional and quality of life assessments.

Finally, the sample size allows for limited exploration of associations between patient demographics, illness characteristics and key outcome measures in the study. A larger cohort, with additional imaging modalities (e.g. CTCA) would allow for more detailed exploration of the risk factors and mechanisms involved in development of chronic cardiovascular disease following critical illness. The outcomes used in this study could be used to plan and power further study examining mechanisms of post ICU LVSD. Such work could even be integrated into clinical trials to explore the strategies for secondary prevention of adverse

cardiovascular events following sepsis or other critical illness, for example reductions in LVEF or NT-proBNP.

8.6 Conclusion

This thesis demonstrates that in a cohort of ICU survivors of sepsis, without immune dysfunction or a prior diagnosis of heart failure or ischaemic heart disease, participants had a high prevalence of LVSD 6-10 weeks following hospital discharge. The presence of LVSD was associated with acute LVSD during ICU admission and biomarkers of cardiovascular dysfunction and inflammation at 6-10 weeks following hospital discharge. LVEF and NT-proBNP were associated with illness severity, key illness characteristics and evidence of cardiac injury and dysfunction at the point of ICU discharge. This supports existing literature demonstrating sepsis is associated with an increased risk of cardiovascular events and demonstrates evidence of plausible pathological mechanisms by which these might occur.

Participants had a degree of impairment and health-related quality of life consistent with other post-ICU literature and further reductions in these measures were observed in participants with LVSD. Further work is required to further quantify and delineate the apparent risk of cardiovascular disease following sepsis and how this is associated with exercise capacity and HRQoL. The study in this thesis may serve as the basis by which this could be further investigated.

Appendices

Appendix 1
Scoping review: data extraction instrument

Scoping Review Data Extraction Instrument	
Scoping Review Title:	Cardiac Dysfunction in Survivors of Sepsis
Review Objective:	Map evidence regarding cardiac dysfunction following sepsis and examine how it might be implicated in functional impairment following intensive care
Review Questions(s):	What is the extent of the evidence examining cardiovascular function following an episode of sepsis? What research methodologies have been employed to explore the long-term cardiovascular effects of hospital admission with sepsis? To what extend does this literature explore the role cardiovascular function might play in functional impairment following admission with sepsis? Does this literature explore any mechanisms by which cardiovascular function might cause long term functional impairment (e.g. ischaemia/failure?

Inclusion/Exclusion Criteria	
Population	Adults
Concept	Cardiac Dysfunction during follow-up
Context	Admission with sepsis
Evidence Source Details and Characteristics	
Citation Details	
Country	
Context	
Details/Results Extracted from Source of Evidence	
Patient Reported Outcome Measures (e.g. performance status, functional questionnaire, NYHA)	
ECG findings reported	
Cardiac Imaging Reported? (e.g. Echocardiographic Findings / CMR)	
Cardiac Biomarkers (e.g. NT-proBNP, Troponin)	
Incident CV outcomes reported (e.g. MI/Heart Failure Admission)	

Appendix 2
Ethical approval

NHS
Health Research Authority

South West - Central Bristol Research Ethics Committee
Ground Floor
Temple Quay House
2 The Square
Bristol
BS1 6PN
Email: centralbristol.rec@hra.nhs.uk

7th July 2022

Professor Tara Quasim
Rm 2.71, Level 2 New Lister Building, Glasgow Royal Infirmary
10-16 Alexandra Parade
Glasgow
G31 2ER

Dear Professor Quasim

Study title:	**Characterisation of Cardiac Function in ICU Survivors of Sepsis: A Pilot Study**
REC reference:	**22/SW/0082**
Protocol number:	**GN22CA029**
IRAS project ID:	**309553**

Thank you for your letter of , responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results

Appendix 3
Consent forms

UNIVERSITY of GLASGOW

NHS Greater Glasgow and Clyde

NHS Ayrshire & Arran

CONSENT FORM Patient Identification Number for this study: _____

Title of Project: Characterising Cardiac Function in ICU Survivors of Sepsis

Name of Researcher: _____ Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. If I withdraw from the study, only data collected prior to my withdrawal from the study will be kept for analysis. ☐
3. I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in research. I give my permission for the research team to access my medical records. ☐
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals appointed by the study Sponsor (NHS GG&C) whose job it is to check the work of the researchers. I give permission for these individuals to have access to my records when relevant to the research. ☐
5. I agree that blood samples collected will be stored and retained anonymously. It will not be possible to identify me from my stored sample. I understand that allowing retention of samples is not a necessary condition to participate in this study. ☐
6. I agree for my sample to be used for future research studies, pending further ethical approval. ☐
7. I agree to my GP being informed of my participation in the study and if there are any significant findings on my MRI scan (if applicable). ☐
8. I agree to my GP being informed if after answering questions researchers feel further psychological support following my ICU admission may be of benefit to me. ☐
9. If am happy to be referred for Post-Intensive Care follow up via the NHS InS:PIRE service if researchers think I might benefit from medical or psychological support and I am not already attending the service. ☐
10. I wish to receive a summary of the study results. Yes ☐ No ☐
    If "yes", I wish to receive the results at:
11. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 4
Patient information sheet

UNIVERSITY of GLASGOW

NHS Golden Jubilee

NHS Greater Glasgow and Clyde

NHS Ayrshire & Arran

PATIENT INFORMATION SHEET

Characterising Cardiac Function in Survivors of Sepsis

A study to examine the causes of Post-Intensive Care Syndrome

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. We suggest this should take about 15 minutes. You should understand enough about the risks and benefits to be able to make an informed decision.

Talk to others about the study if you wish.

Ask us if there is anything that is not clear. Please feel free to contact a member of the research team, if you have any questions or wish to discuss the study further.

Who is conducting the research?
The study is being led by Professor Tara Quasim, Professor of Critical Care Medicine on behalf of the Academic Unit of Anaesthesia, Peri-Operative and Intensive Care Medicine at the University of Glasgow. The study is being organised by a group of clinical and research doctors led by Professor Quasim and includes Dr Joanne McPeake and Dr Philip McCall who work at the University of Glasgow. Dr Kevin Garrity and Dr Christine Docherty are PhD students at the University of Glasgow.

What is the purpose of the study?

More than half of survivors of critical illness will go on to develop symptoms that affect their quality of life. These symptoms can affect patients' physically (such as tiredness and breathlessness), their ability to think, or even their emotions. Some patients experience only some of these symptoms or none at all, but others experience many of these symptoms after intensive care. Together, these symptoms are called 'Post-Intensive Care Syndrome' (PICS). Very little is known about what causes them.

