The impact of chronic liver disease on critically ill patients

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Abstract

In the UK, mortality from liver disease has increased by 400% between 1970 and 2010 with death rates for those under 65 having risen by almost 500% (1). Up to 75% of deaths related to chronic liver disease have an underlying aetiology of alcohol and are preventable (1, 2). Advanced chronic liver disease leads to multi-system clinical manifestations, many of which will require critical care. Evidence supporting this claim is seen in the increase in admissions to critical care for those patients with cirrhosis (3). These patients have higher rates of readmission to ICU (Intensive Care Unit), longer length of ICU stay and have an increased requirement for organ support (4). Despite this, both ICU and hospital mortality in those with cirrhosis have improved since the 1980s where mortality was reported to be up to 100% (5-7).

With fewer beds compared to the USA or other European countries the existing demand on critical care capacity in the UK is increasing. There remains a need for a greater number of centres offering both critical care and hepatology input, with a significant number of hospitals nationwide lacking any hepatology input (8). Assessment of critically ill patients with cirrhosis is challenging, with many prognostic scoring systems in use. To date, no scoring system has been demonstrated to be superior in stratifying which patients would benefit from ICU admission. With the existing pressure on limited critical care beds within the UK and the increased demand to support critically ill patients, identifying those patients who merit admission to critical care will become an increasingly important challenge.

This thesis focuses on the factors used in the decision to admit a patient with advanced chronic liver disease or cirrhosis to critical care, their long-term survival and quality of life. Attention is given to the utility of the Child-Pugh score and when it should be assessed. As the majority of deaths due to chronic liver disease have an underlying aetiology of alcohol, this thesis will also address how an alcohol use disorder can be assessed in the critically ill.

The first investigation of this thesis explores the criteria used in the decision to escalate a patient to intensive care. This is explored through 2 Scottish surveys of consultant gastroenterologists and intensivists. Results highlighted agreement

by both specialities on the importance of Child-Pugh score measured when a patient was clinically stable. Inconsistencies were evident in the escalation of therapy with intensivists more likely to offer intensive care and multi-organ support as compared to gastroenterologists.

In response to these findings, the timing and utility of Child-Pugh score was investigated. This observational cohort study compared Child-Pugh score measured on ICU admission with the score when a patient was clinically stable and short-term mortality. Only Child-Pugh score measured at time of ICU admission was associated with hospital mortality, which contradicted the findings of the previous chapter. The degree of change in Child-Pugh score between these time points was associated with mortality.

Given that the majority of deaths due to chronic liver disease in the UK are primarily caused by alcohol, challenges exist in identifying alcohol use disorders in the critically ill. A prospective study examined the use of a proxy to report an alcohol use disorder in critically ill patients and suggested that a proxy could be used as a reliable historian.

Whilst short-term survival of critically ill cirrhotics has improved, there is a paucity of studies reporting long-term outcomes. An observational cohort study investigated survival at 12 months for cirrhotic patients admitted to a general ICU in the UK. Long-term survival following an ICU stay has improved, in keeping with other studies. When measured on admission to ICU, Child-Pugh class was demonstrated to stratify patients into 3 distinct groups for long-term survival.

With the improvement in survival, the sequelae of an ICU stay were investigated. A prospective observational cohort study explored the long-term quality of life and prevalence of sleep disturbance. A number of survivors reported that their quality of life was worse than, or equal to death. Quality of life and sleep disturbance were influenced by pre-existing comorbidity and events during their ICU. In this study, there was no association found between QOL and insomnia in those with liver cirrhosis.

This thesis addresses the decision to admit a patient with advanced chronic liver disease or cirrhosis to critical care, reports their long-term survival and quality

of life and explores how one preventable cause of chronic liver disease can be assessed in the critically ill by use of a proxy.

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Author's Declaration

The work described in this thesis was performed by me whilst I was employed as an Anaesthetic Clinical Research Fellow at the University of Glasgow and latterly, as an Anaesthetic and Intensive Care Medicine speciality trainee in the West of Scotland. It was carried out between September 2014 and April 2019.

Data collection, analysis and reporting of the long-term outcome study was performed by Mr Alex Warren, a 3rd year medical student who I supervised during an intercalated BSc in Perioperative and Critical Care Medicine. Alex assisted with data collection in the quality of life and insomnia study during a Vacation Research Scholarship awarded by Medical Research Scotland. I was solely responsible for further data collection, analysis and interpretation. The concepts for both studies were my own.

The majority of recruitment in the proxy study was performed by me, with the remainder of recruitment carried out by individuals who are acknowledged in this thesis.

The remainder of the work described in this thesis was performed by myself and the writing of this thesis was my own work.

Charlotte Soulsby

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Grants

- Patient versus Proxy – use of the AUDIT tool to compare alcohol intake in critical care, £1385. John Robertson Bequest 2014-2015, University of Glasgow. March 2015.

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- Campbell J., McPeake J., Shaw M., Puxty A., Forrest E., **Soulsby C.**, Emerson P., Thomson SJ., Rahman TM., Quasim T., Kinsella J. (2015) Validation and analysis of prognostic scoring systems for critically ill patients with cirrhosis admitted to ICU. *Critical Care*. Dec 19(1):364.

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- **Soulsby C**., Kinsella J., Quasim T., Shaw M., Barclay S., McPeake J. (2015) Organ support, readmission and etiological factors in the management of critically ill cirrhotics. *Critical Care Medicine*. Dec 1;43(12):95.

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- McPeake J., **Soulsby CR**., Quasim T., Kinsella, J. (2015) Intensive care referral and admission: do the criteria for liver disease match? *Critical Care*. Dec;19(1):P384.

- **Soulsby CR**., McPeake J., Ashcroft C., Kinsella J., Shaw M., Quasim T. (2015) Utilisation of existing community rehabilitation services by critical care survivors. *Critical Care*. Dec;19(1):P557.

Presentations

Presented at the Scottish Society of Gastroenterology Spring Meeting, Aberdeen, May 2015.

- Intensive care referral and admission – do the criteria for liver disease match?

Presented at the Scottish Intensive Care Society Audit Group, Glasgow, September 2015.

- Intensive care referral and admission – do the criteria for liver disease match?

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- Long term outcome of patients with liver cirrhosis admitted to a general intensive care unit (presented by Alex Warren, BSc student)

- Does the number of comorbidities before ICU admission influence quality of life after ICU? – Awarded Research Snapshot Award

- Timing and utility of Child-Pugh score in patients with liver cirrhosis referred to ICU

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- Intensive care referral and admission - do the criteria for liver disease match?

- The utilisation of existing community rehabilitation services by critical care survivors

Definitions/Abbreviations

4AT 4 ‘A’s Test

AASLD American Association for the Study of Liver Diseases

ACLF Acute-on-chronic liver failure

ALT Alanine aminotransferase

AMT Abbreviated Mental Test

ANOVA One-way analysis of variance

APA American Psychiatric Association

APACHE Acute physiology and chronic health evaluation

APASL Asian Pacific Association for the study of the liver

ARDS Adult respiratory distress syndrome

AST Aspartate aminotransferase

AUC Area under curve

AUDIT Alcohol use disorders identification test

BMI Body mass index

CAGE Cutting down, annoyance by criticism, guilty feeling, and eye-openers

CANONIC Acute-on-Chronic Liver Failure in Cirrhosis

CDT Carbohydrate-deficient transferrin

CLIF-SOFA Chronic liver failure-sequential organ failure assessment

CI Confidence Interval

CHI Community Health Index

COPD Chronic obstructive pulmonary disease

COS Core outcome set

EASL European Association for the Study of the Liver

EASL-CLIF European Association for the Study of the Liver-Chronic Liver Failure

EQ-5D EuroQol-5D

ED Emergency Department

FAST Fast Alcohol Screening Test

GAHS Glasgow Alcoholic Hepatitis Score

GCS Glasgow Coma Scale

GGT Gamma-glutamyltransferase

GMC General medical council

GRI Glasgow Royal Infirmary

GP General Practitioner

HDU High Dependency Unit

HPS Hepatopulmonary syndrome

HRS Hepatorenal syndrome

HUS Health utility score

ICCO Intensive care cirrhosis outcome

ICNARC Intensive Care National Audit and Research Centre

ICU Intensive Care Unit

INR International Normalised Ratio

IQR Interquartile Range

ISI Insomnia Severity Index

MAP Mean Arterial Pressure

MAST Michigan alcohol screening test

MBRS Mean arterial pressure, bilirubin, acute respiratory failure and sepsis

MCV Mean corpuscular volume

MELD Model for end-stage liver disease

MPM Mortality Prediction Model

MODS Multiple Organ Dysfunction Score

NACSELD North American Consortium for the study of End-Stage Liver Disease

NAFLD Non-alcoholic fatty liver disease

NASH Non-alcoholic steatohepatitis

NHP Nottingham Health Profile

NIAAA National Institute of Alcohol Abuse and Alcoholism

OR Odds Ratio

PICS Postintensive Care Syndrome

PT Prothrombin time

QEUH Queen Elizabeth University Hospital

QOL Quality of life

RFH Royal Free Hospital

ROC Receiver Operating Characteristic

SAPS Simplified Acute Physiology Score

SBP Spontaneous bacterial peritonitis

SF-36 36-Item Short Form Survey

SICSAG Scottish Intensive Care Society Audit Group

SIMD Scottish index of multiple deprivation

SIP Sickness Impact Profile

SOFA Sequential organ failure assessment

SSG Scottish Society of Gastroenterologists

TIPS Transjugular intrahepatic portosystemic shunt

USA United States of America

UK United Kingdom

UKELD United Kingdom model for end-stage liver disease

UNOS United Network of Organ Sharing

WHO World Health Organisation

Chapter 1 Literature Review

1.1 Literature review search strategy

A literature search was performed to establish background knowledge and identify current evidence in this area of research. Electronic databases explored included: Medline; EMBASE; Cochrane Library; Web of Science and Google Scholar. The search was conducted using combinations of keywords, which included: cirrhosis, liver, chronic liver disease, alcohol, intensive care, critical care, critical illness, outcome, survival and scoring system. A search was performed to identify relevant books, Government and professional association websites and policies. Any references of articles related to the search were reviewed. The literature search was updated during the research period to ensure new evidence was incorporated into the thesis.

1.2 The Liver

1.2.1 Anatomy of the liver

Located in the right upper quadrant of the abdomen, the liver weighs approximately 1.5kg and accounts for 2% of total body mass (9). Anatomically the liver is described with 4 lobes; left, right, quadrate and caudate or by 9 segments identified by individual anatomical, portal venous, lymphatic and bilious connections. The liver receives its arterial blood supply from the left and right hepatic arteries and venous blood from the hepatic portal vein. Venous drainage occurs through the hepatic veins to the inferior vena cava. The liver produces bile which drains into left and right hepatic ducts which join to form the common bile duct.

The liver mainly consists of individual cells called hepatocytes which are arranged in plates, separated from vascular sinusoids by endothelial and Kupffer cells (10). The vascular sinusoids consist of both hepatic arterial and portal venous blood and drain into the hepatic veins through central veins (10). Hepatocytes form bile, which is secreted into canaliculi and subsequently drains into bile ducts (10). Cells are surrounded by portal tracts which each contain a branch of the hepatic artery, portal vein and bile duct.

The microanatomical arrangement of hepatocytes is in ‘functional units’ which can be explained by ‘acinar’ or ‘lobular’ concepts (10). In the ‘acinar’ concept, hepatocytes are centred on the portal tracts and arranged into 3 zones (10). Zone 1 is most proximal to the portal tracts whilst zone 3 is located proximal to the central vein. Cells within zone 3 are most distal to the hepatic blood supply and as such are most at risk of vascular insufficiency (10). The ‘lobular’ concept describes hepatocytes arranged around central veins, with portal tracts on the periphery of the lobule. Hepatocytes exhibit heterogeneity, with cells in different zones of the liver performing different physiological functions (11).

1.2.2 Function of the liver

The liver performs multiple physiological roles in synthesis and degradation within the body. The physiological roles of the liver can be divided between those located in the hepatic sinusoids and those within the hepatocytes (11).

Hepatic sinusoidal cells secrete prostaglandin E2, prostacyclin, cytokines and nitric oxide (11). Kupffer cells, located within the sinusoids, are macrophages and perform endocytosis. Kupffer cells fulfil an important role in immunity and inflammation; secreting lipids such as leukotrienes and peptides including interleukin and tumour necrosis factor (11). These specialised cells degrade haemoglobin and remove erythrocytes (11). Pit cells within the sinusoids are natural killer cells performing a role in immunity (11). The sinusoids also contain stellate cells which synthesise collagen and growth factor, aiding hepatic regeneration (11). They regulate hepatic vascular tone and store vitamin A (11).

Hepatocytes display functional heterogeneity; controlling nutrient metabolism and energy production (11). They manage the uptake and release of glucose and amino acids, glycogen synthesis and storage, urea and ketone body production (11). As such, the liver regulates acid-base balance within the body. Hepatocytes synthesise and degrade plasma proteins including albumin; determining plasma oncotic pressure and in addition acting as carrier proteins, protease inhibitors and intercellular messengers (11). Hepatocytes synthesise vitamin K dependent clotting factors, activation factors and fibrinolytic factors regulating haemostasis (11). Cytochrome P450 is located within the hepatocytes and is responsible for drug detoxification, whilst the liver also fulfils a significant role in phase 2

metabolism. In addition, hepatocytes are involved in bile formation and excretion.

1.2.3 Pathophysiology of liver disease

1.2.3.1 Liver injury

Damage to liver cells can result from insults such as hypoxia, ischaemia, drug exposure and infection, with initiation of a number of different pathophysiological processes. Inflammation results from liver injury causing a cellular immune response and cell death (9). Insults to the liver can lead to hepatocyte ballooning, with swelling of the cells and necrosis (9). Furthermore liver injury can result in steatosis, with the development of fat droplets within hepatocytes. Whilst all cells in the liver are able to regenerate in response to injury, repeated insult can impair this process and lead to irreversible damage. Fibrosis results from an inability of the liver to regenerate pre-existing cellular arrangement with deposition of excess collagen and nodular formation altering the liver architecture (9). With continued liver insult vascular remodelling occurs and there is endothelial dysfunction with loss of sinusoidal porosity, vascular thrombosis and increased vascular resistance (9). Fibrous tissue obstructs blood flow leading to shunting of blood and angiogenesis. Until the 1970s the processes of fibrosis and cirrhosis were considered irreversible, however studies now illustrate variable resolution of both fibrosis and cirrhosis with cessation of liver injury (12). Furthermore, the rate of regression or deterioration in liver disease is multifactorial and encompasses the aetiology of liver disease, genetic and environmental factors (9).

1.2.3.2 Cirrhosis

The term ‘cirrhosis’ was first noted in the literature in 1819 by Laennec in the ‘Traité de l’Auscultation’ in which the neoformations within the liver were described by their colour (13). ‘Cirrhosis’ originates from the Greek word *kirrhós* which translates as ‘tawny’, reflecting the tan colour of the liver and *osis* meaning condition (12).

Liver cirrhosis occurs as a result of chronic liver injury with the development of inflammation, fibrogenesis and angiogenesis (14). The World Health Organisation

(WHO) defined cirrhosis in 1978 as "*a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules*"(15). A loss of normal architecture leads to increased resistance to liver blood flow and the development of intrahepatic vascular shunts as anastomoses develop between the hepatic artery and portal vein and efferent centrolobular vessels (12). Whilst the histological diagnosis of cirrhosis is definitive, there is a lack of distinction in the literature in the clinical diagnosis of chronic liver disease and cirrhosis, with both terms often used interchangeably to describe advanced liver disease (16).

This thesis will focus upon advanced liver disease and will refer to both chronic liver disease and cirrhosis. For the remainder of this thesis the term 'cirrhosis' will only be applied if patients had knowingly met the diagnostic criteria for cirrhosis described below or when referring to existing research using that terminology.

The diagnostic criteria used for cirrhosis in this thesis were a histological diagnosis on biopsy or clinical evidence of portal hypertension, encephalopathy or oesophageal varices. These criteria have been used in previous research published by the University of Glasgow Anaesthetic Department (17, 18).

1.2.4 Aetiology of chronic liver disease

There are many causes of chronic liver disease and underlying aetiologies include infection, metabolic, vascular, autoimmune, cholestasis or exposure to toxins. Morbidity and mortality from liver disease is often preventable with modification of risk factors or treatment of the underlying aetiology. The 2012 Annual Report of the Chief Medical Officer noted excess alcohol consumption, obesity and undiagnosed hepatitis infection were all preventable causes of chronic liver disease in England and Wales (2). Alcoholic liver disease and Hepatitis C infection are the most common causes of chronic liver disease in the Western world, whilst chronic liver disease secondary to Hepatitis B infection predominates in Asia and sub-Saharan Africa (19). The most common preventable causes of chronic liver disease are discussed in greater detail below.

1.2.4.1 Alcohol

Analysis of United Kingdom (UK) death certification in 2006 demonstrated that over 80% of deaths due to liver disease were due to an underlying aetiology of alcohol (20). Worldwide, the relationship between alcohol consumption and liver mortality is well recognised (21). Excess alcohol consumption leads to accumulation of fat within hepatocytes and collagen production (10). Furthermore, acetaldehyde – the breakdown product of alcohol - causes inflammation of hepatocytes (10). Risk factors for alcoholic liver disease include female gender, ongoing alcohol use and underlying genetic predisposition, whilst progression of liver disease is accelerated by the presence of other liver insults such as viral infection, obesity or drug exposure (22). With cessation of alcohol consumption, the majority of individuals display improvement in symptoms of chronic disease and the histological changes in the liver can reverse (22).