Sepsis is one of the most common reasons people are treated in intensive care and survivors of sepsis can develop symptoms similar to PICS. There are lots of reasons for this, and one reason may be that sepsis affects can the heart.

This study will use magnetic resonance imaging (MRI scans) of the heart taken after being treated in intensive care. The MRI scans will show us if there is still inflammation or abnormal function of the heart in the weeks or months after having sepsis. MRI scans of the heart have long been considered an excellent way to examine heart function, but they have never been used in survivors of intensive care. The researchers want to investigate whether MRI scanning of the heart can be undertaken in patients following intensive care. In addition, blood samples will be tested to find out about how the heart blood vessels are showing signs of damage. We will use questionnaires to ask how people's lives have changed after being in intensive care .

Understanding what happens to the heart after being in intensive care with sepsis may help us to work out the best ways of helping patients recover .

The study will also be part of the PhD qualification from the University of Glasgow for Dr Garrity and Dr Docherty.

Why have I been invited?

You have been invited because you had sepsis and were admitted to the intensive care unit (ICU).

Do I have to take part?

No, it is up to you to decide whether or not to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What would happen to me if I take part?

A doctor from the research team will take you through this information sheet and obtain your permission to participate in this study in writing.

If you decide to take part you will be asked some questions about your health and asked to fill in a short questionnaire. You will also be asked a number of questions to make sure that you have no metal within you and it is safe for you to undergo magnetic resonance imaging (MRI scanning).

The main part of this study involves using MRI scans to look in detail at heart function. Your MRI scan will be undertaken at the Imaging Centre for Excellence at the Queen Elizabeth Hospital 6-10 weeks after you are discharged from hospital. This will be separate to any hospital appointment arranged after you are discharged from intensive care. When you are discharged from intensive care and when you have your MRI scan done, we will take an extra sample of blood from you . At the time of your MRI scan, we will ask you to again fill in the same short questionnaire that you filled in before going home from hospital.

The research team running this study will ensure your travel expenses to and from the hospital for the scan are reimbursed.

What will I have to do?

Magnetic Resonance Imaging

MRI scanning uses a strong magnetic field to create detailed images of heart structure and function. You will be asked to lie in the scanner for approximately 30 minutes. The scanner can be loud when it takes images, and you will be given earplugs and/or headphones to block out some of the sound. Some people find the scanner a claustrophobic or uncomfortable environment; it may not be appropriate for people who are uncomfortable in small or confined spaces to take part.

Blood sampling

At the time of discharge from ICU you are likely to still require some ongoing treatment on the ward. Whilst in the hospital we will use a small needle to take a sample of blood to test for markers of

inflammation and markers of heart and blood vessel damage. Sometimes in ICU you might have a special cannula in one of your arteries for monitoring your blood pressure. If this is the case, we will collect samples from this cannula instead.

We will repeat the samples 6-10 weeks later in the same way. This is a simple procedure that should take no more than a few minutes and isn't too uncomfortable.

Questionnaires

To examine the symptoms experienced by patients following their admission to intensive care, when you attend for a follow-up scan and blood tests we will also conduct a series of questionnaires that help us understand any symptoms you may or may not be experiencing. The questionnaires do not take long to complete and the researchers conducting the study will be on hand to help you complete them. We will look at the data recorded by these questionnaires in combination with blood tests and MRI scan results to try and understand why any symptoms you have reported may have occurred.

Echocardiogram

There is a possibility you have already had an echocardiogram as park of your stay in intensive care. If you have, the researchers will include the results in the study of t. If not, the researchers will undertake one on the ward . This is a type of ultrasound machine. It is completely painless, and involves placing some jelly and a small, flat ultrasound probe on your chest to get pictures of the heart at the time you have been unwell. This takes approximately 10 minutes.

What are the possible disadvantages and risks of taking part?

MRI is generally thought to be a safe non-invasive imaging technique. There are no known risks in properly conducted magnetic resonance imaging. As it involves a strong magnetic field, certain standard precautions will be observed. Most importantly, we will **NOT** study you if you are fitted with a heart pacemaker; if you have surgical clips in your head; if you have suffered injuries which may have left metal particles in your eye or head, or elsewhere in your body; or if you have an artificial heart valve.

In order to get good pictures of your heart we will inject contrast via a small drip (venflon) in your hand or arm during the procedure. Contrast is routinely used in MRI scanning. There are some known side effects of contrast including allergy to contrast and a risk of kidney impairment. We will only give contrast in the study if your kidney tests are normal in order to reduce the likelihood of kidney side-effects. If at any point during the study, your kidney tests are abnormal we will not use contrast during the MRI scanning.

Occasionally research studies using MRI reveal significant unexpected abnormalities which require medical follow-up, either for further investigation or (more rarely) treatment. The scans we are doing are for research, but we review them carefully to avoid missing any such abnormality. If any significant unexpected abnormality is found we will send the report to your GP, and the research team will inform the InS:PIRE clinic and arrange follow-up with the appropriate hospital speciality doctors if this is required.

Taking blood samples is generally a very safe and routine procedure. It does hurt a little and you are likely to develop some bruising. There is also a very small risk of introducing infection to the skin or blood stream when taking blood samples, but the skin will be cleansed before the sample is taken to minimise this risk.

What are the possible benefits of taking part?

There is no direct benefit to you personally. We hope the results of this study will provide information that helps the medical profession reduce the risk of Post-Intensive Care Syndrome in survivors of sepsis.

What happens if I don't want to carry on with the study?

You can withdraw from the study at any time. If you withdraw from the study, no more samples will be collected and no further research scans will be performed. Any samples already obtained will still be used as part of the study.

What happens when the research stops?

Throughout the study and after it stops, your care and follow up will be the same as for those patients who were not in the study.

What if there is a problem?

We don't expect any problems in this study. In the event that something does go wrong however, and you are harmed during the research due to someone's negligence then you may have grounds for a legal action for compensation against the University of Glasgow but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

What will happen to my data?

NHS Greater Glasgow and Clyde (NHS GG&C) is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS GG&C will keep identifiable information about you for 3 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information at https://www.hra.nhs.uk/information-about-patients/ or by contacting NHS GG&C Information Governance Department. Tel: 0141 355 2059 Email: data.protection@ggc.scot.nhs.uk.

The University of Glasgow will be the data processor for the study and will keep research data that is pseudonymised, which means it is labelled only with a study ID code, not your name or other identifiable data. All study data will be held in accordance with The General Data Protection Regulation (2018). The data will be stored in archiving facilities in line with the University of Glasgow retention policy of up to 10 years. After this period, further retention may be agreed or your data will be securely destroyed in accordance with the relevant standard procedures.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have all your identifiable information removed so that you cannot be recognised.

The necessary information will be taken from your medical records, from the hospital computers, from your x-rays and the analysis of blood samples by members of the research team. All data and samples will be pseudonymised by removing all names and addresses as soon as possible after collection and labelling them with study ID codes, so that individuals cannot be recognised.

The pseudnonymised data will be stored securely. The study team will be the only people with direct access; they will analyse the data for the purposes of completing this project. It may also be used for further scientific work in the future; however this would require permission to be granted from an independent Research Ethics Committee. The data may also be reviewed by regulatory authorities responsible for monitoring the quality of research. Your study data will be held and processed on secure, password protected computer networks in NHS GG&C and the University of Glasgow.

Pseudonymised research data will be held for a maximum of 10 years after the study ends and will then be destroyed securely. Your personal details (for example your name and address) will be stored separately for up to 3 years after the end of the study so that we are able to send you a copy of the study results. After this time these details will be destroyed securely.

Your GP will be informed that you took part in the study and will be told if your echocardiogram or MRI scan shows anything we think needs to be checked. Your GP will also be informed if your study results indicate that support with mental health, which is common in survivors of critical illness, is required. The InS:PIRE service, which supports recovery following critical illness, will be informed if psychological support may be of benefit to you.

What will happen to any samples I give?

This study involves taking blood samples which are in addition to those taken for normal patient care.

The samples will be labelled by unique study number only – all data that is identifiable (e.g. names and addresses) will be removed. Samples will be stored and may be used in further research studies (with permission from the an appropriate research ethics committee). Specific consent will be sought for retention of samples and this is not a nessescary condition for participation in the study. Should samples be used in further research studies, we will not share any personalised data with other researchers in the UK or further afield to ensure your confidentiality.

What will happen to the results of the research study?

The study is estimated to run between June 2022 and August 2024. Dr Garrity and Dr Docherty (part of the research team) will submit reports of the study for their PhD qualifications to the University of Glasgow. We will send a summary of the study results to you at the end of the study if you wish; you can tell us on the Consent Form if you would like the results. Individual patients will not be identified in any report / publication of the study.

Who is funding the research?

The study is funded in part by the NHS Endowment Fund. The study has also received external funding from two charities which fund medical research: The Wellcome Trust and The Fiona

Elizabeth Agnew Trust. Doctors and nurses conducting the research are not being paid specifically for including you in this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South West Central Bristol Research Ethics Committee.

Further information and contact details

If you have any questions concerning the study, please ask the person presenting this form to you, or contact Dr Kevin Garrity at Kevin.Garrity@glasgow.ac.uk or Tel: 0141 201 5429. You can also contact Dr Chris McGovern 0141 201 5430, who is not part of the research team, for independent information about the study.

If you have any complaints about any aspect of the way you have been approached or treated during the course of this study, you contact the research team in the first instance. You may also contact the independent Patient Advice and Liaison Service.

Thank you for taking the time to read this information.

Appendix 5
GP letter

UNIVERSITY of GLASGOW

NHS Golden Jubilee

NHS Greater Glasgow and Clyde

NHS Ayrshire & Arran

GP Notification letter (For participants Providing CMR Imaging)

Characterising Cardiac Function in Survivors of Sepsis (CONDUCT-ICU)

A study to examine the causes of Post-Intensive Care Syndrome

Dear Dr,

Your patient ….. (CHI:……..) was recently admitted to ICU with a diagnosis of sepsis. They are currently rehabilitating and have agreed to take part in the CONDUCT-ICU clinical study investigating the underlying mechanisms of Post-Intensive Care Syndrome (PICS).

This is a pilot, prospective cohort study. The study is being co-ordinated by the unit of anaesthesia, critical care and peri-operative medicine at the University of Glasgow. Post-Intensive Care Syndrome refers to the collection of physical, cognitive and psychological sequalae commonly seen in survivors of critical illness. The objective of the CONDUCT-ICU trial is to develop our understanding of the pathophysiological mechanisms underlying the development of PICS, specifically the association between myocardial inflammation and PICS symptoms. Furthermore, we aim to evaluate the feasibility of Cardiac Magnetic Resonance Imaging of assessing cardiac function in survivors of sepsis following intensive care.

This study will involve cardiac magnetic resonance imaging 6-10 weeks following hospital discharge to assess for myocardial inflammation for 35 participants. Blood samples and (if not undertaken whilst in ICU already and echocardiogram) will be obtained at baseline or within 7 days of discharge from ICU. 6-10 weeks after hospital discharge, we will undertake CMR imaging in 35 participants who undergo and for an additional 34 participants we will collect blood samples only. All bloods will be analysed for inflammatory and cardiac biomarkers. At follow up, we will assess symptomatology by gathering a variety of outcome measure questionnaires for all participants.

Your patient has been provided with an information sheet for the trial which explains why she/he has been approached to take part in the trial by providing baseline and follow up CMR imaging data, blood samples and questionnaire responses. The information explains that their participation is entirely voluntary, and emphasises that they are free to withdraw from the trial at any time without prejudicing their future medical care.

Participants will be provided with a summary of the study results if they wish. We will not contact you further regarding your patient's participation in this study unless their echocardiogram or MRI scan indicates a significant abnormality or unless psychological support for your patient, which is often needed in survivors of critical illness, is required. In such an event, we will provide you with the necessary clinical information. If psychological support if required we will offer this through our ICU follow-up service and in addition, encourage them to make an appointment with their GP.