1.2.4.2 Hepatitis B

Whilst it is estimated that there are 180,000 people with Hepatitis B infection in the UK, it remains the most common cause of chronic liver disease in Asia and sub-Saharan Africa (19, 23). In the UK it is mainly transmitted by unprotected sex, whilst transmission in developing countries is more often from mother to child (24). Infection with Hepatitis B virus leads to the formation of antigens on the cell surface of hepatocytes (10). The resulting host immune response destroys native hepatocytes. Chronic liver disease secondary to Hepatitis B infection may progress to cirrhosis in 10-20% of individuals within 5 years, with 15% of those with cirrhosis dying within 5 years (22). Of the individuals with chronic Hepatitis B infection, 5-10% develop hepatocellular carcinoma (22). Vaccination aims to prevent Hepatitis B infection whilst antiviral medications aim to reduce viral DNA load and can lead to antigen loss or seroconversion of individuals (22).

1.2.4.3 Hepatitis C

There are an estimated 200,000 individuals with Hepatitis C in the UK (25). Approximately 34,500 of those individuals live in Scotland, with transmission primarily through use of infected needles in intravenous drug users (26). It can also be transmitted via blood products, unprotected sex, skin piercings and

tattoo equipment or vertical transmission from mother to child (24). The prevalence of Hepatitis C is higher in other areas of the world, including Africa where 5.3% of the general population are estimated to be infected (24). The risk of progression to cirrhosis in those infected with the virus is increased by excess alcohol consumption, male gender, immunosuppression and advanced age (19). Additionally, progression to cirrhosis is increased in those individuals with concurrent insulin resistance secondary to diabetes or obesity (22). Following the development of cirrhosis, survival with Hepatitis C infection remains high, with up to 91% of those with cirrhosis alive at 5 years and up to 79% alive at 10 years (22). However, once an episode of decompensated liver failure occurs, survival reduces to 50% at 5 years (22). Liver damage is believed to result from three different mechanisms. The virus may directly attack hepatocytes, an autoimmune reaction occurs, or similar to Hepatitis B, a host immune response may occur (22). Antiviral medications exist, which aim to decrease Hepatitis C RNA activity and the introduction of new direct acting antiviral agents appear to show promising improvements in survival for those with end-stage liver disease (22, 27).

1.2.4.4 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the term used to describe both steatosis and non-alcoholic steatohepatitis (NASH) (22). Steatosis is defined as excess triglyceride droplets within hepatocytes, with minimal alcohol consumption (22). When steatohepatitis is associated with necroinflammation the term NASH is applied (22). NASH results from the metabolism of free fatty acids to nontriglyceride metabolites, which cause liver injury (22). With increased rates of obesity worldwide, the incidence of NAFLD continues to rise. Approximately 20% of the UK population are estimated to have NAFLD and it is associated with concurrent diabetes, hypertension, dyslipidaemia and advanced age (24). Up to 50% of individuals with NASH progress to fibrosis or cirrhosis (22). To date there are no recognised pharmacological interventions and treatment for NAFLD consists of weight loss and exercise (28).

1.2.5 Epidemiology of liver disease

1.2.5.1 Worldwide

As many individuals are asymptomatic the exact prevalence of liver disease worldwide remains unknown; however, cirrhosis is estimated to be the 14th most common cause of death and is known to account for 1.03 million deaths per year (29). Mortality from cirrhosis increased between 2005 to 2015 worldwide, however global differences exist (30). Mortality from cirrhosis reduced in east Asia and Europe whilst an increase was noted in central Asia, north Africa and the Middle East (30). These trends are attributed to Hepatitis B vaccination and improvements in treatment of Hepatitis C in developed countries, with increased alcohol consumption and prevalence of Hepatitis C in those countries with increased mortality (30). In 2008 it was estimated up to 1% of the population have histological cirrhosis based on the population prevalence in the United States of America (USA) and Europe (19).

1.2.5.2 United Kingdom

Between 1970 and 2010, mortality rates from liver disease in the UK have increased by 400%; higher than other countries in western Europe (Figure 1-1) (1). Between 2015 and 2017, UK mortality due to liver disease in men was reported as 24.3 deaths per 100,000 and in women the mortality rate was 13 deaths per 100,000 (31). In the UK, liver disease is the third highest cause of premature mortality, with the majority of patients dying within working age (18-65 years) (1). As emphasised in the 2012 Annual Report of the Chief Medical Officer, liver disease was the only cause of premature mortality which had increased in England in contrast to other European countries where premature mortality from liver disease had decreased (2). Death rates in those under 65 have risen by almost 500% (1). Up to 75% of deaths due to liver disease have an underlying aetiology of alcohol (1). In England and Wales 600,000 people are diagnosed with liver disease and 60,000 of these individuals are known to have cirrhosis (1).

Figure 1-1 Graph to show percentage change in standardised UK mortality rates for those aged 0-64 years (1)

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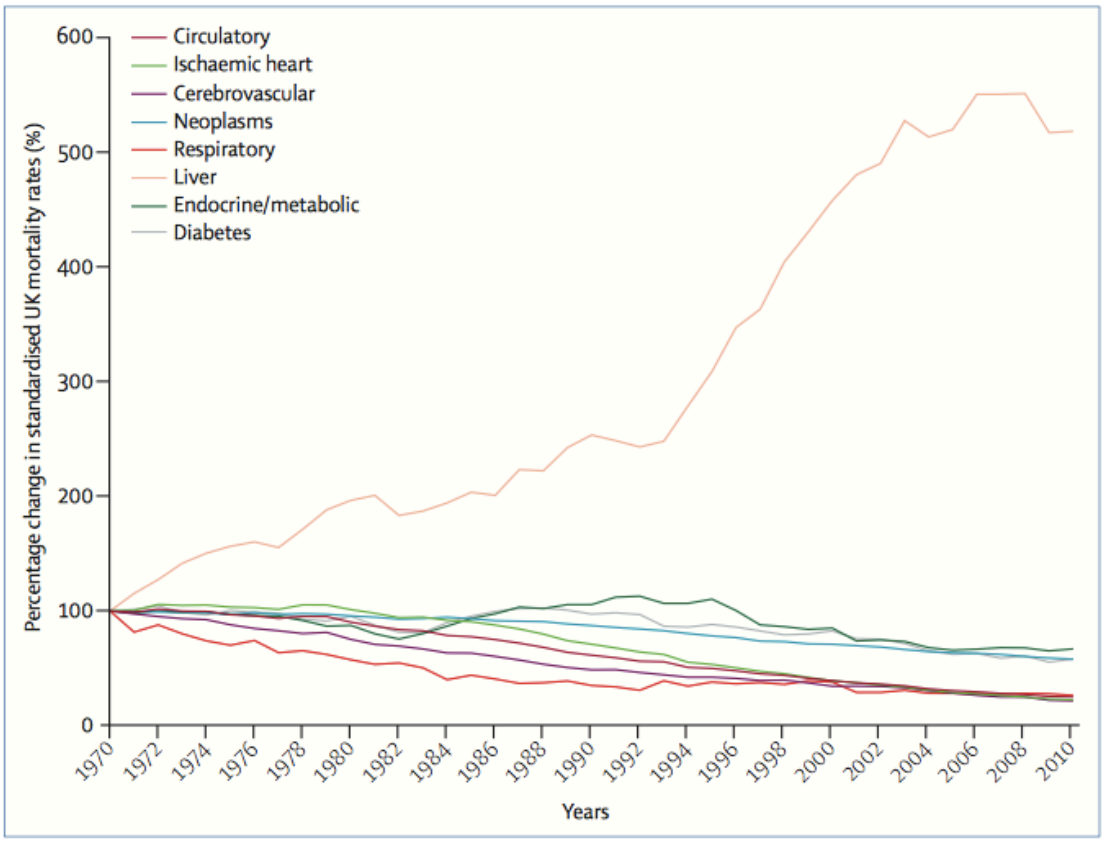
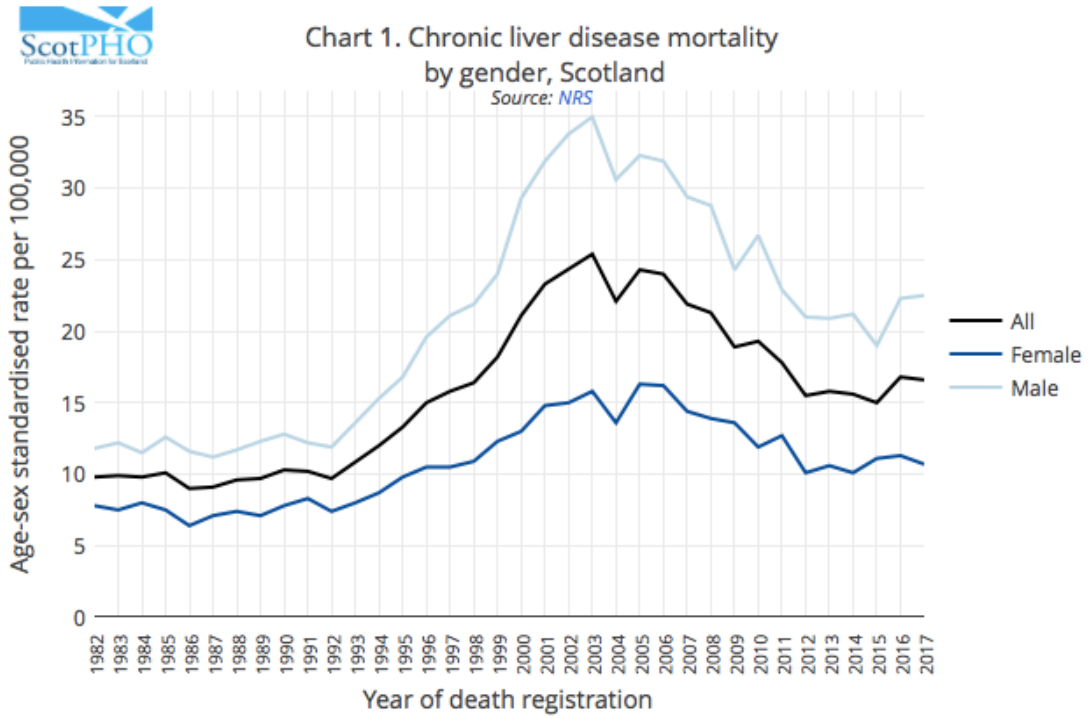


In Scotland, the 2017 death rate for chronic liver disease was 16.6 per 100,000, similar to the 2016 death rate (32). Mortality from chronic liver disease appeared to peak in 2003 at 25.4 per 100,000 people (32). Male mortality (22.5 per 100,000) is twice as high as female mortality (10.7 per 100,000) (Figure 1-2) (32). Reflecting the rest of the UK, alcohol remains the most common underlying aetiology of chronic liver disease causing mortality (32). Mortality secondary to chronic liver disease was highest in NHS Greater Glasgow and Clyde (32). The burden of alcohol in Scotland is discussed in greater detail in Chapter 5.

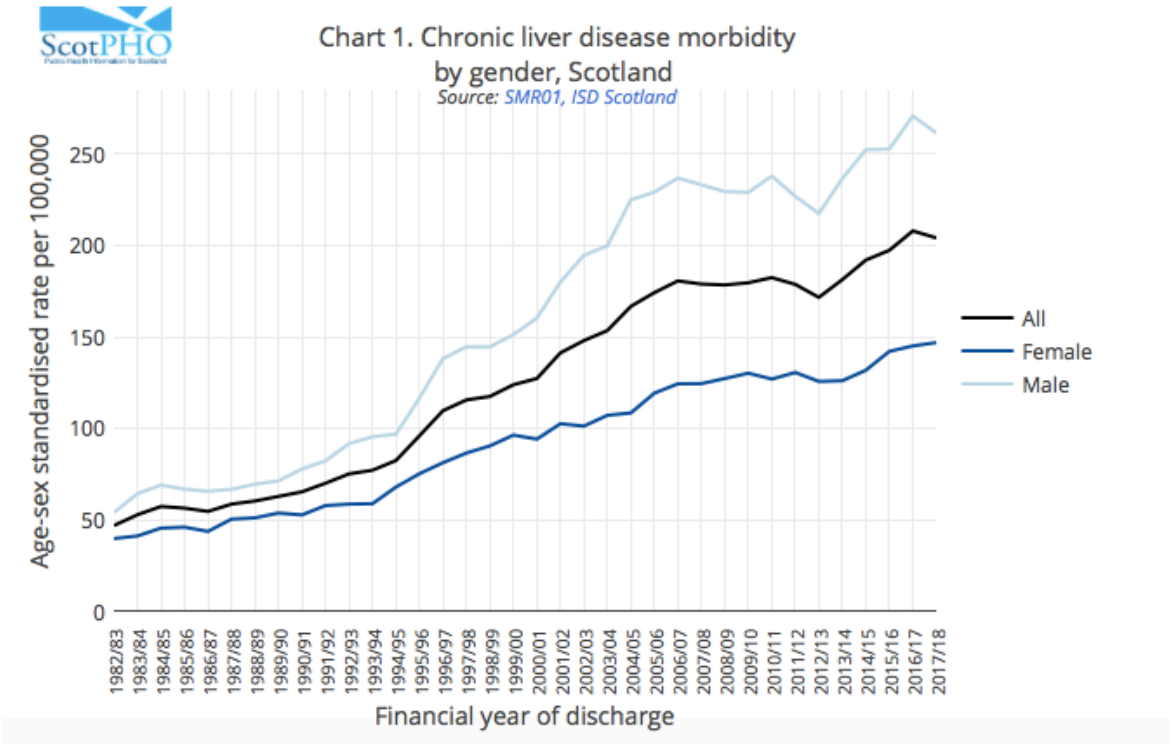
Figure 1-2 Graph of chronic liver disease mortality by gender in Scotland (32) Reproduced from the Scottish Public Health Observatory



In 2018 the Lancet Commission on Liver Disease in the UK stated that alcoholic liver disease would soon become the most common cause of working years lost, thus having a significant economic impact upon individuals with chronic liver disease, their dependents and society as a whole (27). Mortality from liver disease is associated with increased socioeconomic deprivation, with both incidence and mortality from liver disease being higher in the north of England compared to the south (27). Furthermore, the impact of chronic liver disease is reflected in the number of hospital admissions in Scotland with a dramatic increase from 47.1 per 100,000 in 1982/3 to 208 per 100,000 in 2016/7 (Figure 1-3) (32).

Figure 1-3 Graph of chronic liver disease morbidity in Scotland, as measured by number of admissions (32)

Reproduced from the Scottish Public Health Observatory



1.2.5.3 Deprivation

The association between socioeconomic deprivation and poor health is long established in the literature (33). Carstairs and Morris examined UK deprivation and mortality in the 1980s, concluding that the higher rates of mortality in Scotland, compared to England and Wales was in part related to deprivation and most evident in younger adults (34). This replaced previous acceptance that mortality was related to social class (34). Townsend defined deprivation in 1987 as "*observable and demonstrable disadvantage relative to the local community or wider society or nation to which an individual, family or group belongs*" (35). Deprivation was classified into material deprivation which included diet, housing, health and work and subjective deprivation encompassing social support and education (35).

Deprivation has been measured using a number of tools including the Underprivileged Area Score to assess primary care need (36), the Carstairs index (37) developed for Scotland and the Townsend index designed for Northern England (38). The Index of Multiple Deprivation was published in 2000 and widely used in current studies in England (39). It measures deprivation over 7 domains;

income, employment, health, education and training, housing, access to services and crime.

In Scotland deprivation is measured by the Scottish Index of Multiple Deprivation (SIMD), which was first published in 2004 using the same 7 domains as the Index of Multiple Deprivation (40). The SIMD divides areas of Scotland into 6976 small data zones of approximately 760 people. Each data zone is ranked in order of deprivation from most deprived (ranked 1) to least deprived (ranked 6976) (40).

1.2.5.4 The Glasgow effect

Whilst inequalities in health can be explained in part due to deprivation, epidemiological studies highlight higher mortality in Scotland when socioeconomic differences have been accounted for (41). Between 1981 and 2001 Scotland's excess mortality had increased to 8% when compared with England and Wales (41). This 'excess' mortality was particularly evident in Glasgow and the term 'Glasgow effect' has been used extensively in the literature (42). In 2000 mortality was examined in 3 post-industrial UK cities – Glasgow, Manchester and Liverpool with similar levels of deprivation and it was reported excess mortality between Glasgow and the 2 other cities had risen since the 1970s (Figure 1-4) (42). The excess mortality was particularly evident in those of working age and mortality in areas with low socioeconomic deprivation remained higher in Glasgow compared to Liverpool or Manchester (42).

Whilst no single cause has been identified for the difference in mortality, a recent study concluded that excess mortality in Glasgow may result from high levels of deprivation, town planning and government policies whilst Liverpool and Manchester benefitted from migration and social capital (43). However, another suggested hypothesis to explain the variation in mortality is a difference in the culture of substance misuse. The underlying causes of premature mortality in Glasgow are reported to result from alcohol, suicide, drug use and violence (43). Alcohol sales are reported to be higher in Scotland compared to England and Wales, with a higher proportion of individuals consuming alcohol within the home (43). Furthermore, there is believed to be a greater incidence of binge drinking, with increased use of concentrated spirits.