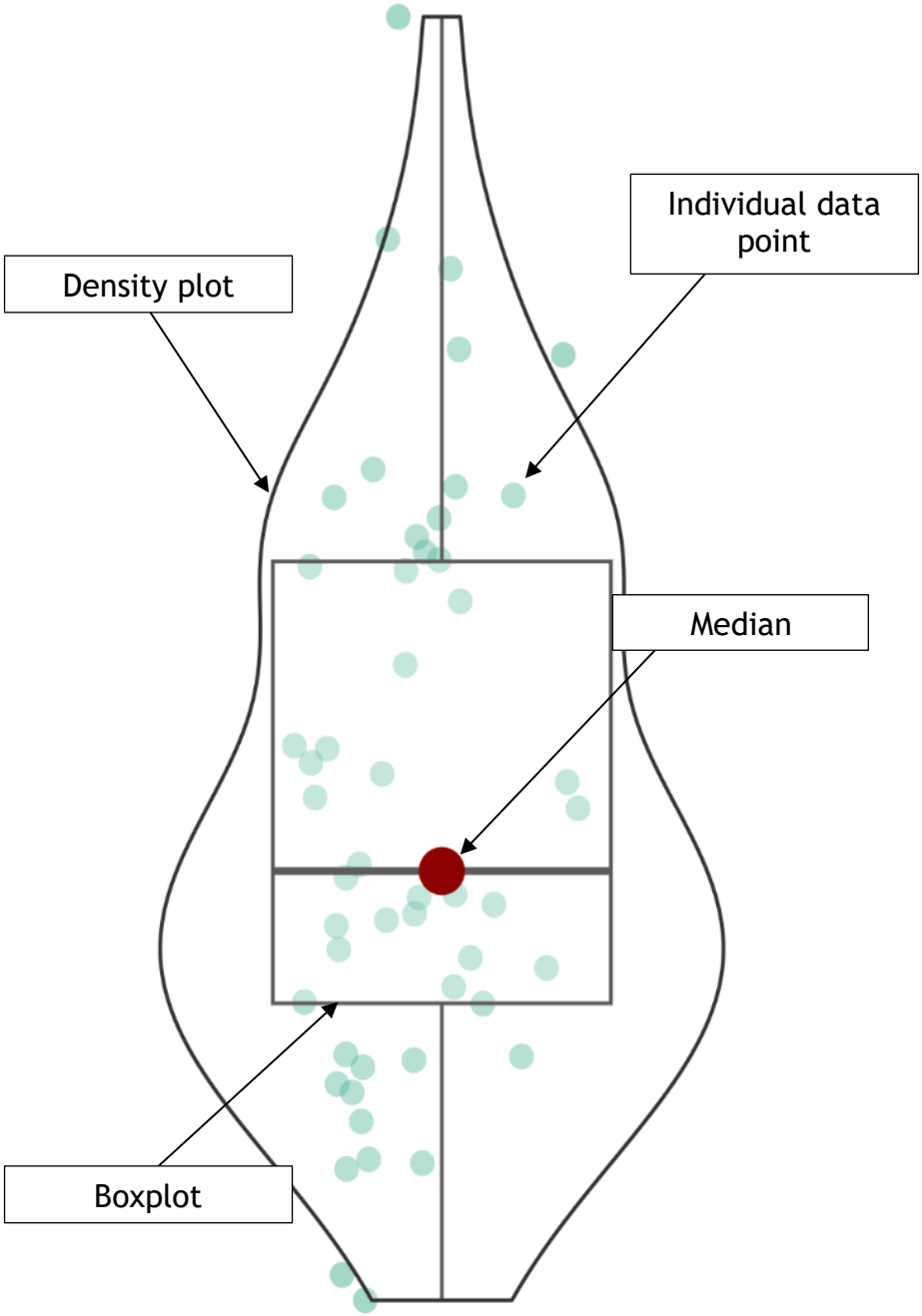
Should you have any questions or require further information about this research, please do not hesitate to contact the CONDUCT-ICU team on the emails below

Dr Kevin Garrity, Email: kevin.garrity@glasgow.ac.uk
Dr Christie Docherty, Email: christie.docherty@glasgow.ac.uk

Kind regards
Yours sincerely,

Enc. CONDUCT-ICU Patient Information Sheet

Appendix 6
Anatomy of a violin plot



Appendix 6 - Anatomy of a violin plot.

The above plot depicts a standard violin plot utilised in the thesis to visualise biomarker values and their distribution. The light coloured dots indicate individual data points. The median is indicated by red dot in the middle of the plot. A boxplot frames the data, with a box indicating the median and interquartile range, and the 'whiskers' (straight vertical line) indicating the maximum and minimum values in the data. The distribution of the data is depicted by a superimposed density plot, where greater horizontal width of two curves indicates the density of datapoints around this particular value. In this thesis, often two violin plots are shown to visualise how the data changes over time (Point of ICU discharge to 6-10 weeks post discharge) or between different sub-groups (LVSD vs no LVSD).

Appendix 7
CMR protocol

CONDUCT-ICU

Study Specific Standard Operating Procedure

MRI Acquisition

Version 3.0

Date: 16/01/22

Authors: Kenneth Mangion

Contributors: Kevin Garrity

Sponsor: NHSGG&C

REC Reference Number	309553
Sponsor Protocol Number	GN22CA029

CONFIDENTIAL

Table of Contents

1. Purpose

To describe the cardiovascular magnetic resonance (CMR) imaging in CONDUCT-ICU.

To optimise CMR acquisition for myocardial blood flow (ml/min/g tissue).

2. Scope

Team members involved in supervising and performing CMR as part of this study.

3. Background

There are over 250,000 admissions to intensive care annually in the UK[1 2]. With advances in technology and treatment, survival from common admitting diagnoses such as sepsis has improved.[3] Whilst survival from critical illness has improved over the last decades, it is now recognised that up to 60% of survivors suffer from long lasting impairments following critical illness. Commonly identified impairments are described as encompassing three broad domains: physical, cognitive, and psychological. Collectively, they have often been termed Post Intensive Care Syndrome (PICS). Presently, there are limited data longitudinally examining the pathophysiological mechanisms which may be involved in the range of symptoms experienced.

This protocol is part of CONDUCT-ICU, a novel study in survivors of sepsis aiming to understand mechanisms of cardiovascular dysfunction following critical illness with sepsis and if they might play a role in post-intensive care syndrome.

Table 1 Schedule of Research Data Collection

	ICU Discharge	6-10 weeks post-hospital discharge
Consent	X	
Baseline Demographics	X	
Patient Reported Outcome Measure / Functional Status		X
CMR		X
Biomarkers		
• Myocardial Dysfunction (hs-Troponin I, BNP)	X	X
• Renal Function (Urea + Electrolytes)	X	
• Inflammatory markers	X	X

4. Overview and key points

Prospective, multi-site, observational, cardiovascular imaging and biomarker cohort study in 45 survivors of severe sepsis previously admitted to ICU.

5. Eligibility criteria

Inclusion criteria

1. Able to comply with the study procedures
2. Written informed consent.

Exclusion criteria

1. Implantable cardiac device i.e. pacemaker, implantable defibrillator.

6. Invitation to attend

The participants should be contacted by telephone the day before the scan to check on

1) wellbeing,

2) MRI exclusion criteria e.g. metallic foreign body,

7. CMR set-up

MR imaging will be obtained in patients who have given written informed consent and who have satisfied the local safety criteria for CMR.

CMR safety checks include renal function (GFR >45 ml/min) and contra-indications to MRI: ferrous metal foreign body, severe claustrophobia. *If GFR is <45ml/min then a non-contrast CMR scan will be performed.*

8. Measurements to be recorded at the time of each CMR examination

- Participant ID
- Date, time,
- Height and weight, calculate BMI

- A full blood count (FBC) should have been obtained before the scan to permit measurement of extracellular volume. The FBC may be available from the routine standard of care test or the safety assessment bloods scheduled for each visit.
- Record heart rate, systolic blood pressure, diastolic blood pressure during study.

9. Patient preparation

Patient preparation includes:

- Explain to the patient the steps involved in the CMR scan and answer any questions
- Insert intravenous cannula x1 for gadolinium contrast media
- Complete the standard of care MRI checklist, as per local rules
- Confirm no contraindications to MRI e.g. pacemakers, brain clips, foreign bodies, insulin pump
- Confirm the eGFR is known >45 mL/min
- Take the patient into the CMR room and give guidance and reassurance on lying in the scanner,
- Prime the pump injector with the contrast media
- Apply ECG electrodes – may need to shave the chest; ensure good R-wave detection
- Confirm the heart rate detection and blood pressure

After the scan, guide the patient out from the scanner room and give summary feedback

10. CMR acquisition

General points

- Reassure the patient
- Provide guidance on breathing manoeuvres and breath-holding
- Confirm ECG detection
- Perform a perfusion test scan to check image quality, timing and artefacts
- Practice the breath-holding manoeuvre before starting the scan.

Protocol set-up

The MRI protocol will include

- Standard localisers,
- Coronal and sagittal HASTE renal acquisitions (including both kidneys in the field of view)

- Cine imaging for cardiac dimensions and function including long axis left ventricular imaging e.g. 4 and 3 chamber acquisitions,
- T2 mapping (Short axis stack and HLA = all scans)
- T1-mapping (; 3 short axis slices and HLA in rest protocol)
- First-pass perfusion imaging
- Cine imaging of the LV short axis stack
- Late gadolinium enhancement imaging
- Post-contrast T1 mapping (3 short axis MOLLI)

Please ensure the same slice positions are used throughout the scan.

11.CMR protocol pre-contrast

	Acquisition method	Guidance	Duration (minutes)
PRE -CONTRAST SCAN	Localisers/ Planning (heart)	X1 Bright blood, 4,3, 2 chamber	2/
	T2 mapping (heart)	SA full stack, HLA	2/
	T1 mapping (heart)	SA Basal, Mid-LV, apex, HLA	2/
	Contrast injection		
POST CONTRAST	Cardiac Perfusion	3 of 5 SA	5/
	Cine SSFP	SA full stack, 4,3,2 chamber	2-5 /
	Late gadolinium enhancement	SA full stack, 4,3,2 chamber	6/
	T1 mapping (heart)	SA Basal, Mid-LV, apex	2/

Localisers and planning

The CMR protocol includes three orthogonal 'white blood' sequences (axial, sagittal and coronal) and long axis cine imaging (vertical long axis, horizontal long axis and 3 chamber view) to identify the LV outflow tract (LVOT). The localizer acquisitions should be conducted according to the site's best practice.

T2 map

T2 mapping using a T2w SSFP sequence should be acquired with a short axis LV stack, slices aligned to T1 maps, from the mitral valve to apex (usually 10 slices in total). Extra slices are acquired basally to MV that incorporate LVOT and also potentially to apex

T1 map – pre-contrast (MOLLI)

Plan the 3 short-axis (basal, mid, apical) perfusion slices – T1-maps should match these slice positions

Stress protocol – include single mid-LV and 4 Ch T1 map only.

MOLLI: Three short axis (basal, mid and apical positions) and one 4-chamber T1-maps should be acquired. Use the 5(3)3 MOLLI method for the pre-contrast imaging only. Two options are available in the Myomaps package according to heart rate (see vendor instructions). A different variant is used for the post-contrast MOLLI (see below).

Contrast administration – first pass perfusion

Key points

The intravenous contrast agent is gadobutrol (Gadovist®, Bayer; 1.0 mmol/ml solution for injection) at a dose of 0.05 mmol/kg at 4 ml/s and a 20 ml flush. This dose is used for stress and rest imaging. The dose enhances linearity in signal intensity. Imaging is acquired during the first-pass of contrast through the heart.

An automated pump injector (e.g. Medrad) should be used for intravenous injection of the contrast media.

Perfusion imaging: pulse sequences and slice position

The pulse sequence acquisition will depend on the field strength of the CMR scanner. A fast low-angle shot (FLASH) pulse sequence will be used at 3.0T.

The perfusion method consists of a dual sequence approach. The first pulse sequence acquisition involves a low resolution acquisition to estimate the arterial input function (AIF) from the dynamic signal intensity change in the LV blood pool. The second pulse sequence acquisition for higher resolution imaging of signal intensity changes in the LV myocardium. Usually linear order base to apex short axis scans are prescribed using a long axis cine in a systolic phase. The perfusion images are acquired more in systole. In this way, acquisition of the LV outflow tract can be avoided. Copying slice positions between modalities i.e. cine – T1 – perfusion, can lead to mis-registration.

Ideally, similar (but not necessarily identical) slice positions should be used as for the perfusion and T1-mapping.

Pixel mapping myocardial perfusion

A dedicated perfusion pulse sequence will be used- NIH C2P sequence. Typical features of the pulse sequence involve a low flip angle low resolution protocol for AIF imaging with 2 echoes and short echo times to minimize T2* losses at high concentration. The non-linearity of saturation recovery is minimised by using a short saturation delay using a small matrix and parallel imaging to reduce the number of phase encode lines. The remaining non-linear response is corrected by converting to gadolinium concentration units by means of a look-up-table calculated by a Bloch simulation of the specific imaging protocol, which was recalculated for each scan as part of the image reconstruction. Myocardial perfusion is then calculated using a blood tissue exchange model and pixel-wise perfusion maps are automatically generated in-line.