Figure 1-4 Excess mortality in Glasgow compared to Liverpool and Manchester (42)

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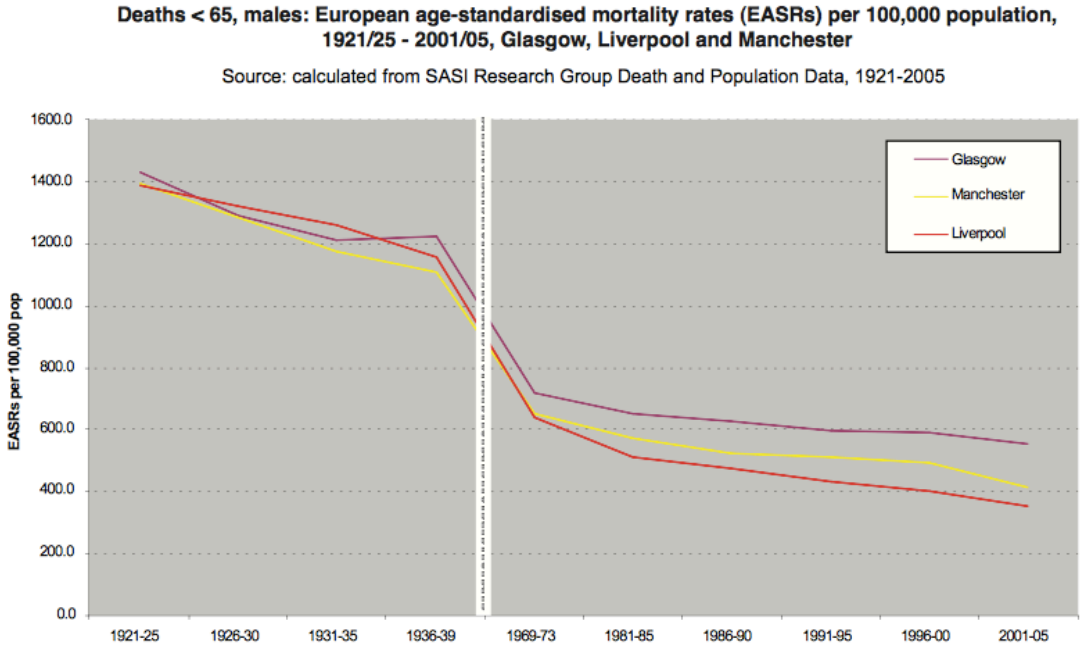

1.3 Classification of liver disease

Terminology describing the classification of liver failure has evolved over time, differing between centres (44). Variations in the time course between the onset of the symptoms of disease and deterioration in liver function have been used to differentiate between acute and chronic liver failure. The concept of acute-on-chronic liver failure (ACLF) has been introduced in recent decades and it was proposed that acute liver failure, ACLF and decompensated chronic liver disease were 3 separate clinical entities at the World Congress of Gastroenterology in 2014 (45).

1.3.1 Acute liver failure

Lucké and Mallory described 2 forms of acute hepatitis in US Army personnel in 1946 (46). The first type described by the authors was fatal within 10 days and they termed this ‘fulminant’ hepatitis. The other form of hepatitis was noted to have a slower deterioration over 4 to 6 weeks and was labelled ‘subacute’ (46).

In 1970 in response to the recognition of halothane induced hepatic injury, the term ‘fulminant hepatic failure’ was introduced and defined as a “*potentially reversible condition, the consequence of a severe liver injury, with an onset of*

encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease"(47). In 1985 the term 'late-onset hepatic failure' was introduced to define the development of encephalopathy between 8 and 24 weeks after initial symptoms of disease (48).

An alternative classification was proposed in France in 1986 which reflected the time between the specific development of jaundice and the onset of encephalopathy (49). Fulminant liver failure was used in cases with an interval of less than 2 weeks between the onset of jaundice and development of encephalopathy and subfulminant liver failure was applied to a time interval of between 2 and 12 weeks and the authors argued that this classification indicated prognosis (49). This classification is still used in centres outwith the UK, including the USA (50).

Current nomenclature used within the UK classifies acute liver failure based upon the time between the onset of jaundice and development of encephalopathy proposed by O'Grady (44). The onset of jaundice was used in preference to other symptoms of liver disease as this was demonstrated to predict outcome (44). Acute liver failure was divided into 3 groups; hyperacute, acute and subacute with the time from jaundice to encephalopathy 0-1 week in hyperacute liver failure, 1-4 weeks in acute liver failure and 4-12 weeks in subacute liver failure (44). Furthermore, each group within this classification of acute liver failure has been demonstrated to exhibit differences in the severity of clinical features and prognosis. Different time intervals between the development of jaundice and encephalopathy can indicate specific aetiologies of acute liver failure (51).

The O'Grady classification has been criticised as it introduced ambiguity with acute liver failure divided into 3 classes with one named acute liver failure (52). In addition, it has been noted that encephalopathy may not reflect deterioration as it is not specific to liver function (52).

1.3.2 Chronic liver failure and cirrhosis

Chronic liver disease describes a wide range of diseases encompassing fatty liver, steatohepatitis, chronic hepatitis, and cirrhosis (10). As explored earlier,

cirrhosis describes a histological change in the architecture of the liver (section 1.2.3) but within the literature the term ‘cirrhosis’ is often used to describe end-stage chronic liver disease. Liver cirrhosis is classified into asymptomatic or ‘compensated’ cirrhosis and ‘decompensated’ cirrhosis based upon the presence of portal hypertension or liver dysfunction (53). Deterioration in liver function in those with chronic liver failure can progress to chronic decompensation which is often irreversible (54). Alternatively, individuals with compensated chronic liver disease can experience a potentially reversible acute decompensation known as ACLF explored in section 1.3.3 (54).

Definitions of compensated cirrhosis vary but reflect a clinical state whereby there are no clinical complications of cirrhosis and portal pressure is normal or not elevated sufficiently to cause ascites (53). Transition from compensated to decompensated cirrhosis results from increased portal pressure and deterioration in liver function, marked by the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy and jaundice (53). Deterioration is accelerated by variceal bleeding, renal impairment, hepatopulmonary syndrome (HPS), sepsis and hepatocellular carcinoma (53).

Liver cirrhosis was classified into 4 stages of increasing severity at the Baveno IV consensus conference in 2005 (55). This was based upon combined data of 1649 patients from two Italian studies of cirrhotic patients admitted between 1974-1980 and 1981-1984 (56, 57). Each stage was defined by the presence or absence of oesophageal varices and ascites (55). Stages 1 and 2 reflect individuals in compensated cirrhosis whilst stages 3 and 4 describe those with decompensated cirrhosis (Figure 1-5) (53).

Figure 1-5 Clinical stages of cirrhosis with outcomes at 1 year (53)
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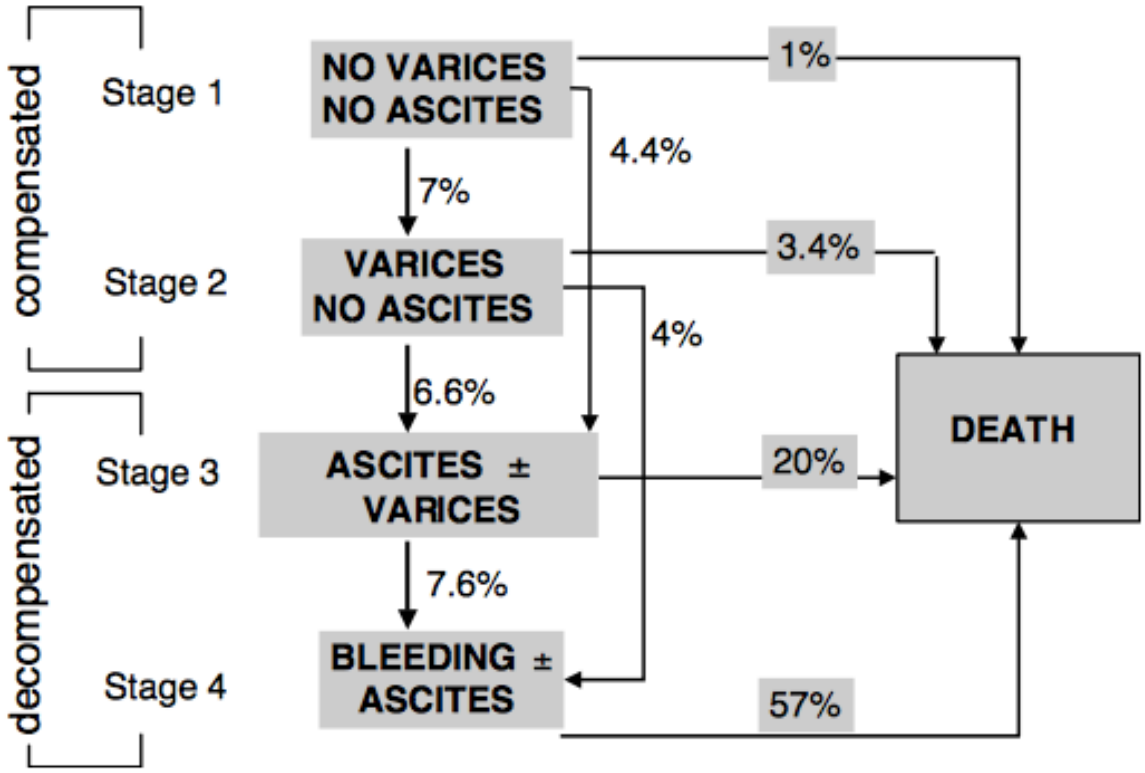

Most studies investigating survival in liver cirrhosis are based only on individuals admitted to hospital. A 2012 cohort study based on 4537 individuals with cirrhosis listed on the UK General Practice Research Database found 1 year survival for compensated and decompensated cirrhosis to be 87.3% and 75% respectively, with survival at 5 years 66.5% and 45.4% (58). A 2006 systematic review of 118 studies described median survival for compensated cirrhosis to be over 12 years, exceeding that of decompensated cirrhosis, which is approximately 2 years (53). The majority of deaths in those with cirrhosis result from complications of cirrhosis rather than concurrent comorbidities (59). Annual mortality in the stages of cirrhosis classified at Baveno IV is 1% in Stage 1, 3.4% in Stage 2, 20% in Stage 3 and 57% in Stage 4, with almost 50% of deaths occurring within the first 6 weeks following an initial variceal bleed (Figure 1-5) (53).

1.3.3 Acute-on-Chronic liver failure

ACLF first appeared in the literature in 1995 and described a state whereby both acute and chronic disease processes were evident (60). Unlike the chronic decompensation of chronic liver disease it is postulated that ACLF is potentially reversible if precipitants of liver insult are controlled and organ support provided during the acute deterioration (54). Whilst the underlying pathophysiology is not yet fully understood, ACLF encompasses an altered host response to liver injury in a patient with existing liver disease (61). It is recognised that this involves pro-inflammatory cytokine production, neutrophil dysfunction and subsequent immune system dysregulation (61). The literature suggests that ACLF may be considered in a similar manner to the systemic inflammatory response syndrome and multi-organ failure evident in those with sepsis (62).

A 2013 systematic review identified 13 different definitions of ACLF (63). Until 2014 there was a global divide in its definition with the Asian Pacific Association for the study of the liver (APASL) defining ACLF as an "*acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease*" (64). The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), however, proposed ACLF to be "*an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure*" (65). These definitions lacked consensus in the recognised precipitants of ACLF, prior decompensated cirrhosis and the timeline of acute illness (45).

In 2013 the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium published the Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study and proposed 3 diagnostic criteria for ACLF (66). The diagnosis of ACLF required an acute decompensation of liver disease, organ failure and a 28 day mortality rate of 15% (66). ACLF was noted to be a significant cause of death in cirrhotics and those without prior episodes of acute decompensation appeared to develop a more severe form of ACLF with higher levels of inflammatory mediators and increased short-term mortality (66).

A united definition was proposed at the World Congress of Gastroenterology in 2014 and is based on the findings of 2 prospective observational studies; the CANONIC study and North American Consortium for the study of End-Stage Liver Disease (NACSELD) (45). It was defined as "*a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterised by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset*" (45). ACLF can be precipitated by a physiological insult such as sepsis, gastrointestinal bleed or surgery or by liver injury due to viral infection, alcohol ingestion or drug exposure (54).

As the diagnostic criteria for ACLF have only recently been agreed upon, there is a lack of awareness and confidence in determining which critically ill patients have ACLF rather than chronic decompensation of liver function. Given this clinical challenge it was the MD student's experience that few patients are documented to have this diagnosis, in particular in retrospective clinical notes. As such, the body of work in this thesis concentrates upon patients diagnosed with chronic liver disease and those with identified cirrhosis.

1.4 Clinical manifestations of chronic liver disease

Whilst chronic liver disease is often asymptomatic for many years it can lead to complications within most systems in the body. There are a number of clinical manifestations of chronic liver disease which are discussed in further detail below.

1.4.1 Ascites

Ascites is defined as the excess free fluid within the peritoneal cavity (67). Ascites is the most common complication of cirrhosis, occurring in more than 50% of patients within 10 years of a diagnosis of cirrhosis (68). Whilst ascites can develop secondary to non-cirrhotic causes such as cardiac failure or malignancy, 75% of patients presenting with ascites have an underlying diagnosis of cirrhosis (68). Once ascites is present in those with cirrhosis, 2-year mortality is up to 40% (68). Uncomplicated ascites is defined as not infected nor accompanied by

hepatorenal syndrome (HRS) and is classified into grades 1-3 (68). Without immediate access to ultrasound the scoring of ascites is subjective (Table 1-1).

Table 1-1 Grading of Ascites (68)

Grade of Ascites	Definition
1	Mild ascites evident only on ultrasound examination
2	Moderate ascites which is easily palpable on physical examination and associated with symmetrical abdominal distension
3	Large or gross ascites with marked abdominal distension

Ascites is defined as refractory when it remains present despite use of medical treatment including diuretic therapy or dietary salt restriction or in the presence of diuretic-induced complications including hepatic encephalopathy, renal impairment or electrolyte abnormalities preventing their use (68). Refractory ascites is also defined by a recurrence of grade 2 or 3 ascites following paracentesis (68). Refractory ascites occurs in up to 10% of cases of ascites (69).

The development of ascites in those with cirrhosis has been explained by a number of different theories. The 'overfill' hypothesis describes increased renal sodium retention due to a signal from the liver resulting in larger plasma volume (22). The 'underfill' hypothesis describes increased renal sodium retention as a compensatory mechanism following the development of ascites secondary to portal hypertension (70). This occurs in response to the increased plasma oncotic pressure and decreased venous portal pressure which result from the development of ascites and loss of intravascular volume (22). Finally there is a peripheral arterial vasodilatation hypothesis (70). The increased resistance to hepatic blood flow with the development of cirrhosis (section 1.2.3) leads to portal hypertension, collateral vein formation and shunting of blood into the systemic circulation (69). Local vasodilators such as nitric oxide increase vascular capacitance through splanchnic arterial dilatation and decreasing effective arterial blood volume and reducing arterial blood pressure (69). In an effort to expand plasma volume and maintain blood pressure, sodium and water are retained (69). Fluid accumulates in the abdominal cavity as a result of

altered intestinal capillary pressures and permeability secondary to vasodilatation and portal hypertension (69).

The initial management of uncomplicated ascites introduces dietary sodium restriction, which is successful in approximately 10% of patients (22). Those with dilutional hyponatraemia are treated with fluid restriction (69). To achieve both a negative sodium balance and loss of ascitic fluid, diuretics can be introduced (69). If ascites is refractory, large volume or has not improved with pharmacological therapy, therapeutic paracentesis and albumin replacement can be instigated (69). This has proven to be more effective with shorter hospital duration than diuretic therapy (69). Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is an alternative to repeat paracentesis, however, 2 randomised controlled trials did not show a survival benefit, nor improvement in patient quality of life (QOL) when TIPS was undertaken (71, 72).

1.4.2 Portal hypertension and variceal bleeding

Portal hypertension is defined as an increased portal venous pressure, reflecting a raised hepatic venous pressure gradient, predicting the development of varices and decompensation (55). Approximately 60% of individuals with decompensated cirrhosis and 30% of those with compensated cirrhosis have endoscopic findings of varices at diagnosis (73). Analysis of a national American endoscopic database demonstrated increased incidence of varices in Child-Pugh class B or C, reflecting the correlation between deteriorating liver function and increased hepatic venous pressure gradient (74). The incidence of new varices in cirrhotics reported by Italian group is 5% at 1 year, 17% at 2 years and 28% at 3 years (75). There remains significant mortality associated with variceal bleeding with 6-week mortality reported to be between 10-20% (55).

Portal hypertension results from an increased resistance to portal blood flow and increased portal venous inflow (76). Increased resistance results from both structural change in the liver (section 1.2.3) and raised vascular tone due to endothelial cell dysfunction and altered vasoactive substance availability (76, 77). In the sinusoidal microcirculation, nitric oxide has been demonstrated to be an important regulator of vasodilatation (77). Increased portal venous inflow results from splanchnic vasodilatation and raised cardiac output (78).

Therapeutic management of portal hypertension and variceal bleeding comprises pharmacological and non-pharmacological intervention. At diagnosis, it is recommended that all cirrhotic patients should be screened for evidence of varices (55). The Baveno V consensus workshop recommended that in those with small varices and Child C class cirrhosis, non-selective beta-blockers should be considered to prevent variceal haemorrhage (55). Individuals with medium or large varices, irrespective of Child-Pugh score, should be considered for prophylactic band ligation of varices and treatment with non-selective beta-blockers (55). Beta-blockers reduce portal venous inflow by decreasing both cardiac output and splanchnic blood flow (79). In acute variceal bleeding, volume resuscitation, antibiotic prophylaxis and vasoactive drug administration should be followed by prompt upper gastrointestinal endoscopy (55). Vasopressin promotes splanchnic vasoconstriction, reducing portal venous inflow (73). In those individuals with Child-Pugh Class C or Child-Pugh Class B with bleeding these treatments are more likely to fail (55). As such, TIPS should be considered and can be used as a bridge to liver transplantation (55). Balloon tamponade can be considered in massive uncontrolled haemorrhage as a temporary solution to reduce bleeding (55).