Typical first-pass imaging parameters:

Saturation recovery with inversion pulse. Myocardial slice parameters - T1 105 ms for SSFP at 1.5T, 110 ms for FLASH at 3.0T; TR/TE = 142/1.04 for 1.5T SSFP; TR/TE = 146/1.0 for 3.0T FLASH; acquisition window 5000 ms; one concatenation; ***3 SAX*** slices. If three slices cannot be acquired within the R-R cycle then use 2 concatenations. Specifically, acquire a minimum of 60 measurements. Increase to 90 measurement if the cardiac output is low. Start the scan and administer the gadolinium contrast media bolus after 8 heart beats. If 2 concatenations are used, then use 45 measurements and administer gadolinium bolus after 16 heartbeats.

Left ventricular function

The cine-CMR for LV mass and function will be collected during the interval between perfusion imaging and late gadolinium enhancement imaging. Cine-CMR should be acquired with a short axis LV stack, slices aligned to T1 maps, from the mitral valve to apex (usually 10 slices in total). Extra slices are acquired basally to MV that incorporate LVOT and also potentially to apex (usually 10 slices in total).

Steady-state free precession (SSFP) cine breath-hold sequences (with parallel imaging acceleration) using a trueFISP sequence (multi-slice single-shot breath-hold true fast imaging) will be used. The heart will be imaged in multiple parallel short-axis (SAX) planes 8-mm thick separated by 2 mm gaps, equating to approximately 10 slices and 30 cardiac phases.

Typical SSFP imaging parameters:

Voxel size 2.0 x 2.0 x 8.0 mm; TR/TE actual TR =30 ms (35 ms worst case) /1.12 ms; flip angle 55°, matrix 192 x 192 pixels; slice thickness 8 mm, with 2 mm gap.

Late gadolinium enhancement imaging

Imaging for myocardial scar and fibrosis will be scheduled for 10 - 15 minutes after the second IV dose of Gadovist contrast media.

In general, a local, preferred method of dark blood late gadolinium enhancement (LGE) imaging should be used. A free-breathing dark blood phase sensitive inversion recovery (PSIR) motion-corrected (MOCO) late gadolinium enhancement technique (LGE) is recommended. A full stack, aligned to the T1 maps (and T2 maps and cines), and at least one long axis view (vertical long axis, horizontal long axis or 3 chamber view) will be acquired. Phase-sensitive inversion recovery CMR techniques reduce variability relating to myocardial nulling which is required for late gadolinium enhancement imaging of infarct vs. unaffected myocardium. If a phase-sensitive protocol is not used, a modified Look-Locker inversion time scout will be performed prior to using an inversion recovery turbo gradient echo sequence. Phase swaps will be performed where appropriate to rule out artefact.

Poor breath-holding during late enhancement imaging

A single shot technique or MOCO PSIR LGE technique (if available) will be used as an option for those patients with difficulty breath-holding.

Typical late enhancement imaging parameters:

Matrix 192 x 256 pixels; flip angle 25°; TE 3.36 ms; bandwidth 130 Hz/pixel; echo spacing 8.7ms and trigger pulse 2. The voxel size is 1.8 x 1.3 x 8 mm. Inversion times individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

Post-contrast T1 mapping

One mid-ventricular short axis T1-map should be acquired each using the MOLLI and ShMOLLI techniques. The acquisition should be matched to the pre-contrast mid-LV T1-map scans. For MOLLI, the post-contrast T1-map should be acquired using the 4(1)3(1)2 variant for post-contrast imaging. For ShMOLLI, simply append the pre-contrast mid-ventricular native T1-map and acquire. The timing of the scan is expected to be >15 min after the second dose of gadolinium contrast media.

12.Accelerated protocol

If the patient is tolerating the scan poorly, please focus on acquiring this cardiac imaging protocol:

Acquisition method	Guidance	Free-breathing	Duration (minutes)
Localisers/ Planning	X1 Bright blood, 4, 3, 2 chamber	No	2/2
Contrast injection			
Cine SSFP (retro- gated or compressed sensing)	SA full stack, 4 chamber	No	10/12 (2: compressed sensing)
Late gadolinium enhancement (single shot for poor breath-holding)	SA full stack, 4 chamber	No	8/20

13.CMR annotation

All MRIs must be anonymised prior to upload to the eCRF with all patient identifiers removed.

The method used is the same as that for other data such as the ECGs and CTCA, the required method is detailed below:

ID: CONDUCT-ICU_Participant No_YYYYMMDD

Name: CMR_TIMEPOINT (Visit 1 or 2)

Example: ID: CONDUCT-ICU_054_20200612; NAME: CMR_Visit_1

14.CMR data storage

The raw, source de-identified data should be stored either manually as SIEMENS .dat files or ISMRM .dat files. Instructions can be provided.

15.CMR analyses

The CMR analyses will be described in a separate SOP. The outcome parameters are listed in the Appendix.

In general, pixel-wise perfusion maps will be automatically generated in-line to represent fully quantitative MBF estimates in mL/min/g of myocardium. The pixel-wise perfusion method uses a series of automated post-processing steps on the raw Digital Imaging and Communications in Medicine (DICOM) images to generate fully quantitative pixel maps..

Central laboratory analyses will be undertaken in the University of Glasgow.

Appendix 8
Lab protocol

CONDUCT – ICU

Characterisation of Cardiac Function in ICU Survivors of Sepsis

Sample Handling and Processing Manual

Main Study

	Name	Signature	Date
Complied By:	Kevin Garrity Christie Docherty	[redacted] [redacted]	12/10/2022
CI Acceptance:	Tara Quasim	[redacted]	13/10/2022

CONDUCT-ICU
Laboratory Sample Handling and Processing Manual

1. Purpose

To describe the procedures to collect and process blood samples from the CONDUCT-ICU study.

2. Sample Collection

Dedicated clinical research fellows will collect study samples using vacutainers with pre-prepared barcodes, as described below. These will be made available from the NHS biorepository and collected prior to recruitment. These are anonymised with study ID numbers. Samples will be processed in accordance with the SOP below.

Samples will be brought to the Biorepository as described below. Samples should be transferred with notice of their arrival to allow any contingency measures to be put in place. Samples should be transferred Monday – Friday between 9am-4pm. Please notify the Biorepository of any samples being collected.

Where there is going to be a period of absence from the Biorepository labs due to illness or holiday, there are contingency plans in place. The laboratory staff at the Biorepository should inform clinical research fellows of such periods with as much notice as possible. Contact details are in section 7 below to help facilitate dialogue with team members.

Efforts to minimise time from sample collection to processing should be made as described below.