1.4.3 Hepatic encephalopathy

Hepatic encephalopathy is a diagnosis of exclusion and defined as neuropsychiatric abnormalities in those with liver disease which cannot be attributed to other causes (80). It is estimated that 20-80% of those with cirrhosis may develop hepatic encephalopathy (81). The clinical symptoms of hepatic encephalopathy can fluctuate in severity, are often reversible and can be caused by multiple factors (81). There are a number of different hypotheses surrounding the development of hepatic encephalopathy. The first attributes encephalopathy to a rise in the ammonia concentration within the blood due to portosystemic shunting, or a decrease in metabolism due to liver dysfunction (22). Ammonia crosses the blood brain barrier causing astrocyte swelling, oedema and increasing oxidative stress (81). Interestingly, the severity of symptoms are not linked to the level of ammonia within the blood (81). Unlike the cerebral oedema and raised intracranial pressure which can occur in

cirrhosis this does not occur in hepatic encephalopathy (81). An alternative hypothesis concerns inflammation, which may result in increased blood-brain barrier permeability and altered binding site activity for benzodiazepines (22). Other hypotheses include an increase in benzodiazepine-like compounds in the brain, manganese accumulation in the basal ganglia or altered tryptophan metabolites (22).

Disagreement concerning the definition of hepatic encephalopathy exists. In 1998 at the World Congress of Gastroenterology a standard nomenclature for hepatic encephalopathy was proposed based upon the underlying diagnosis, clinical course and severity (Table 1-2) (80). It has since been suggested that the term minimal encephalopathy be replaced by covert encephalopathy to emphasise the clinical significance of this diagnosis (82). The diagnosis of hepatic encephalopathy is based on a clinical or neuropsychiatric assessment examining factors such as attentiveness, cognitive impairment, behaviour and consciousness (80). Recognised precipitants include gastrointestinal bleed, sepsis, uraemia, medication, constipation, dehydration or electrolyte disturbances (80). The West Haven criteria have been used to describe the severity of symptoms demonstrated by individuals with hepatic encephalopathy (Table 1-3) (83).

Table 1-2 Classification of Hepatic Encephalopathy (80)

Type of Hepatic Encephalopathy	Definition	Subcategory	Subdivision
A	Encephalopathy associated with acute liver failure		
B	Encephalopathy associated with portal-systemic bypass in the absence of intrinsic hepatocellular disease		
C	Encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts	Episodic Hepatic Encephalopathy Persistent Hepatic Encephalopathy Minimal Hepatic Encephalopathy	Precipitated Spontaneous Recurrent Mild Severe Treatment-dependent

Table 1-3 West Haven Criteria (83)

Stage	Features
0	No abnormality detected
1	Trivial lack of awareness, euphoria, anxiety, shortened attention span, inability to perform addition or subtraction
2	Lethargy, disorientation, personality change, inappropriate behaviour
3	Somnolence or semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behaviour
4	Coma

Management of hepatic encephalopathy depends on the severity of clinical symptoms. Individuals with decreased conscious level may require airway protection and any potential precipitants such as sepsis, dehydration following diuretic use and gastrointestinal bleeding must be addressed (22).

Treatments for hepatic encephalopathy are limited and at present include lactulose and Rifaximin (84). The mechanism of action for lactulose is unknown and it is hypothesised that it acidifies colonic contents and evacuates bacteria from the bowel (84). Rifaximin is a non-absorbable antibiotic which has been shown to improve outcomes in hepatic encephalopathy (84). With treatment symptoms of encephalopathy should improve within 72 hours, however, second line pharmacological interventions include Metronidazole, Neomycin or Vancomycin to promote gut motility.

1.4.4 Hepatorenal syndrome

HRS is defined as impaired renal function in the presence of intrarenal arteriolar vasoconstriction and extra-renal vasodilatation (85, 86). Individuals develop circulatory dysfunction with insufficient cardiac output and their renal function does not respond to fluid therapy (85, 86). HRS develops in those with overt liver failure and includes individuals with acute or chronic liver disease (85). A study of 234 cirrhotics with ascites demonstrated an incidence of HRS of 39% within 5 years, with median survival of less than 2 weeks (87).

HRS can develop spontaneously or secondary to infection – in particular spontaneous bacterial peritonitis (SBP), bleeding or insufficient albumin administration following paracentesis (85). HRS is classified into Type-1 and Type-2. Type-1 HRS is recognised by a deterioration in renal function within 2 weeks with serum creatinine doubling to over 226 µmol/l (85). It is associated with a poor prognosis and is commonly attributed to SBP (85). Type-1 HRS may present with hypotension and vasoconstriction accompanied by cardiac, liver dysfunction and hepatic encephalopathy (85). The deterioration in renal function in Type-2 HRS is slower with a serum creatinine between 133-226 µmol/l and often occurs in the presence of refractory ascites (85).

It is understood that whilst the splanchnic circulation is vasodilated in HRS, other body systems such as the brain undergo vasoconstriction (85). Furthermore, the reduction in cardiac output can lead to renal hypoperfusion (85).

HRS is potentially reversible and the mainstay of HRS treatment is volume replacement with albumin and vasopressor use (85). TIPS can also be used to improve survival and individuals can be considered for liver transplantation (85).

1.4.5 Hepatopulmonary syndrome

Cirrhosis is associated with a number of different respiratory complications, with up to 70% of individuals exhibiting arterial hypoxaemia (16). This is due to ventilation-perfusion mismatch, impaired diffusion, intrapulmonary shunting and decreased hypoxic pulmonary vasoconstriction (16, 88). It may result from comorbidities such as chronic obstructive pulmonary disease (COPD) or complications of liver disease such as ascites (89).

Hepatopulmonary syndrome (HPS) describes decreased oxygenation and intravascular pulmonary vasodilatation in those with liver disease (90). It is graded from mild to very severe depending upon the alveolar-arterial oxygen gradient and partial pressure of oxygen (89). Individuals present with dyspnoea, although this is non-specific and can be secondary to other diagnoses such as portopulmonary hypertension (89).

Portopulmonary hypertension is an increased pulmonary vascular resistance due to vasoconstriction and thrombosis which ultimately causes right heart failure (89). The incidence of HPS is reported to be up to 32% in those considered for liver transplantation, although this figure excluded the majority of cirrhotics who are not assessed for transplantation (91). In those with HPS who did not receive a liver transplant 5 year survival was 23%, much lower than the survival rate of 63% in the control group of matched patients of similar liver disease severity (92).

At present, treatment for HPS is limited to liver transplantation, with individuals offered symptom control with long-term oxygen therapy (89).

In those with chronic liver disease the incidence of adult respiratory distress syndrome (ARDS) is higher (16). It is understood that this is due to greater numbers of inflammatory mediators due to impaired liver function and impaired immune function (16). Additionally those with alcoholic liver disease are more likely to have reduced glutathione, which is required to prevent oxygen free radical damage (16). The current mortality rate for those with ARDS and cirrhosis is between 35-70% (16).

1.4.6 Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy describes "*cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities*" (93). The splanchnic vasodilatation and decreased vascular resistance evident in cirrhosis causes a functional hypovolaemia and a 'hyperdynamic circulation' develops (78). Cardiac dysfunction may only be evident when there are extra demands on cardiac output, during exercise or illness (16). It is therefore difficult to ascertain the prevalence of cirrhotic cardiomyopathy, however it has been reported that cardiac dysfunction is present in up to 50% of those offered liver transplantation (94). Furthermore, heart failure is a common cause of death following liver transplantation (95).

Cirrhotic cardiomyopathy occurring in chronic liver disease is due a number of different mechanisms including impaired adrenergic receptor function, changes in the cardiac cell membrane and increased levels of nitric oxide which is a negative inotrope (94). To date, there are no medical interventions proven to be of benefit in cirrhotic cardiomyopathy, however, liver transplantation may improve cardiac function (94).

1.4.7 Coagulopathy

Historically, it has been accepted that those with chronic liver disease are 'autoanticoagulated' and are at high risk of bleeding (96). Cirrhosis is associated with altered haemostasis and in the presence of portal hypertension individuals develop thrombocytopenia due to platelet sequestration in the spleen (16). This is associated with platelet function defects, decreased pro- and anti-coagulant

proteins and a reduction in the proteins required for fibrinolysis (96). However, despite such changes and in the presence of abnormal haemostatic tests such as prothrombin time (PT) and platelet count, it is now believed that this specific group of patients may have 're-balanced haemostasis'(97). Compensatory mechanisms exist to promote coagulation (96). These include increased levels of von Willebrand factor and factor VIII with decreased levels of plasminogen, proteins C and S and antithrombin (97). It is accepted that this haemostatic balance can tilt towards a bleeding tendency in the presence of portal hypertension, bacterial infection and renal impairment (97). One study demonstrated a 0.5% incidence of venous thromboembolism in patients with cirrhosis admitted to hospital (98).

Whilst the treatment of active bleeding involving transfusion of blood products is established, little is agreed regarding prevention of bleeding or thrombosis (96). Patients undergoing liver transplant are at high risk of bleeding, however, evidence now suggests a restrictive approach to transfusion rather than prophylactic administration of blood products achieves better outcomes (99). Evidence exists to suggest those with cirrhosis should be anticoagulated to prevent thrombosis, however, there is no universal agreement on how this is approached (16).

1.4.8 Bacterial Infection

Bacterial infections are the most common cause of decompensation in patients with chronic liver disease, with up to 50% of deaths attributable to bacterial infection (100). The incidence of bacterial infection is higher than the general population of hospitalised patients (100). Up to 45% of individuals presenting with gastrointestinal haemorrhage have been demonstrated to have an underlying bacterial infection (100). Chronic liver disease is specifically associated with the development of SBP, although the incidence of respiratory, urinary and skin infections is significant (16). When compared to other critically ill patients, those with cirrhosis are more likely to have bacterial infection with a higher rate of Methicillin-resistant Staphylococcus aureus (101).

The high incidence and mortality of bacterial infections in those with chronic liver disease is due to impaired immune function (section 1.2.2). With an

existing ‘hyperdynamic state’ (section 1.4.6) the body is unable to meet the demands of increased cardiac output required in sepsis and cardiovascular collapse occurs (16).

SBP is a bacterial infection of ascitic fluid in the absence of any other source of intra-abdominal sepsis (102). The incidence of SBP is between 10-30% (103). One-year mortality following the development of ascites is approximately 30% (103). SBP is often asymptomatic and there must be a high suspicion of SBP in those with hypothermia, ascites, sepsis, hepatic encephalopathy and renal failure (16). Risk factors for SBP include hyponatraemia and upper gastrointestinal haemorrhage (104). Treatment of SBP includes antibiotics and albumin, to prevent the development of HRS (16).

1.5 Critical illness and liver disease

1.5.1 Definition of critical care

Levels of care required by patients admitted to hospital have been categorised by the Department of Health in the 2000 report ‘Comprehensive Critical Care’ which reviewed adult critical care services in the UK (Table 1-4) (105).

Table 1-4 Levels of patient care as classified by the Department of Health (105)

Level 0	Patients whose needs can be met through normal ward care in an acute hospital
Level 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
Level 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
Level 3	Patients requiring advanced respiratory support of at least 2 organ systems. This level includes all complex patients requiring support for multi-organ failure

Level 2 care is typically provided in a High Dependency Unit (HDU) whilst Level 3 care is provided only in an Intensive Care Unit (ICU). However, many hospitals in the UK now have critical care units providing both Level 2 and 3 care.

1.5.2 Organisation of critical care in the UK

There are 24 ICUs in Scotland with 15,072 admissions to ICU and 31,859 admissions to HDU in 2017 (106). In 2017-2018 there were 148,817 admissions to critical care units in England, Wales and Northern Ireland where there are 196 general Critical Care Units (107).

1.5.3 Organisation of liver services in UK

Whilst intensive care is offered to critically ill patients with liver disease in ICUs throughout the UK, the 2009 National Plan for Liver Services UK highlighted that the development of specialist care for those with liver disease was focussed in only 3 centres: Queen Elizabeth Hospital, Birmingham, King's College Hospital, London and Royal Free Hospital, London (8). All 3 sites have specific Level 3 units for the management of critically ill patients with liver disease and offer liver transplantation. Whilst these 3 units specialise solely in managing patients with liver disease, the vast majority of such individuals will not be admitted to one of these units. There are four additional transplant centres in the UK situated in Cambridge, Edinburgh, Newcastle and Leeds (108). A further 8 centres within the UK have a "critical mass" of hepatologists (8). None of these centres are based in Scotland.

There were 990 consultant gastroenterologists in the 2009 National Plan for Liver Services Report, with an estimated 10% specialising in liver disease (8). Forty-three percent of consultant gastroenterologists had no specialist training in Hepatology and in the 2013 NCEPOD report, only 3% of those admitted with complications of liver disease were reviewed on admission by a consultant in hepatology (8, 109). Despite acknowledgement of the lack of specialists within this field, a recent report by the Lancet noted that less than 50% of gastroenterology trainees had experience of working in units offering specialist liver services such as out of hours endoscopy, TIPS or even liver clinics (27). Nationally, hepatologists are based in transplant or specialist referral centres,

with the majority of district general hospitals lacking a specialist hepatology service (1).

The dearth of hepatologists is mirrored in Scotland with 103 gastroenterologists listed in the 2013 Survey of Liver Services in Scotland. Thirty-four clinicians (33%) had a liver interest, defined as more than 50% of clinical commitment to liver or biliary disease (110). Eleven individuals (10.7%) exclusively practiced hepatology, 6 of whom were academics in the Royal Infirmary of Edinburgh (110). Eleven hospitals (45.8%) had no clinician with a specific hepatology interest (110).

1.5.4 Precipitants for admission to critical care

Critically ill patients with chronic liver disease may require admission to critical care with organ failure as a direct consequence of their chronic liver disease or for another reason, complicated by their comorbidity. In addition to organ support, critical care aims to reverse causative factors and avert deterioration in liver function (111). There are multiple precipitants recognised to cause a decline in liver function and they include infection, alcohol ingestion, gastrointestinal bleeding, viral hepatitis, surgery, ischaemia or iatrogenic causes such as drugs (111). In a study of patients with alcoholic liver disease admitted to ICU in Scotland between 2005 and 2010, the most common underlying reasons for admissions were reported to be variceal haemorrhage, pneumonia and septic shock (4).

Cardiovascular support offered in critical care encompasses invasive arterial and central venous monitoring, echocardiography and pulmonary artery catheterisation to assess blood pressure, fluid status and cardiac function. Vasopressors and inotropes can be commenced to treat hypotension, maintain tissue perfusion and cardiac contractility, which can be required in patients with complications of chronic liver disease such as sepsis or cardiomyopathies (sections 1.4.6, 1.4.8).

Respiratory support may be required in the form of invasive or non-invasive ventilation for those individuals with hypoxia secondary to severe respiratory tract infection, HPS or increased intra-abdominal pressure due to ascites

(sections 1.4.5, 1.4.8). Renal replacement therapy or vigilant management of an acute kidney injury may be required for complications of chronic liver failure such as HRS or ascites (section 1.4.4).

Those with complications of chronic liver disease such as portal hypertension who present with gastrointestinal haemorrhage may warrant admission to critical care (section 1.4.2). They may require resuscitation with blood products, sedation or respiratory support to facilitate investigation and treatment of haemorrhage. Coagulation abnormalities may predispose these patients to haemorrhage or thrombosis and can require input to correct abnormalities (section 1.4.7).

Neurological support can encompass management of seizures or decreased conscious level secondary to hepatic encephalopathy. Individuals may require airway protection with intubation and invasive ventilation for a reduced Glasgow Coma Scale (GCS) or additional nursing support for agitation (section 1.4.3).

1.5.5 Liver transplantation

Whilst the focus of this thesis is on critically ill patients with chronic liver disease outwith the transplant setting, it would be remiss not to mention individuals undergoing liver transplantation. Most patients will be admitted to intensive care postoperatively following a liver transplant due to the mortality and morbidity associated with the procedure (112). Postoperatively, individuals may require an extended period of mechanical ventilation and they are at increased risk of infection and renal failure (112). Additionally, intensive care provides an environment for enhanced monitoring, enabling early identification of any issues with organ graft function (112). Outwith the immediate postoperative period, with immunosuppression, patients are at increased risk of infection in the first year following transplant and may require critical care admission (113). Liver transplantation is more extensively offered to those with decompensated liver disease, comorbidities and poor functional status, with these factors having an increased risk of postoperative complications (112).

There are 7 centres in the UK offering liver transplant, with 8428 transplants performed between 2008 and 2018 (114). Edinburgh Royal Infirmary is the only

liver transplant centre in Scotland and performed 92 transplants between April 2017 and March 2018 (114). Thirty-one percent of those listed for elective liver transplants in Edinburgh had liver failure secondary to alcoholic liver disease (114).

1.5.6 Survival of patients admitted to critical care

The Scottish Intensive Care Society Audit Group (SICSAG) produces an annual audit of patients admitted to critical care in Scotland (106). In 2017 the annual SICSAG audit reported that 81% of patients admitted to ICU in Scotland survived to hospital discharge (106). At present, annual published data does not facilitate analysis of mortality by underlying aetiology of admission or chronic disease, such as chronic liver disease.

1.5.7 Survival of patients with cirrhosis admitted to critical care

Existing studies in the literature have reported short-term mortality for critically ill cirrhotic patients since the early 1980s. In 1983 Goldfarb et al. examined survival in 100 French cirrhotic patients requiring mechanical ventilation (5). Hospital mortality was reported at 89% and rose to 100% in those with septic shock, severe cirrhosis or acute hepatitis (5). ICU mortality was described at 100% in a small group of cirrhotic patients with septic shock admitted to a general ICU in 1992 (6). Similarly, Shellman et al. reported a 2% survival within 72 hours of admission to ICU for those individuals with Child-Pugh Class C requiring mechanical ventilation and renal failure (7).