3. Summary Sample Collection Schedule

Biological Sample	Purpose	Recruitment (Visit 1)	6-10 week post ICU follow-up (Visit -2)
Serum SST	CRP TNF-α IL-1β IL-6 IL-10 Biobanking	8mls	8mls
EDTA	NTproBNP hsTnT hsTNI Biobanking	8mls	8mls
Total volume of blood drawn		**16mls**	**16mls**

4. Sample Collection Pack

4.1. Recruitment and 6-10 week Follow-Up Visits

Sample Collection

4ml SST Vacutainer	X2
4ml EDTA Vacutainer	X2

Sundry Items

Sample Collection Record Log Sheet

Barcode Labels

Case Report Form

Lab Request Forms

Blood Collection Set

Alcohol Swab

Cotton Swab

Plaster

Tourniquet

Blood Transfer Unit and Sharps Bin

5. Patient IDs, Time-Point Identifiers and Sample Tube Labels

5.1. Patient IDs

Each participant will be assigned a participant study ID. This is recorded in the CRF and the sample collection record log. Sample collection record log will be kept in the study notes. Pre-printed barcodes will link the study ID assigned to the biobank samples stored. Patient ID numbers take the form xxx

5.2. Study Site & Visit Number

The site of collection, date and visit number should be recorded in the eCRF and CONDUCT-ICU sample collection record log.

5.3. Sample Tube Labelling

Samples labelled will be labelled with the following unique study codes:

Sample Labelling

Sample Type	Label
SST	TS-xxx-Visitx-Suffix
EDTA	TE-xxx-Visitx-Suffix

Vacutainer and Aliquotted Blood Sample Barcodes

Purpose	Prefix	Number	Visit	Suffix	LABEL
Parent SST Tubes	TS-	xxx	1,2	1,2	TS-xxx-x-x
Parent EDTA Tubes	TE-	xxx	1,2	1,2	TE-xxx-x-x
Aliquots					
SST Serum	AS-	xxx	1,2	1,2,3	AS-xxx-x-x
EDTA Plasma	AE-	xxx	1,2	1,2,3	AE-xxx-x-x

In the event a barcode cannot be found or used, manually label tubes with a black laboratory grade permanent marker pen using the above system. This should be recorded in the comments on the CONDUCT-ICU sample collection record log. Barcode labels can be added to aliquots at first thaw for analysis.

6. Sample Collection Procedure

6.1. Preconditions

- No fasting is required prior to the test
- Test may be performed at any time of day

6.2. Blood Collection Procedure

Set out a disposable white 'sharps tray' with the following:

- Barcoded vacutainers (see above)
- Blood collection set
- Alcohol Wipe
- Gauze Swab
- Plaster
- Tape

- Explain the procedure to the patient. Total amount of blood taken will be 16mls (about 3 teaspoons).
- Ensure the patient is sitting/lying comfortable with their arm supported.
- Attach needle to vacutainer holder.
- Apply torniquet to patient's upper arm and palpate to find a suitable vein.
- Wash hands or use alcohol scrub. Clean patient's arm with alcohol wipe.
- Allow to dry prior to venepuncture.
- Insert needle into vein and attach vacutainer to holder.

To avoid cross-contamination, take the samples in the following order.

1) SST Serum Separator 2 x 4mls
2) EDTA 2 x 4mls

- Slacken tourniquet once good blood flow has been achieved
- Allow at least 10 seconds for a complete blood draw into each tube. Ensure blood has stopped flowing into the tube before removal.
- Once full sample has been taken, remove the tourniquet
- Cover puncture site with guaze swap and remove needle from arm. **After** needle is removed then apply pressure to the area.
- Instruct patient to keep their arm straight and press firmly for several minutes.
- All sample bottles should be gently inverted 8 times to ensure thorough mixing.
- Dispose of used needle, swab and vacutainer holder in sharps bin
- Dispose of swab in clinical waste bag
- Check patient's arm and ensure puncture site has stopped bleeding.
- Check if patient is taking anticoagulant medication.
- Ask patient if they are allergic to plaster. If not, apply to the puncture site.

- **Ensure all vacutainers are labelled as above using relevant patient ID**
- Time the sample was taken must be recorded in the CRF
- Primary vacutainers must be immediately stored cold and to be returned within 24 hours to the NHS Biorepository between Monday-Friday 9am-4pm.

8. Laboratory Sample Processing

8.1. University Blood Samples

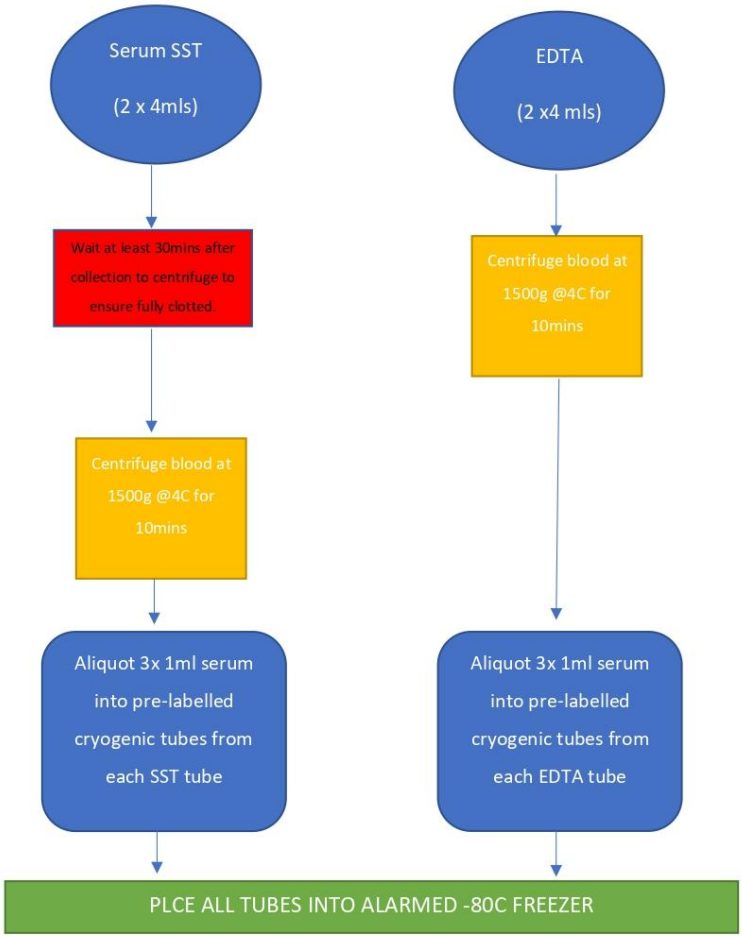
CONDUCT-ICU blood samples will be centrifuged according to the following protocol at the GGC Biorepository laboratory housed within the laboratory building of Queen Elizabeth University Hospital, Govan Road, Glasgow. The resulting plasma/ serum should be aliquoted into appropriately labelled transfer tubes and stored temporarily on site in a -80 Biorepository freezer. Batches will be sent (by taxi or private car) by arrangement to the main BHF GCRC University of Glasgow Metabolic Medicine biomarker lab (see section 7 for contacts).