Mortality decreased over the following 2 decades with studies reporting ICU mortality in cirrhotics to be between 36.6% and 60% (115-119). The most recent study of ICU outcome for cirrhotic patients in the UK was published in 2018 and demonstrated an improvement in survival with ICU mortality reported to be 31% (120). The mortality reported by McPhail et al. is mirrored in results published by Majumdar et al. who report 32.4% mortality in non-elective ICU admissions in Australia and New Zealand (121). Both studies report on large national cohorts of patients admitted over a number of years. In addition to the figures reported for cirrhosis each study highlights the improvement in survival for other cohorts of patients admitted to ICU with multi-organ failure over this time period (120,

121). The reason for this is most likely multifactorial; encompassing reductions in the incidence of ventilator associated pneumonia and catheter-related infections and improvements in staff training (120). In the UK study it is noted that organ failure scores on admission to ICU have declined over the last decade, suggesting that the severity of illness in those admitted to ICU has reduced (120). Thus improved survival may also reflect a change in admission policy to include patients with less severe critical illness, exclusion of those unlikely to survive or identification and admission of critically unwell patients at an earlier point in their illness with greater potential for reversibility (120).

Mortality is recognised to be lower in those requiring critical care secondary to upper gastrointestinal haemorrhage, with ICU mortality reported at 24% in a study of 243 cirrhotics (118). A 2012 systematic review demonstrated an ICU mortality of 40-50% in those with cirrhosis secondary to alcoholic liver disease (122). Mortality remains unchanged with a contemporary study of 2463 individuals admitted to Scottish ICUs with alcohol-related liver disease reported an ICU mortality of 44.1% (4).

Worldwide hospital mortality in those with critical illness and cirrhosis is reported to be between 32%-89% (117, 123-127). Higher mortality is reported in subgroups of critically ill cirrhotics with renal failure and those who have required mechanical ventilation during their hospital admission (125, 127, 128). Mortality at 6 weeks following ICU admission was reported as 65% in a UK cohort of critically ill cirrhotics, however, in those with multi-organ failure affecting 3 or more systems mortality rose to 90% (129).

Locally, the short-term outcome of the critically ill patients with cirrhosis admitted to Glasgow Royal Infirmary (GRI) was explored, with ICU mortality reported to be 30% and hospital mortality 46% (18). These figures are similar to other recent studies of cirrhotic patients and demonstrate that overall trend is an improvement in mortality (120).

1.5.8 The demand on critical care resources

Critical care beds are in high demand in UK hospitals, with a 2018 survey by The Faculty of Intensive Care Medicine reporting the majority of critical care units

had pressure on limited bed numbers (130). Coupled with a shortage of critical care nurses, this has led to patients being transferred to different hospitals for critical care, use of theatre recovery to increase bed capacity and cancellation of elective operations (130). A 2015 UK study of unwell ward patients demonstrated that ICUs at capacity prevented prompt admission of patients, leading to deterioration and increased mortality (131). To maintain patient safety and quality of care it is recommended that critical care units run at 85% of capacity, however this survey concluded that the fill rate was 87% in England, 95% in Northern Ireland, 100% in Wales and 84% in Scotland (130).

In comparison to other European countries of similar wealth the UK has fewer ICU beds per head of population (132). A 2012 study found the UK had 6.6 ICU beds per 100,000 of the population, compared to 29.2 beds per 100,000 in Germany and 11.6 per 100,000 in France (132). The USA has a reported 28 ICU beds per 100,000 population (133). Furthermore, it is predicted that the demand on critical care beds will continue to rise worldwide, in the UK this is predicted to be an increase of 5% per year with a 100% rise in demand by 2033 (134).

A 2012 study found that 2.6% admissions to ICU in England, Wales and Northern Ireland had liver cirrhosis between 1995 and 2008 (3). Of those admissions, 1.8% had cirrhosis named as the primary or secondary reason for ICU admission whilst for 0.8%, cirrhosis was a listed co-morbidity (3). Further analysis of data revealed that the numbers of those admitted to ICU with cirrhosis has increased from 2.8% between 2003-2005 to 5.4% between 2006 and 2008 (3). A recent study investigating ICU admissions for those with alcoholic liver disease reported 5.2% of admissions to ICU in Scotland between 2005 and 2010 had alcoholic liver disease (4). When compared to other groups of patients admitted to ICU, including those with severe comorbidities such as cardiovascular disease causing angina at rest, those with alcoholic liver disease had higher rates of readmission to ICU and a longer ICU length of stay (4). In contrast to the other ICU admissions those with alcoholic liver disease required more organ support (4).

These trends reflect the increased incidence of chronic liver disease and cirrhosis, highlighting the particular problem of alcoholic liver disease, which is preventable (section 1.2.5). With the existing pressure on limited critical care beds within the UK and the increased demand to support critically ill patients,

deciding which patients merit admission to critical care will become a greater challenge.

1.6 Assessment of scoring systems

Assessment of critically ill patients with cirrhosis is challenging, with many different prognostic models and scoring systems in use. Scoring systems are used for a variety of reasons. They are used within diagnosis and prognosis of disease and to guide clinical decision-making (135). Further, scores can be used in prediction of an event. Predicting patient prognosis is imperative in effective utilisation of resources for both surgical and medical management. Scoring systems may facilitate standardisation of clinical practice and ultimately improve quality of care (135). To interpret the result of a scoring system, it is important to know the probability that result gained is correct using positive and negative predictive values (136). The positive predictive value of a test is the ability to identify those with positive results who have a disease whilst the negative predictive value identifies those who do not have a disease with a negative result (136). Each scoring system must be evaluated on different populations to ensure validity. When considering the utility of scoring systems there must be a balance between the 'rule in' and 'rule out' capabilities. The more sensitive the system the more likely it is to correctly 'rule out' disease or the likelihood of an event and the more specific a system the more likely it is to 'rule in' a disease or event (137).

Prognostic models for patients admitted to critical care are broadly categorised into evaluation of severity of illness, such as the Acute Physiology and Chronic Health Evaluation (APACHE) (138) and models quantifying organ dysfunction and failure, such as the Sequential Organ Failure Assessment (SOFA) (139). The type of organ failure is significant with evidence suggesting that renal failure in particular has an impact on mortality (66). Specific scoring systems for individuals with liver disease exist, although to date, prognostic models designed for the overall critically ill population have been found to have better predictive ability for predicting prognosis in critically ill cirrhotics (140).

1.6.1 Chronic liver disease scoring systems

1.6.1.1 Child-Pugh score

In 1973, Pugh et al. modified an existing scoring system used for the assessment of mortality in those who had oesophageal transection for the treatment of oesophageal varices, which had been designed by Child and Turcotte (141). Initially developed to assess risk in those treated with porto-caval shunting in 1964, the Child and Turcotte's score graded encephalopathy, ascites, bilirubin, albumin and body nutrition (141). Pugh modified this score, adding prothrombin time and omitting body nutrition (141). The 5 factors in the Child-Pugh score are graded from 1 to 3, with 3 denoting increased abnormality and each factor given equal weighting Table 1-5) (141). A healthy individual will score 5 points, whilst an individual with end stage liver disease will score a maximum of 15 points (141). Individuals were graded into groups A, B and C based upon good, moderate and poor operative risks respectively (141).

The variables in the Child-Pugh score and their measurement do introduce error. Measurement of ascites and encephalopathy are subjective (142). Assessment and detection of ascites and encephalopathy have changed since 1973 with the widespread introduction of ultrasound in ascites and the use of psychometric analysis and use of electroencephalography. PT varies between different laboratories and the sensitivities of the reagents used for measurement (142). Furthermore, the variables measured in Child-Pugh score can be altered by medical intervention such as use of albumin, diuretics, paracentesis or use of blood products, with no guidance on timing of the score (142).

Table 1-5 The Child-Pugh score (141)

Clinical and biochemical measurements	1	2	3
Encephalopathy	None	Grade 1 and 2	Grade 3 and 4
Ascites	None	Mild	Moderate-Severe
Total Bilirubin (mg/dL)	<34	34-50	>50
Serum Albumin (mg/dL)	>35	28-35	<28
Prothrombin time (seconds prolonged)	<4	4-6	>6

Child-Pugh Class	Score
A	5-6
B	7-9
C	10-15

Existing work by the MD student's research group investigated the addition of lactate to the Child-Pugh score. This score was demonstrated to outperform existing scoring tools in the prediction of ICU mortality in critically ill cirrhotic patients (17). The addition of lactate to the model for end stage liver disease (MELD) and the UK model for end stage liver disease (UKELD) was shown to improve their predictive abilities in a cohort of patients admitted to a tertiary liver referral centre in London (143).

Validation and utility of the Child-Pugh score is discussed in further detail in Chapter 4.

1.6.1.2 Model for End-stage Liver Disease

Malinchoc et al. described a scoring system used to predict short-term survival of patients undergoing elective TIPS which was termed the MELD (144). The score comprised the variables creatinine, bilirubin, International Normalised Ratio (INR) and aetiology of cirrhosis (144). This scoring system has been subsequently adapted for use in individuals awaiting liver transplantation (145). The aetiology of liver disease was excluded from the MELD score as it was not found to predict survival (145). In addition to those undergoing TIPS, MELD has been validated in other groups with cirrhosis including those hospitalised with complications of chronic liver disease and clinically stable patients with chronic liver disease who do not require hospital admission (145). The validation of the MELD in the inpatient group was limited as it excluded individuals with sepsis, renal disease, hepatocellular carcinoma, cardiopulmonary comorbidity and those who used alcohol within one month prior to admission (145).

One advantage of the MELD score is that it is a continuous scale, with no ceiling, which claims to rank patients based on severity of liver disease (146). Unlike Child-Pugh scoring which uses subjective measurement of ascites and hepatic encephalopathy, MELD is based upon only objective factors. A limitation of the MELD score is the use of INR as a marker for liver disease which may be altered by medical intervention (59). MELD excludes assessment of ascites and hepatic encephalopathy and therefore patients without deranged liver function may have a low MELD score but may have severe liver disease (59).

The MELD score measures short-term mortality in end-stage liver disease with a score of 30 or over indicating an individual is more likely to die if not transplanted within a short time frame (147). For those with a MELD score of under 9, 3-month mortality is 1.9%, 6% for a score of 10-19, 19.6% for a score of 20-29, 52.6% for 30-39 and 71.3% for a MELD score of over 40 (146). For each unit increase in the MELD score there is a 4-9% rise in predicted increased mortality (148).

Scoring systems for liver disease continue to evolve with studies suggesting the addition of hyponatraemia to the MELD score may improve predictive value for disease severity and mortality, in particular for those awaiting liver

transplantation (149). Evidence suggests that both renal function and nutritional state are significant prognostic factors in cirrhotic patients and should be considered in scoring tools (150).

1.6.1.3 Chronic Liver Failure-Sequential Organ Failure Assessment

The chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score is a modified SOFA score, developed specifically for a study which aimed to further develop diagnostic criteria for ACLF and identify those at most risk of short-term mortality (66). The CLIF-SOFA score grades organ systems from 0 to 4 based on increasing dysfunction (66). The variables measured include bilirubin, creatinine, grade of hepatic encephalopathy, INR, mean arterial pressure (MAP) and Pa02/Fi02 ratio or Sp02/Fi02 ratio (66). If MAP is below 70mmHg, the use and volume of vasopressor is incorporated within the score (66). The initial study examined all patients admitted with cirrhosis to 29 European hospitals, all of which had specialised liver units, intensive care facilities and offered liver transplantation. In this population, the CLIF-SOFA score measured on study enrolment, was demonstrated to correlate with development of ACLF and mortality (66). In those with ACLF, the CLIF-SOFA score was shown to be as accurate as MELD and more accurate than Child-Pugh in predicting 28-day mortality (66). The CLIF-SOFA score has been demonstrated to have good predictive power for short-term mortality in those with an acute decompensation of alcoholic liver disease (151). It has also performed well in prediction of 6-month mortality in a group of critically ill cirrhotics (152).

1.6.1.4 Royal Free Hospital score

The Royal Free Hospital (RFH) score was designed as a prognostic model for critically ill cirrhotic patients (129). Based upon the factors found to independently predict mortality in a group of critically ill patients admitted to the Royal Free Hospital in London, the RFH score includes measurements of bilirubin, urea, lactate and inspired oxygen concentration (129). The RFH score is only one of 3 prognostic scoring tools designed using data from critically ill patients with cirrhosis, the others being the Intensive Care Cirrhosis Outcome (ICCO) score and the Mean Arterial Pressure, Bilirubin, Acute Respiratory Failure

and Sepsis (MBRS) score (153-155). The RFH score was validated on a cohort of patients with cirrhosis admitted to the Royal Free Hospital, demonstrating similar prognostic accuracy to SOFA whilst it was found to be superior to MELD, Child-Pugh and CLIF-SOFA (153). The score has been further validated in an external cohort of UK critically ill cirrhotic patients, outperforming existing established scoring systems (156).

1.6.1.5 United Kingdom Model for End-stage Liver Disease

The UKELD model was designed to predict transplant waiting list mortality in the UK (157). Whilst the MELD scoring system has been adopted to prioritise organ allocation in the USA it was not developed for use in transplantation (145, 157). In addition the MELD score may be low in those with high risk of mortality such as individuals with ascites or hyponatraemia (158).

UKELD was developed using data from 1103 patients on the transplant list in the UK (157). The most common underlying aetiology of liver disease in this population was alcoholic liver disease and Hepatitis C (157). INR, bilirubin and sodium were all found to predict mortality in those on the waiting list. At the author's discretion, creatinine was added to the score as its inclusion was believed to add value to the score (157). The score was subsequently validated with a prospective cohort of 452 patients (157). Whilst a higher UKELD score was associated with death on the transplant list, there was no association between UKELD and survival following transplant in the initial paper (157). A UKELD score of 60 has been demonstrated to predict 50% survival at 1 year, enabling identification of those at high risk of short-term mortality without transplantation (159). The UKELD model is limited in that it excludes those with hepatocellular carcinoma and scoring occurs when individuals are placed on the list and thus changing clinical picture during waiting time is not taken into account (157).

The UKELD score has been examined outwith the transplant setting in critically ill cirrhotic patients in the UK and was found to have a similar predictive value to the both the MELD and Child-Pugh scores (17, 156).

1.6.1.6 Intensive Care Cirrhosis Outcome

The ICCO score consists of variables found to predict ICU and hospital mortality in a cohort of cirrhotic patients admitted to Austrian critical care unit (154). The score incorporates bilirubin, cholesterol, lactate and creatinine measured on ICU admission (154). The ICCO was subsequently prospectively validated on 70 patients admitted to the same unit (154). ICCO outperformed APACHE III in mortality prediction in this cohort, with the authors reporting that no patient with an ICCO score of above +2.6 survived (154). This score has not been utilised widely in studies, as such there is little evidence to its validity in an external cohort. The ICCO score was excluded from analysis within this thesis as serum cholesterol measurements are not routinely measured on ICU admission. In the acute phase response to critical illness, cholesterol levels are known to decrease in certain individuals and may be affected by multiple different factors (160).

1.6.1.7 Mean arterial pressure, Bilirubin, Acute respiratory failure and Sepsis

Whilst a number of scoring systems include assessment of renal dysfunction in critically ill cirrhotics, the MBRS score was designed specifically to predict mortality in this population (155). This scoring tool was designed using data from patients admitted to a Taiwanese ICU with a high mortality of over 80%, as such the application may be limited in a UK cohort due to differences in the underlying aetiologies of chronic liver disease (155). The MBRS score reflects organ dysfunction by including MAP and liver impairment with the inclusion of bilirubin (155). The MBRS was measured following admission to ICU and therefore would be affected by medical intervention. It is therefore of limited value in helping decide whether or not to offer intensive care (155). The use of MBRS in other populations of critically ill cirrhotics is limited, with a paucity of evidence to support its wider use (153).

1.6.1.8 Glasgow Alcoholic Hepatitis Score

The Glasgow Alcoholic Hepatitis Score (GAHS) was designed to predict mortality in individuals with alcoholic hepatitis (161). The score was derived using clinical data of patients with alcoholic liver disease admitted to Glasgow Royal Infirmary and the Victoria Infirmary, Glasgow (161). The GAHS incorporates 5 variables;

age, serum bilirubin, blood urea, PT and peripheral white blood cell count – all scored on day 1 of hospital admission (161). Individuals receive a score from 5-12, with a score greater than 8 associated with poor prognosis (161). Day 1 and 7 GAHS scores were more accurate in predicting the 28 and 84 day outcomes than the MELD score (161). Whilst this score has been validated in 8 centres in the UK, it has not been validated outwith the UK (161, 162). The GAHS has been examined in cohorts of critically ill cirrhotic patients and has been demonstrated to have good predictive value for mortality when compared to the established scores of Child-Pugh and MELD (17, 156). This may be explained by the predominance of underlying aetiology of alcoholic liver disease in critically ill cirrhotic patients in the UK (156).

1.6.2 General critical illness scoring systems

1.6.2.1 Acute Physiology and Chronic Health Evaluation score

The APACHE score was designed in 1981 to enable assessment of the severity of illness of critically ill patients (138). The authors note that the APACHE score should apply to groups of patients rather than be used as a tool to inform medical care on an individual basis (138). The APACHE classification is based upon age, pre-admission health evaluation and an objective score of 34 physiological variables reflecting acute illness (138). In 1985 the original authors revised APACHE, creating APACHE II and reducing the 34 measured variables to 12 (163). The revised score gave greater weighting to GCS and renal dysfunction whilst the significance placed on arterial oxygen concentration and inspired oxygen requirement was refined (163). Individuals can have a maximum APACHE II score of 71, with physiological variables measured within the first 24 hours of ICU admission (163). A score of 0-4 predicts a mortality of 1.9%, whilst a score over 35 indicates a 84% chance of mortality (163). Further refinements to the APACHE score have been made, with the APACHE III prognostic system published in 1991 (164). APACHE III incorporated 5 new variables; blood urea nitrogen, urine output, serum albumin, bilirubin and glucose (164). Furthermore, the authors designed an equation to predict death incorporating underlying disease and location of patient prior to ICU admission (164). Patients admitted from hospital wards, transfers and readmissions to ICU were noted to have higher death rates than those admitted directly from the emergency department (ED),

although this study was based on an American healthcare model (164). APACHE IV incorporated new variables including requirement for mechanical ventilation and adjustment of GCS when sedation or paralysis was used (165).

All versions of the APACHE scoring system have been extensively validated, with APACHE II reported to be the most commonly used tool worldwide for assessment of severity of illness (166). APACHE II has been found to predict mortality in populations of critically ill cirrhotic patients (119, 129, 167).

1.6.2.2 Simplified Acute Physiology Score

The SAPS was proposed as an outcome predictor which incorporated commonly measured variables in the critically ill (168). Whilst the authors acknowledged the value of the first version of the APACHE score it was thought that error was introduced by the likelihood of missing measurements (168). The SAPS utilises 13 variables plus age, which are all measured in the initial 24 hours following ICU admission (168). In 1993, the SAPS II was published and aimed to use statistical modelling to predict outcome using data from 13,152 patients admitted to 137 ICUs in Europe and North America (169). SAPS II incorporated 12 physiological variables, plus age, type of admission and adjustment for three comorbidities; acquired immunodeficiency syndrome, metastatic cancer and haematological malignancy (169). The SAPS II score has been demonstrated to accurately predict mortality in populations of cirrhotic patients (170, 171). A subsequent study has created the SAPS 3 score, which utilised data from 16,784 critically ill patients admitted to ICUs in 35 countries worldwide (172). As with the SAPS II, the SAPS 3 incorporates information regarding the type of admission, patient age and comorbidities, however, it assesses physiological variables within 1 hour of ICU admission (166, 172). To date, validation of the SAPS 3 model in the critically ill cirrhotic population is lacking within the literature.

1.6.2.3 Mortality Prediction Model

The mortality prediction model (MPM) aims to predict ICU outcome using 7 variables, with one model utilising values measured on admission to ICU and another using values recorded during the first 24 hours of admission (173). Both models were updated in the publication of the MPM II model (174). The MPM II

utilises a greater number of variables, with 15 variables included in the admission model MPM_0 and 13 variables in the MPM_{24} (166, 174). The admission MPM (MPM_0-III) was revised to more accurately predict mortality assessing 16 variables within 1 hour of ICU admission (175). No studies were identified within the literature assessing the prognostic ability of the MPM in the cirrhotic population.

1.6.2.4 Sequential Organ Failure Assessment

The SOFA score was developed at a consensus meeting by the European Society of Intensive Care and Emergency Medicine to describe the severity and complications of organ dysfunction in the critically ill and was not designed to predict mortality (139). The SOFA combines scores from 6 different organ systems: cardiovascular, respiratory, hepatic, renal, coagulation and neurological over the first 24 hours of admission (139). The cardiovascular system is assessed using MAP or inotropic requirement, the respiratory system is assessed using the Pa02/Fi02 ratio, the hepatic system is assessed by serum bilirubin concentration, renal using creatinine or urine output, coagulation by platelet count and neurological using GCS (176). Each system is graded from 0 to 4, with a score of 4 indicating greatest dysfunction and a maximum score of 24 (139).

Despite not being developed to predict outcome, the SOFA has been demonstrated to predict prognosis in individuals with cirrhosis and compares favourably with APACHE II or Child-Pugh (129, 177). Unsurprisingly, it was reported that length of ICU stay increased with greater organ dysfunction as reflected in the SOFA score (177).

1.6.2.5 Multiple Organ Dysfunction Score

The Multiple Organ Dysfunction Score (MODS) was designed to measure severity of organ dysfunction in critically ill patients (178). Similar to the SOFA score, organ failure is measured in 6 physiological systems: respiratory, renal, hepatic, cardiovascular, haematological and neurological (178). Each system is scored from 0 to 4, with a score of 4 given to the most severe organ impairment and a maximum score of 24 (178). MODS and SOFA are very similar in the variables

included to ascertain the level of organ dysfunction with the exception of the cardiovascular system (176). MODS uses the pressure-adjusted heart rate and does not make allowance for inotrope use (176). In a study of 949 patients admitted to a Belgian ICU, assessment of cardiovascular dysfunction as measured by the SOFA score had greater correlation with mortality than the pressure-adjusted heart rate measured in MODS (176).

1.7 Summary and research questions

This literature review has described the importance of the liver, explored the pathophysiological deterioration in liver function and the development of cirrhosis in chronic liver disease. There has been a focus upon preventable aetiologies of chronic liver disease in particular excess alcohol consumption. The MD student has outlined the increased prevalence and mortality of chronic liver disease and the lack of specialist liver services in the UK to meet demand. There has been exploration of the reasons why patients with advanced chronic liver disease require intensive care, the improvement in short-term survival in those admitted and the limitations in scoring systems used to predict mortality. With limited critical care provision and increased demand, deciding which patients to admit to the ICU can be challenging.

This thesis focuses on the decision to admit a patient with advanced chronic liver disease or cirrhosis to critical care, their long-term survival and quality of life and addresses how one preventable cause of chronic liver disease can be assessed in the critically ill.

1.7.1 What criteria are used in the decision to offer intensive care to a patient with chronic liver disease?

Individual factors involved in the decision to offer patients intensive care have been investigated extensively. However, there is a lack of evidence examining whether differences exist in the degree of influence each factor has on the referring gastroenterologist and receiving intensivist.

1.7.2 When should the established prognostic scoring tool Child-Pugh be measured to inform the decision to admit a patient?

Child-Pugh score was the first scoring tool used to predict mortality in liver disease. The score is used worldwide to inform the decision regarding whether to admit a patient to intensive care. Debate exists as to whether its value in prognostication lies in measurement when a patient is stable, to reflect chronic liver dysfunction, or at the time of admission to ICU, where it may reflect acute illness and organ dysfunction.

1.7.3 Can a proxy be used to measure alcohol intake in a patient admitted to intensive care?

Alcoholic liver disease is one of the preventable causes of chronic liver disease and cirrhosis. Prompt recognition and treatment of patients who consume excess alcohol would inform acute medical management and facilitate targeted health intervention. Gaining an accurate alcohol history is challenging, particularly if the patient is critically ill. If a proxy is found to provide a precise alcohol history this would provide valuable information in the intensive care setting.

1.7.4 What is the long-term survival of patients admitted to intensive care with cirrhosis?

Multiple studies demonstrate that the short-term survival of patients with cirrhosis admitted to intensive care is improving. However, there are few studies reporting the long-term survivorship of patients with cirrhosis admitted to intensive care outwith tertiary referral centres or beyond 6 months. Information on the long-term outcomes could inform the clinical decision whether to admit patients to ICU and give valuable information to patients who have capacity to make the decision to undertake intensive treatment.

1.7.5 What is the long-term quality of life of patients who survive intensive care?

QOL following intensive care stay is considered to be one of the most important outcomes for survivors. Sleep is known to contribute to QOL and is disturbed

whilst patients are admitted to hospital. Moreover, little is known about the QOL and sleep in the subgroup of critical illness survivors with cirrhosis. Determining the prevalence of insomnia and the long-term QOL in survivors of critical illness could inform patients about recovery following discharge and facilitate targeted interventions if QOL or sleep were found to be impaired.

Chapter 2 Methodology

This chapter aims to introduce the research methods utilised in this thesis and explores the concepts involved in research design. It incorporates the approaches to statistical analysis used throughout the thesis.

2.1 Research design

Research can be quantitative or qualitative. Some studies combine aspects of both and are described as mixed methods research. The majority of the studies in this thesis use quantitative methods, however, Chapter 3 involves qualitative research and as such both methodologies are discussed in further detail.

2.1.1 Quantitative research

Quantitative research is the collection of numerical data (179). Data are measured using defined research instruments and analysed using statistical techniques (179). This thesis involved a number of different techniques to answer study questions. Chapter 3 entailed the creation of 2 surveys and incorporated different techniques including likert scales and vignettes to answer questions. Chapters 4 and 6 comprised the analysis of existing data whilst Chapters 5 and 7 utilised established measuring tools to answer study questions.

2.1.1.1 Likert scale

A Likert scale consists of a statement and a scale consisting of different categories to indicate respondent agreement with the statement (180). The scale includes a range of responses enabling the respondent to rank whether they ‘agree’ or ‘disagree’ with the statement and usually includes a middle response of ‘neither agree nor disagree’(179). The statements in the Likert scale must relate to the same topic.

A Likert scale is an example of a multiple-indicator measure, which facilitates assessment of different aspects of a concept and gives a broader range of information from the respondent (179).

2.1.1.2 Vignettes

Vignette questions supply a hypothetical scenario and the respondent must decide on their response based upon the scenario (181). It is argued that because a vignette includes a scenario it encourages the respondent to reflect on their answer, rather than using an open question enquiring about their beliefs or attitude on a topic (181). In order to be successful a vignette must be realistic to the respondent.

2.1.2 Issues of rigour

In research it is important that a number of concepts are understood when designing a study. To ensure the credibility and quality of the research performed in this thesis, it was considered important to explore the concepts of reliability and validity. Both criteria are essential in determining whether findings can be incorporated into clinical practice.

2.1.2.1 Reliability

Reliability is defined as "*the degree to which a measure of a concept is stable*" and the consistency of measurement (179). It determines whether the study can be accurately replicated and if a measurement can be interpreted the same way in different situations (179, 182).

When a measurement tool is used within a study the reliability of that tool must be questioned (179). There are a number of different indices of reliability such as internal consistency, test-retest and inter-rater reliability (183). Assessment of the internal consistency reliability of a psychological tool is the most commonly reported measure of reliability (183). To ensure the internal reliability of a measurement tool, the indicators used must be related and assess the same concept if the answers are combined to create a total score (179). Literature suggests that a reliability of 0.80 is required for tests used solely in research and a reliability of 0.90 is necessary for a test to be used to determine important clinical decisions (184). To maintain internal reliability the measurement tools used within this thesis were chosen as they had been widely tested for internal reliability.

Where more than one person was involved in data collection the inter-observer consistency had to be maintained (179). To ensure consistency, objective measurements were used where possible within each study.

2.1.2.2 Validity

Validity is defined as the "*integrity of conclusions that are generated from a piece of research*" (179). In order to ensure a study draws sound conclusions, different aspects of validity must be appreciated. Measurement or construct validity concerns the ability of a measurement tool to appropriately assess the variable in question and assumes that the tool is reliable (179). Concurrent validity is a type of measurement validity. It describes a comparison of how well a tool performs in the measurement of a variable compared to an existing tool which has been validated (179). Face validity is an alternative form of measurement validity and concerns whether a question truly reflects the concept in question (179).

Conclusion validity concerns the ability of data to support the conclusions made in a study (185). Internal validity concerns the ability of data to support an outcome within a study, whilst external validity is whether the data and conclusions made in a study can be applied outwith the study to other populations (185).

2.1.3 Study sites

Data collection and patient recruitment was undertaken at 2 hospitals in Glasgow, with the exception of the national Scottish survey discussed in Chapter 3.

GRI ICU consists of 12 Level 3 beds and 8 Level 2 beds and is a tertiary referral unit for burns, pancreatic disease and oesophageal surgery. It is located to the North-east of Glasgow city centre. As highlighted in Chapter 1, Glasgow has one of the highest rates of alcohol use in Western Europe. Many patients admitted to the hospital have problems related to alcohol, either as the primary cause of their admission or indirectly complicating their health. GRI was chosen as the primary site for each of the studies in this thesis for a number of reasons.

Firstly, this site has recently undertaken research within the ICU and the University of Glasgow into the assessment and management of alcohol-related admissions to the ICU and attendance at the ED (186, 187). Secondly, the MD student had worked in the ICU as a core Anaesthetic trainee and as such was familiar with the hospital, staff and electronic patient record systems. GRI utilises the NHS Greater Glasgow and Clyde electronic patient record (Clinical Portal, Orion Health, Auckland, New Zealand) to record inpatient and outpatient hospital attendances, correspondence and the results of any investigations. Case notes in the ICU are computerised and use Philips IntelliVue Clinical Information Portfolio or CareVue Revision D.03, which is used in other ICUs but is not universal across NHS Greater Glasgow and Clyde (188).

The QEUH in Glasgow houses a critical care unit for both ICU and HDU patients comprising 20 ICU beds and 39 HDU beds. The hospital is located in the South-west of Glasgow and receives approximately 850 admissions to critical care per year. It is a regional unit for trauma and vascular surgery and houses the regional infectious diseases and renal units. The QEUH was chosen as a research site as it is the largest hospital in Glasgow and uses the same electronic patient record systems as GRI.

The MD student did not work in a clinical capacity at either hospital during patient recruitment. This prevented any confusion regarding role when recruiting patients in the study described in Chapter 5.

2.1.4 Participants

Participants are described in each separate chapter of this thesis as they differ between studies. Participants included critically ill patients, their close contacts and consultants in gastroenterology and intensive care. Ethical approval was sought for each study when required and is documented within each chapter. It was appreciated that this group of patients and their contacts are a vulnerable group within the population. Survivors of critical illness experience physical, social and psychological problems following an ICU stay whilst contacts of critically ill individuals experience significant psychological strain (189).

2.1.5 Informed consent

All participants were asked to give consent to their involvement in the research in this thesis. For those who could not give consent, such as patients who were admitted to ICU, consent was sought once the individual had improved clinically. Information sheets were provided prior to consent, with participants informed of their right to decline involvement in the research.

2.1.6 Confidentiality and data management

Patient confidentiality was maintained at all times with completed documentation relating to each study kept anonymous. This was performed in accordance with the Data Protection Act 1998. All information recorded was kept on an encrypted memory stick and raw data remained locked within University of Glasgow Anaesthetic department.

2.2 Statistical software

Two different statistical software programmes were used in this thesis. R was used for all data analysis with the exception of Chapter 6. In Chapter 6, the MD student supervised an undergraduate BSc student who performed data analysis as part of an intercalated degree. The student was given statistical lectures using SPSS and as such was required to use this software for data analysis.

2.2.1 R

R is a statistical software package which enables the user to write programming language and perform statistical tests (190, 191). It is based on the statistical software S-plus and uses descriptive code to perform functions (191).

There are a number of reasons why R software was utilised. It is used worldwide by many researchers as it is considered to be superior to other statistical software in its abilities to manipulate data and draw high-quality plots (191). R software is free, open source and can be used on multiple computer platforms (191). Furthermore, there is expertise in using R software within the University of Glasgow Anaesthetic department facilitating assistance with data analysis when required.

In all data analysis, coded data were initially entered into a Microsoft Excel spreadsheet (2011). Data were then imported from the spreadsheet to the statistical package RStudio version 1.0.136 © 2009-2016 RStudio, Inc.

2.2.2 SPSS

SPSS is a statistical program which was the original abbreviation for the Statistical Package for the Social Sciences (179). It is a commercial software product owned by IBM and as such a license and payment is required to use the software. The statistical packages offered by SPSS are limited to the version of SPSS, unlike R in which packages are frequently added. However, SPSS has the advantage of not requiring the user to learn a programming language and as such may be regarded as easier to operate. As a commercial product there is official user support available for SPSS, which is not available for R.

As with R, coded data were entered into a Microsoft Excel spreadsheet (2011) and then imported to the SPSS Data View Sheet.

2.3 Data analysis

Identification of the type and spread of data are essential in determining that the correct statistical tests are chosen to analyse data. Assistance in data analysis was provided by a clinical physicist in the University of Glasgow Anaesthetic department.

2.3.1 Scales of measurement

To interpret data it is important to determine the type of variable measured. Data can be continuous, whereby a score is given on a measurement scale, such as height or number of days.

Categorical data are separated into distinct entities and is described as binary, nominal and ordinal (182). Binary variables are those with only 2 choices such as ‘yes or no’. If there are more than 2 categories, the data are described as nominal such as admission speciality. Ordinal data describes ranked categories, such as a Likert scale.

2.3.2 Measures of central tendency

Once data are collected it is vital to ascertain the frequency of distribution of the values. To do this it is customary to identify a central value to represent the dataset (192). Measurement of central tendency can be reported as the mode, median and mean. The mode is the most commonly occurring number. The median is identified by ranking the values in ascending order and identifying the middle number. The mean is obtained by adding all the values together and dividing the total by the number of values.

2.3.3 Measures of variability

In this thesis, data were initially analysed to determine the spread around a central tendency using histograms. This established whether each variable examined displayed parametric (normally distributed data) or non-parametric data (lack of a normal distribution). The central value in parametric data were described as a mean, whilst the central value in non-parametric data were given as a median.

To describe the spread of data around a central value different terms are used. The range describes the spread of all scores from highest to lowest. Parametric data are described using the variance and the square root of variance - standard deviation. Non-parametric are described using the interquartile range (IQR). Data are split into 4 quartiles and an IQR describes the middle 50% of values.

2.3.4 Statistical significance

Statistical significance is the confidence that the results provided by data analysis are true and have not occurred at random. It is the ability of results to accurately reject a null hypothesis. Statistical significance is set as a probability level. Medical research commonly uses a 5% (0.05) probability level, which indicated that there is up to a 5% chance that the difference found by a statistical test occurred at random (192). The threshold for statistical significance set in this thesis was $p<0.05$, as per comparable studies in the literature.

In research there are often multiple statistical tests performed on datasets rather than using multivariate analysis or creating a single model. Such tests will provide a number of p-values, which can increase the likelihood of a Type I error where results are incorrectly identified as significant. To reduce the error resulting from multiple testing the p-values are adjusted using a Bonferroni correction (193).

2.3.5 Univariate analysis

Univariate analysis concerns analysis of one variable. Data can be described using frequency, measures of central tendency and variability (179).