A) SST Vacutainers (4ml x2)
   - Note collection time of all vacutainers in sample collection record log in study specific file on MS teams. Complete all relevant information, using a barcode scanner where relevant, in the document before saving. Include a copy of a parent vacutainer barcode sample on collection record log.
   - **The SST vacutainer should be allowed to stand for at least 30mins from collection prior to being centrifuged.**
   - Centrifuge blood samples at 1500g @4°C for 10 minutes
   - Aliquot serum into 1ml aliquots in 1.5ml Cryovials. Label cryovials with appropriate barcodes.
   - If less than the requested 3x 1ml aliquots is obtained then the maximum obtained should be stored and deviation recorded.
   - Place capped barcoded cryogenic tubes into 10x10 cryovial box (as per below guide), then into -80°C freezer.

B) EDTA Vacutainers (4ml x2)
   - Note collection time of plasma tubes in sample collection record log & eCRF, as well as parent and transfer tube barcodes.
   - Centrifuge blood samples at 1500g @4°C for 10 minutes
   - Aliquot plasma into 1ml aliquots in 1.5ml cryovials. Label cryovials with appropriate barcodes.

- If less than the requested 3x 1ml aliquots is obtained then the maximum obtained should be stored and deviation recorded.
- Place capped barcoded cryogenic tubes into 10x10 cryovial box (as per below guide), then into -80°C freezer.

8.2. Laboratory Sample Processing Summary



8.3. Storage

- Aliquoted samples will be stored in a -80 freezer in the GGC Biorepository.
- Samples will be boxed in 10x10 cryovial boxes according to sample type (EDTA/SST). Study boxes will be labelled using *"CONDUCT-ICU, Box X, Sample Type"* where X is the sequential box number.
- Boxes are filled entirely using sequentially received samples, before another box is started.
- Boxes are filled from A1-A10 positions, then B1-B10 etc
- Each position has an aliquot with the corresponding barcode information completed in the CONDUCT-ICU sample collection record log in the MS teams channel.
- If a sample is missing due to insufficient sample, this information should be recorded in the database using 'null'. The corresponding box positions are left empty.

8.4. Other information and deviations

This lab manual should be used in conjunction with other lab SOPs relevant for the storage and management of CTIMPs/Observational Studies.

In particular, a "Deviation record" should be noted on the sample record form if there is significant deviation from this manual. Information for specific samples should be completed in the comments section.

In certain cases where there has been a deviation from protocol the sample may need to be destroyed. If the sample is potentially viable, options for it to remain in the study should be explored. If there is any ambiguity in specific cases then the Biorepository should contact Principal Investigators, Christie Docherty and Kevin Garrity for clarification.

A specific non-exhaustive list of examples would include:

- Samples that have been inappropriately treated (e.g. frozen in transit while still in the whole blood storage) should be recorded in the collection log, and a deviation form completed. Samples should be destroyed in this case.

- If the biorepository has been contacted to expect samples and none are received or if fewer samples are received than indicated on the form then this should be identified and recorded in the collection log.
- Any samples which are received using identifiable information to label them (name, DOB) should be considered potentially viable as these samples have been transferred from an NHS-to-NHS site. These samples should be relabelled and should continue in the study. A deviation should be recorded on the sample record log form.

8.5. Contingency Plan

Lab staff at the GGC Biorepository should notify the PIs if there will be no staff availability to process samples. If possible, we will make alternative arrangements to have the samples stored and processed via alternative and secure means (e.g. at satellite BHF lab in QEUH) if resources permit. Samples should be treated in accordance with the protocol above. Samples should be returned to primary CONDUCT-ICU boxes in the Biorepository as soon as practically possible.

9. Appendix 1 – Sample Record Log (Study Bloods)

Affix label here

Site Name	Study ID	Visit Number
		1 ☐ 2 ☐

Samples Collected

Tube Type	Collected (Y/N) If N state number collected	Destination
SST 4ml (Serum) X2		NHS Biorepository
EDTA 4ml (Plasma) X2		NHS Biorepository

Dispatch samples to destination	
Sample Collection	Date:
	Time:
Sent by (print name)	
Signature	

Samples Received at NHS biorepository

Samples Received	Date:
	Time:
Number of Samples Received	SST:
	EDTA:

Comments/ Deviations:

Appendix 9
EuroQol 5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

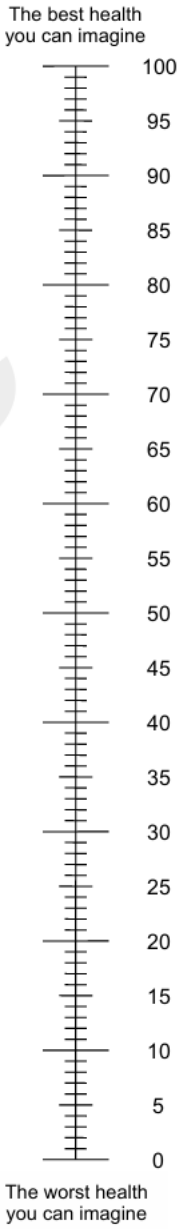
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10
Hospital anxiety and depression scale (HADS)

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Appendix 11
Short form 36 vitality domain

Do you feel full of pep?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little bit of the time
- None of the time

Do you have a lot of energy?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little bit of the time
- None of the time

Did you feel worn out?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little bit of the time
- None of the time

Did you feel tired?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little bit of the time
- None of the time

Appendix 12
MRC breathlessness scale

MRC Dyspnoea Scale	
1	Breathless only with strenuous exercise
2	Short of breath when hurrying on the level or up a slight hill.
3	Slower than most people of the same age on a level surface or Have to stop when walking at my own pace on the level.
4	Stop for breath walking 100 meters or After a walking few minutes at my own pace on the level
5	Too breathless to leave the house.

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