2.3.6 Bivariate analysis

Bivariate analysis concerns the analysis of two variables to determine if there is a relationship between them. The choice of statistical test depends upon the type of variables analysed and a variety of bivariate tests were used within this thesis.

In the analysis of 2 independent groups and a numerical or ordinal variable the tests used depend on the distribution of data. In the presence of a parametric distribution the independent t-test is used to determine the presence of a relationship between the mean of each of the variables (182). If the data display a non-parametric distribution the Mann-Whitney or Wilcoxon rank sum test are utilised instead, both of these tests are equivalent and use ranking rather than actual values (182).

If 2 non-parametric categorical variables are measured a Pearson's Chi-square test is used to determine if there was a relationship present (182). A Fisher's exact test is used with smaller sample sizes of under 5.

2.3.7 Multivariate analysis

Multivariate analysis concerns the analysis of multiple variables. Using multivariate analysis is preferable when comparing a number of independent groups with a single nominal or ordinal variable (193). The alternative is to use

multiple tests comparing each individual group with the variable. This would increase the likelihood of a high Type I error (section 2.3.4).

One-way analysis of variance (ANOVA) is used to compare the means of different variables (194). In these populations it must be assumed that the data are normally distributed with the same variance within each group (193). Whilst a one-way ANOVA can be used for 2 variables, it is convention to use a t-test for 2 variables and ANOVA for 3 or more variables (182).

The Kruskall-Wallis is used for non-parametric data to determine if there is a relationship between 3 or more variables (182).

2.3.8 Confidence intervals

A confidence interval (CI) is a range of values around a statistic in which there is a set certainty that the true value is found (182). When a 95% CI is used there is a 95% probability that the true value lies within the range of values given. The width of a CI determines the precision of a result (193). A narrow CI suggests that the result is precise, however, studies with a smaller sample size or greater variability in results will have wider CI. To reflect similar studies a 95% CI was used within this thesis.

2.3.9 Odds Ratios

Odds are the ratio of the probability of an event occurring compared to the event not occurring (195).

The Odds ratio (OR) represents the ratios of the probability of an event occurring or not occurring in 2 different groups (179). An OR of 1 indicates that the probability of an event occurring in 2 different groups are the same and that there is no relationship between the variables (179).

2.3.10 Linear regression

A linear regression model is used to analyse and quantify relationships between 2 continuous variables (194). Regression analysis predicts an outcome variable

from a predictor variable (182). Simple regression describes 1 predictor variable, whilst multiple regression involves more than 1 predictor variable (182).

To perform linear regression a graph is drawn with a dependent variable on each axis and a straight line drawn through the data. A linear regression line is represented by the equation $\boldsymbol{Y = a + bx}$ (Figure 2-1) (193). $\boldsymbol{a}$ and $\boldsymbol{b}$ are the regression coefficients (Table 2-1). A linear regression model calculates an equation that minimises the distance between the fitted line and the data (194).

Figure 2-1 Estimated linear regression line (193)
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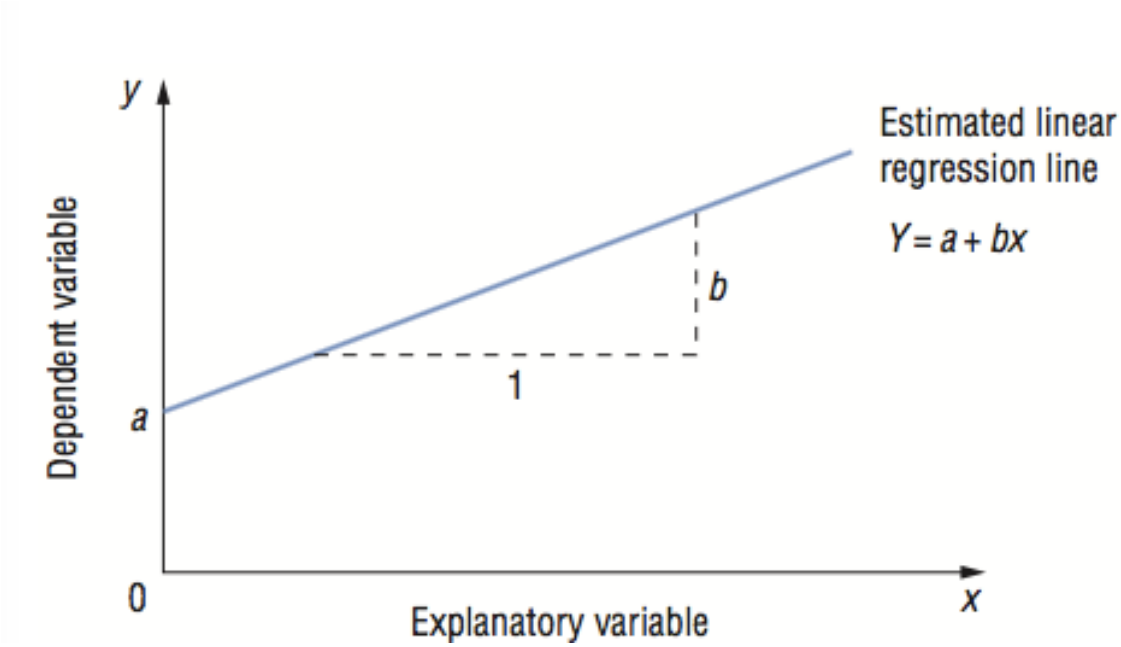


Table 2-1 Elements of the simple linear regression equation (193)

Elements of equation	Represent
x	Predictor variable
y	Dependent or response variable
Y	Value of ***y*** which lies on the estimated straight line for a given value of ***x***
a	Intercept of the line; value of ***Y*** when ***x = 0***
b	Gradient of the line; amount by which ***Y*** increases if ***x*** is increased by 1 unit

R^2 is the coefficient of determination and indicates the goodness of fit of the data points to the straight line produced by the model (193). R^2 indicates the proportion of the variability in the model which is explained by the regression

(193). R^2 is usually expressed as a percentage and has a value of between 0 and 100%. If the R^2 is 100% then the model explains all of the variability of the response data around its mean, whilst if R^2 is 0% the model will explain none of the variability.

An adjusted R^2 is performed to determine the goodness to fit on a multiple linear regression model (193). It is a modification of R^2 to adjust for the number of different predictor variables in the model. It describes the proportion of the variability of ***y*** which is explained by its relationship with each of the ***x***'s (193).

The variables included within predictive models can be selected using different types of selection processes. A backward selection process begins by including all variables judged to be predictive in the model. Variables are removed in turn, with those least likely to influence the model removed first until removing any further variables from the model significantly affects the fit of the model (193). A forward selection model adds variables considered to add to the predictive ability of the model in succession until no further variable significantly improves the model (193). A stepwise selection uses both forward and backward selection of variables. It initially uses a forward selection process of variables but ensures that all variables included to that point significantly add to the model (193).

2.3.11 Logistic regression

Logistic regression is similar to linear regression but it is used when one of the outcome variables measured is binary, such as the presence or absence of a disease (193). A logistic regression model can determine which of the predictor variables predict the outcome variable and gauge the probability of a particular outcome occurring (193). The probability of an event occurring is described using the OR and CI.

A Wald statistic is reported with a logistic regression model. This indicates whether the coefficient for a predictor variable differs significantly from zero (182). If a Wald statistic is reported as zero then the variable is not significant and should be removed from the model.

2.3.12 Survival analysis

Survival analysis is a collection of statistical methods exploring the concept of 'time to an event' (196). In many cases the event will be death, however, it may refer to hospital discharge or time to readmission. Due to the constraints of research there will be individuals who have not experienced the 'event' by the end of the data collection period. In survival analysis it is possible that there will be individuals who have not died by the end of the study. The term given to the survival time for such patients is 'censored', whereby it is unknown when the patient will die but they have not died by the end of the data collection period (196). Censoring will also apply to those lost to follow up as their survival will be unknown (196). To appropriately interpret survival analysis a specific time point must be chosen from which to measure survival (196). Survival time could be measured from an event such as ICU admission or discharge.

The Kaplan-Meier method is used within survival analysis (197). It allows for censoring and enables estimation of the probability of survival at each time point measured (197). A survival curve is plotted with survival probability measured on the y-axis and time on the x-axis (197).

The log-rank test is used to determine if there is a statistically significant difference between survival times of each group as measured on a survival curve. It assesses the hypothesis that there is no difference in the survival times of each group (193).

2.3.13 Receiver-operating characteristic curves

Receiver-operating characteristic (ROC) analysis is used within medical research to determine the accuracy of diagnostic tests and statistical models which divide individuals into 2 categories (198). A ROC curve can also be used to determine the discriminative ability of a scoring system (199). A graph is plotted of a true positive rate, or the sensitivity, against the false positive rate (1-specificity) (200).

To ascertain the performance of a scoring system the area under the ROC curve (AUC) is calculated (200). An AUC of 1 denotes a perfectly accurate scoring

system, whilst an AUC of 0.5 indicates that the performance of a scoring system is random (198). In comparative clinical studies an AUC of 0.8 has been determined as the threshold for clinical use (201).

Chapter 3 Admission and referral to critical care of patients with liver disease

3.1 Introduction

The literature review explored the clinical manifestations of advanced liver disease and the precipitants for critical care admission in this population. It highlighted the current demand on critical care in the UK and the challenges clinicians face in determining which patients to admit to intensive care when capacity is limited.

This chapter further investigates the decision to admit or refer a patient with chronic liver disease to critical care.

3.2 Ethical dilemmas in critical care and liver disease

Introduced in response to the polio epidemic in the early 1950s, the concept of intensive care has developed from the provision of positive pressure ventilation through the use of 'iron lungs' to the delivery of multi-organ support for patients at high risk of death (202). Such medical advances coupled with increased incidence and survival of those with chronic disease has raised demand and pressure on finite resources, with challenges arising in the allocation of critical care beds (203, 204). Critical care utilisation varies worldwide, with differing attitudes and thresholds for admission, reflecting both healthcare organisation and funding. ICU capacity is difficult to define with no standard definition of an ICU bed (205). For example there are 6.6 beds per 100,000 of the population in the UK, which rises to 29.2 beds per 100,000 in Germany, introducing variation in bed capacity (132).

There are many ethical aspects to consider in deciding which individuals should be offered critical care, in particular individuals perceived to have self-inflicted illness, including specific aetiologies of liver disease (204). Beauchamp and Childress describe a 4 principle approach to medical ethics encompassing autonomy, beneficence, non-maleficence and justice which apply when deciding if critical care admission is appropriate (206). The importance of decision-making is reflected in guidelines with the General Medical Council (GMC)

recommending a joint partnership between doctor and patient, with the onus on the clinician to outline options for patients using clinical knowledge and judgement (207). Individuals should be informed of both non-survivorship and the potential risks and burden of an ICU stay. Guidelines for ICU admission have been published by the American Society of Critical Care Medicine which suggests models based on prioritisation, diagnosis and objective parameters (208). A prioritisation model stratifies individuals at risk, with those at highest priority requiring invasive treatment only available within the ICU and those at lowest priority at low risk of requiring intervention or individuals with irreversible disease facing imminent death (208). The diagnosis model suggests diseases which commonly require ICU admission whilst the objective model encompasses vital signs, laboratory values, radiological findings, electrocardiogram record and physical findings on examination (208). Whilst these guidelines suggest the proposed models are used to inform site and population specific policies, they also highlight the value of scoring tools and emphasise the overriding value of clinician judgement to assess every individual case (208).

The capacity to understand disease processes, what intensive treatment strategies involve or potential outcomes may be impaired by critical illness with an ICU candidate unable make an informed decision regarding care (209, 210). The Adults with Incapacity (Scotland) Act 2000 provides a framework to aid in decision-making with regular review of capacity and clinicians acting in the best interest of the patient (211). The presence of an advanced directive can provide a useful insight into the patient's wishes, however challenges will remain for those who express a wish for intensive care but for whom clinicians' perceive no potential benefit (212).

Decision-making involved in ICU admission is complex, with the aim to admit critically unwell individuals, whilst excluding those 'too sick or well to benefit' (208, 213). Results of a European survey in 1990 suggested that bed availability and likely survivorship were the 2 most influential factors in a clinician's decision to admit to ICU (209). A subsequent survey of critical care practitioners showed that QOL, probability of survival, reversibility of acute disease and any chronic illness were important factors in offering individuals ICU management (214). Social standing, psychiatric history, societal cost and cost-benefit of ICU care were not deemed significant (214). Sprung et al. further examined factors

associated with ICU triage decision-making and described the influence of patient age, admission diagnosis, severity of disease, operative status and bed capacity (215). Seniority of the admitting clinician, ability to examine patient, presence of comorbidities and level of functional ability are known to influence the decision (216). Physiological reserve, prognosis of disease and quality of life, treatment availability and response to therapy already initiated, require consideration (212). Admission to ICU can be influenced by the referring consultant; with difference in seniority and the relationship between intensivist and referring clinician playing important roles (217).

Whilst individual factors involved in ICU triage decisions have been evaluated extensively within the literature, there is a paucity of evidence examining whether any differences exist in the degree of influence each factor has in decision between the referring specialty and intensivist. This study intends to identify whether differences exist between gastroenterologists and intensivists in the decision-making surrounding ICU triage, level of care offered and prognosis of patients with chronic liver disease.

3.3 Study question and aims

3.3.1 What criteria are used in the decision to offer intensive care to a patient with chronic liver disease?

With the increased burden of chronic liver disease in the population and improved ICU survival, the pressure to admit individuals with advanced liver disease to ICU will increase. Historically, the survival of critically ill patients with cirrhosis has been poor and has acted as a barrier to ICU admission. Whilst there is a good working relationship between the gastroenterologists and intensivists within GRI there was an increasing interest by both specialties in exploring the characteristics of patients who warrant ICU admission. This would attempt to reduce barriers and ensure those who may benefit from an ICU stay were admitted.

Individual factors involved in the decision to offer patients intensive care have been investigated extensively within the literature. However, there is a lack of

evidence examining whether differences exist in the degree of influence each factor has on the referring gastroenterologist and receiving intensivist.

3.3.2 Aims of Survey 1

- Identify criteria used in decision-making for ICU admission for patients with liver disease, the weighting given to each and determine any differences in opinion between gastroenterologists and intensivists in non-transplant units

- Establish whether there are differences between specialties in the management of each grade of Child-Pugh liver disease and presentation of gastrointestinal bleed or sepsis

3.3.3 Aims of Survey 2

- Explore the level of organ support offered to individuals with different aetiologies and severity of liver disease and whether management differs between gastroenterologists and intensivists

- Determine opinion on readmission following ICU discharge

- Establish clinicians' estimated 1 year mortality of each grade of Child-Pugh if stable and ICU mortality

3.4 Methodology

3.4.1 Design

3.4.1.1 Use of a survey for data collection

There are a number of research instruments which can be used to collect data on clinical practice and opinions. They include surveys, focus groups and structured interviews. A questionnaire-based survey was used in this chapter in favour of focus groups or structured interviews as the individuals targeted were spread throughout Scotland with time constraints due to clinical commitments.

An electronic survey was chosen as it was considered to have a number of advantages. This enabled individuals to complete questions at a convenient time, avoided geographical barriers and accelerated response rates with minimal financial cost (179). Online based surveys have the advantage that individuals are required to answer each question to progress and are thus unable to leave questions unanswered, with the ability to determine how many questions respondents can view and in what order. Using a web-based survey enabled distribution to respondents using a link embedded in an email facilitating distribution through a national organisation – the Scottish Society of Gastroenterologists (SSG), ICU secretarial staff and to individual email addresses.

A postal survey was considered, however this would have involved difficulties in distribution as individual consultant names would be required. Furthermore, each respondent would incur inconvenience as they would be required to post back a response, incurring financial cost (179).

It was acknowledged that web-based surveys have reduced response rates compared to postal surveys and whilst it could be expected that NHS consultants are computer literate, they may have more than one email address (218). Features which impact upon a doctor's decision to complete a survey are the perceived time required to complete a survey, relevance of the subject matter, understanding that the results will be used appropriately and confidentiality maintained (218). To improve the response rate a cover email provided details of the MD student and supervisors, the intended use of the survey and an assurance of anonymity of answers. Respondents were given the option to email the MD student directly to be informed of the results.

A combination of open and closed questions were utilised within each survey. The closed questions concerned factors used in a clinician's decision to admit or refer a patient and enabled direct comparison of each specialty. An open question added a qualitative element to the research and was included to allow clinicians to add additional comments on their practice, potentially introducing other aspects overlooked in the survey design.

3.4.1.2 Validity and reliability

In order to ensure both validity and reliability the MD student designed a draft of both surveys. Both surveys were reviewed by 2 consultant intensivists (Professor John Kinsella and Dr Tara Quasim) and a consultant gastroenterologist (Dr Stephen Barclay). This review by those with expertise in admitting and referring patients to ICU provided face validity confirming that each question within the survey appropriately reflected the research question. The amended survey was subsequently piloted to trainee doctors working within intensive care and gastroenterology. Respondents were asked to comment on readability, clarity of questions, layout and time taken to complete the questionnaire. In addition, respondents were encouraged to annotate the survey noting readability and clarity of questions to ensure that any ambiguity in the questions was addressed. Concurrent validity was addressed by asking both specialties identical questions, with certain answers predicted not to differ between the groups asking the questions (179). It would be expected that there should be no difference between specialities in the influence of certain factors such as sex and employment, which have been demonstrated not to influence decision-making in this setting.

Following an initial pilot, the survey was transferred into an online format using the 'surveymonkey' web-based software for self-completion. The survey was tested for usability prior to distribution to identify technical problems in question completion and eliminate any grammatical errors.

3.4.1.3 Design of Survey 1

In response to the findings of the literature review, physiological and social criteria were identified which were purported to impact on decision-making in ICU admission. Criteria included demographic factors, chronic health status, current clinical status and aetiology of liver disease and underlying cause of admission. Respondents were questioned as to whether they would refer (gastroenterologists) or admit (intensivists) patients to ICU (Appendix 1). Eighteen criteria were subsequently chosen and a likert scale designed to rate the influence of each factor on the decision to admit or refer an individual to ICU. The scale ranged from 1 (no influence on decision) to 5 (significant factor in

decision). A free text box was included, enabling respondents to list any additional factors used within their clinical practice. Respondents were asked a closed question on whether intensive care was indicated in individuals with Child-Pugh A, B or C liver disease presenting with gastrointestinal bleeding or sepsis (Appendix 1). These scenarios aimed to determine if aetiology of presentation altered management.

To measure the influence of each factor on each clinician's decision to admit or refer a patient to intensive care, a multiple-indicator measure was required (section 2.1.1.1) (179). A likert scale was chosen as it would measure the intensity of influence each factor had on offering ICU care to an individual on a 5 point scale (179). In order to utilise the likert scale effectively, every respondents was given a statement and asked how each factor influenced their decision. All factors making up the scale were identified within the literature to impact upon ICU triage.

3.4.1.4 Design of Survey 2

The MD student designed a second survey to further examine findings of the initial survey. This survey was reviewed prior to distribution using the same method and individuals as Survey 1 (section 3.4.1.2). The aim was to explore ICU admission and level of organ support offered to patients, re-referral/readmission to ICU, mortality of liver disease and the role of underlying aetiology of chronic liver disease. This second survey comprised 3 parts; 3 vignettes, a closed question estimating percentage mortalities and open question exploring the role of aetiology.

3.4.1.5 Vignettes

The use of vignettes was chosen to explore whether differences existed in consultant behaviour when presented with scenarios based on common presentations of critically ill cirrhotic patients (section 2.1.1.2) (Appendix 2). In this survey, the vignettes were designed to enable the respondent to consider a range of factors in making the decision to offer intensive care and the level of organ support offered. These factors included the severity of liver disease (using Child-Pugh grading), nature of presenting complaint, underlying aetiology of

chronic liver disease and clinical progression during hospital admission. These themes were included in the vignettes to examine conflicting results from the first survey. The role of clinical progression during hospital stay was included as the concept of reversibility had been introduced by 1 respondent in the first survey. The level of organ support offered to an individual was examined in the second survey in response to both discussion between the survey reviewers and comments received by the MD student from respondents to the first survey.

Each case study provided a summary of history and examination, laboratory and radiology results, Child-Pugh grade when stable and clinical progression since hospital admission (Appendix 2). The objective was to provide clinicians with realistic scenarios to explore decision-making without giving confounding factors to complicate their choice. The advantage of vignettes was that each respondent had to reflect on a case scenario and consider a number of different factors which mirrored routine practice rather than answering a closed question on a specific issue such as grade of liver disease (179, 181).

Three vignettes were composed. To improve credibility they were based on case presentations of patients admitted to the ICU at GRI. Three cases were chosen as both the MD student and survey reviewers considered that this would provide sufficient differences in case scenarios whilst ensuring that the survey could be completed within a reasonable time-frame. The presentations of haematemesis and sepsis were chosen as both had been identified to have differing prognoses. Higher survival rates being achieved by patients admitted to ICU with haematemesis as compared to sepsis (section 1.5.7).

Each respondent was asked whether they would opt for ICU management and if the answer was ‘yes’ they were asked to determine whether the patient would be offered single organ or multi-organ support. This question was included to enable the respondent to reflect on a ceiling of care for each patient.

To explore the responses received in the first survey on the topic of readmission, each vignette asked the respondent whether the patient would be readmitted to ICU if they survived to ward or hospital discharge. Following the introduction of the concept of ‘reversibility’ in the responses to the initial survey, 2 cases asked respondents to determine if they would continue to offer ICU care if the initial

presenting complaint (haematemesis or sepsis) resolved but the patient developed a new problem requiring ICU care (sepsis or renal failure).

An abbreviated version of each case scenario is given below, with a full version in Appendix 2.

Case 1

A 55 year old woman presented to the ED (Emergency Department) with abdominal pain, diarrhoea and vomiting. She had a past medical history of Type 2 diabetes, obesity and a 10 year history of alcohol excess. She was drinking a litre of vodka each day. She had been graded Child-Pugh B at a liver outpatient clinic.

Following admission under general medicine she was commenced on intravenous fluids and Tazocin. Blood cultures revealed a gram negative bacteraemia. Over the following 2 days she deteriorated with increasing oxygen demands. She was diagnosed with a pleural effusion and ascites and was graded Child Pugh C at consideration for ICU admission.

Case 2

A 35 year old man presented to the ED following multiple episodes of haematemesis within the previous 24 hours. He has evidence of hypovolaemic shock and has a further episode of haematemesis in the ED. He is graded Child-Pugh C. He requires an emergency upper gastrointestinal endoscopy and placement of a sengstaken tube for a variceal bleed.

He had a past medical history of alcohol excess and had a previous admission 6 months earlier with jaundice and ascites. During that admission he was graded Child-Pugh C and was noted to have oesophageal varices.

Case 3
A 64 year old man presented to the ED with a 6 day history of shortness of breath and malaise. He had clinical findings suggestive of respiratory tract infection and severe sepsis. He was graded Child-Pugh B. He required vasopressor support for hypotension and was hypoxic despite 15 litres of oxygen. He had a past medical history of Type 2 diabetes, obesity, peripheral vascular disease and a previous stroke. He had been diagnosed with non-alcoholic fatty liver disease and graded Child-Pugh A at an outpatient clinic.

3.4.1.6 Mortality estimation

Respondents were asked to estimate 1-year mortality for individuals with stable Child-Pugh A, B and C liver disease and ICU mortality for each grade of liver disease should they be admitted to ICU. This question was included as there is a paucity of literature providing figures for survival of individuals with stable and unstable liver disease. The results would ascertain if there was agreement between gastroenterologists and intensivists on perspective of survival. To investigate the conflict which arose between specialties in survey 1, each respondent was asked whether aetiology of liver disease influenced their decision to admit a patient to ICU and to describe the impact on their decision-making. The aim of this was to determine if the difference between specialties was reproducible and further investigate the underlying reasons for this difference.

3.4.2 Participants

The goal of both surveys was to reach every consultant gastroenterologist and intensivist in Scotland. Consultants working within the liver transplant centre in Edinburgh Royal Infirmary were excluded as the survey was designed to examine practice of management of liver disease in non-transplant units. The first survey invitation was distributed in October 2014. Every ICU secretary in Scotland was emailed and requested to distribute an online link to the survey to consultant

intensivists within their department. Access to gastroenterologists within Scotland proved challenging as there is no national database of all consultant gastroenterologists. Consultants involved in the management of individuals with liver disease in Scotland can encompass gastroenterologists, hepatologists and those with interests in other medicine areas, particularly out of hours. All consultant gastroenterologists based in Scotland listed on the online directory of UK consultants SpecialistInfo were contacted with an email invitation and online survey link by their NHS email addresses (219). As there was no guarantee that this internet directory was comprehensive all consultant members of the SSG were emailed a survey link. The 2013 Scottish Survey of Liver Services found 103 gastroenterologists working within Scotland, which is the number used as a denominator within this survey to determine a response rate (110). To maximise the response rate a reminder for survey completion was distributed 1 month after the initial invitation.

3.4.3 Ethics

As respondents were recruited as research participants due to their professional role, formal ethical approval was not deemed necessary, as per the guidance issued by the NHS Health Research Authority (220). Respondents were made aware that their electronic survey responses were anonymous. This would encourage individuals to answer honestly, without fear of consequences and improve response rates (179, 221).

3.4.4 Data analysis

The surveys described in this chapter involved mixed methods research. Both the qualitative and quantitative results are presented together for each topic explored in the surveys.

The quantitative research was analysed using percentages to represent proportions. The average responses to the Likert scale were expressed as a median score.

Thematic analysis was used to assess qualitative data and identify recurrent themes given by respondents to the survey. Key quotes were selected and included within the results.

3.5 Results

3.5.1 Results of Survey 1

3.5.1.1 Responses

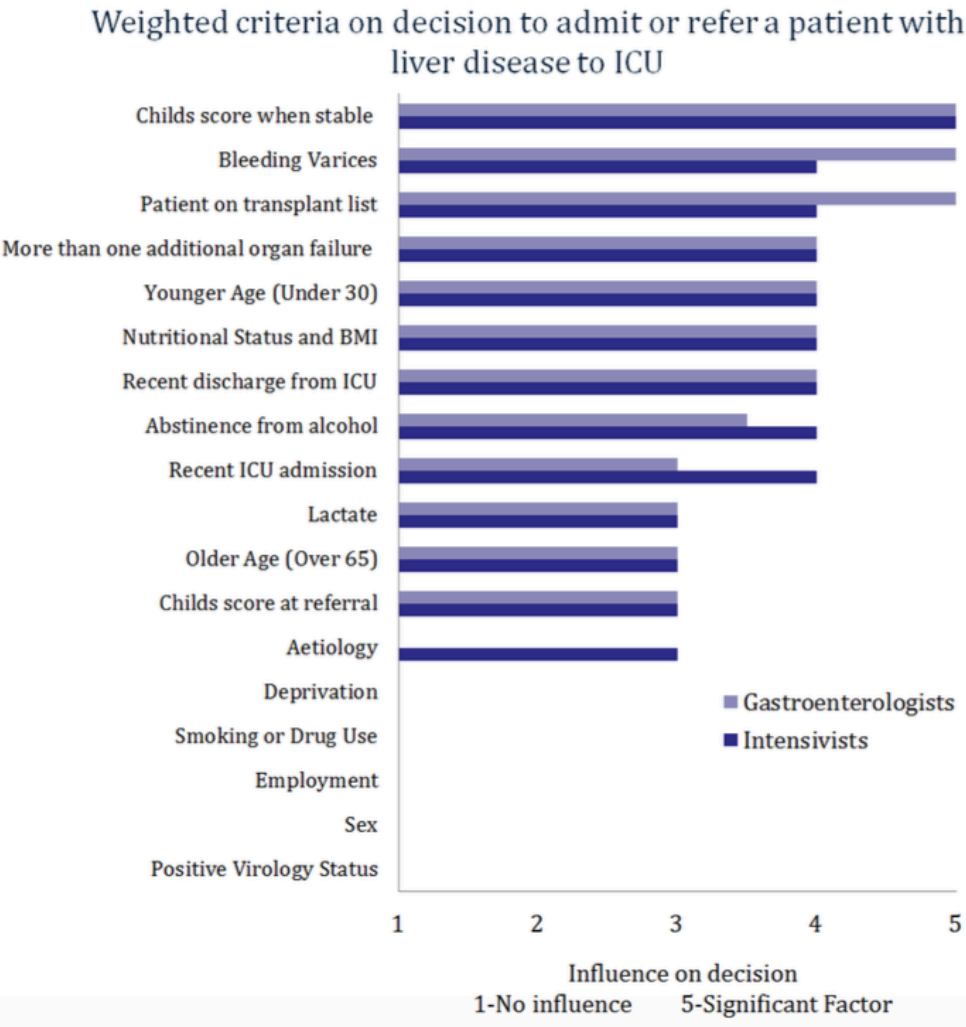
35 of 103 consultant gastroenterologists and 65 of 143 consultant intensivists replied, representing a response rate of 34% and 45% respectively.

3.5.1.2 Weighting of factors involved in the decision to admit or refer patients with liver disease to ICU

Survey participants were asked to rate the significance of different factors on their decision to refer (gastroenterologists) or admit (intensivists) a patient with liver disease to ICU from 1 (no influence on decision) to 5 (significant factor in decision).

The only factor given a median rating of 5 by both gastroenterologists and intensivists was Child-Pugh score when stable (Figure 3-1). ICU admission secondary to bleeding varices was given a median rating of 5 by gastroenterologists and 4 by intensivists, likewise presence on the liver transplant list was rated 5 by gastroenterologists and 4 by intensivists. Individuals with more than one additional organ failure, nutritional status and body mass index (BMI) of below 18.5, age under 30 and ICU stay during the same hospital admission were given a median rating of 4 by both groups of clinicians. ICU admission within the previous year was given a rating of 4 by intensivists and 3 by gastroenterologists, whilst 6-month abstinence from alcohol was given a median weighting of 4 by intensivists and 3.5 by gastroenterologists. Lactate of over 2mmol/L, age over 65 and Child-Pugh score at time of referral to ICU were all given a rating of 3 by both groups of clinicians. Aetiology of liver disease was given a median rating of 1 by gastroenterologists and 3 by intensivists. No significance was placed on deprivation, virology status, sex, smoking or drug use or employment by either group of respondents.

Figure 3-1 Results of Survey 1 – Criteria used in the decision to admit or refer a patient with liver disease to ICU



3.5.1.3 Additional factors involved in decision-making

Participants were asked to list any additional factors judged to be influential in deciding whether ICU management was appropriate using free text. Gastroenterologists and intensivists both listed pre-morbid functional state, physiological reserve, comorbidities and engagement or compliance with therapy as factors which influenced their decision. The presenting diagnosis, an identified precipitant factor for deterioration, perceived reversibility of illness and survival were listed by both groups as important. One intensivist answered that their decision to admit a patient would depend on "*whether I think they are going to survive*" and a gastroenterologist added that the "*likelihood of a positive outcome*" would influence their decision. Patient and family wishes were sought by both specialties. The opinion of colleagues was deemed to be

important with intensivists utilising the views of a consultant involved in the patients' long-term care, with one noting "*consensus can be useful*". Intensivists took into account white cell count and both groups noted the importance of complications such as hepatic encephalopathy and renal failure. Intensivists listed MELD-Na score, demand for critical care beds, levels of organ support required and potential for tertiary level care as significant factors, whilst gastroenterologists placed importance on the patient's psychological status. If the admission was the patient's first presentation of disease gastroenterologists listed this to be influential on their decision. One intensivist commented "*if this is the first presentation I would admit whereas with progressive presentations I would be less likely to admit*".

3.5.1.4 Child-Pugh grade and reason for admission

Each specialty was asked whether they would refer or admit individuals with different grades of Child-Pugh cirrhosis with gastrointestinal bleeding for ICU management (Table 3-1).

Table 3-1 Percentage of specialist who would refer or admit each Child-Pugh grade with gastrointestinal bleeding to ICU

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Gastroenterologists	79.4%	85.7%	80.0%
Intensivists	98.5%	100%	81.0%

Each specialty was asked whether they would refer or admit different grades of Child-Pugh cirrhosis with sepsis for ICU management (Table 3-2).

Table 3-2 Percentage of specialist who would refer or admit each Child-Pugh grade with sepsis to ICU

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Gastroenterologists	82.9%	94.3%	76.4%
Intensivists	96.9%	92.2%	33.3%

3.5.2 Results of Survey 2

3.5.2.1 Responses

31 of 103 consultant gastroenterologists and 42 of 143 consultant intensivists replied, representing response rates of 30.1% and 29.4% respectively.

3.5.2.2 Levels of organ support

For Case study 1, a patient with Child-Pugh C cirrhosis with sepsis secondary to respiratory tract infection, 48.4% of consultant gastroenterologists would refer the patient to ICU, whilst 57.1% of consultant intensivists would admit the patient. Of those who would refer or admit the patient 57.1% of gastroenterologists and 69.6% of intensivists would offer multi-organ support.

For Case study 2, a patient with Child-Pugh C cirrhosis with haematemesis, 93.3% of consultant gastroenterologists and 95.2% of consultant intensivists felt ICU admission was appropriate. Of those, 38.5% of gastroenterologists and 57.5% of intensivists would offer multi-organ support.

For Case study 3, a patient with Child-Pugh B cirrhosis with sepsis secondary to respiratory tract infection, 93.1% of gastroenterologists would refer the patient to ICU and 94.7% of intensivists would admit the patient to ICU. Of those 77.8% of gastroenterologists and 94.4% of intensivists would offer multi-organ support.

3.5.2.3 Continuation of intensive care

In Case study 2 following resolution of haematemesis, the patient deteriorated whilst in the ICU developing a new problem of sepsis. Consultants were asked whether they would continue care. 90.0% of gastroenterologists and 78.6% of intensivists supported continuation of care.

In Case study 3 following resolution of sepsis secondary to respiratory infection the patient develops renal failure whilst in ICU. 85.7% of gastroenterologists and 81.6% of intensivists would support continuation of ICU care.

3.5.2.4 Readmission to intensive care

In Case study 1, respondents were asked if they would readmit the patient following ICU discharge, but prior to hospital discharge. 33.3% of gastroenterologists and 28.6% of intensivists would readmit the patient to ICU. Respondents were asked would they admit the patient to ICU if they re-presented following home discharge with reduced functional ability and continued alcohol intake. 10.0% of gastroenterologists and 9.5% of intensivists would consider readmission.

In Case study 2 respondents were asked if they would readmit a patient discharged to the ward following the development of recurrent sepsis. 60.0% of gastroenterologists would re-refer the patient, whilst 28.6% of intensivists would readmit. If the same patient survived to hospital discharge 90.0% of gastroenterologists and 76.2% of intensivists would readmit the patient if they later presented with gastrointestinal bleeding, whilst 53.3% and 31.0% respectively would readmit if the patient presented with sepsis.

In Case study 3 respondents were asked whether they would readmit the patient following ICU discharge following the development of hospital acquired pneumonia. 75.0% of gastroenterologists would refer the patient to ICU, whilst 71.1% of intensivists would readmit the patient. If the same patient survived to hospital discharge and represented with sepsis six months later, 75.0% of gastroenterologists would refer the patient and 83.8% of intensivists would readmit.

3.5.2.5 Mortality of chronic liver disease

Respondents were asked to estimate the percentage 1-year mortality in a stable patient with Child-Pugh A, Child-Pugh B and Child-Pugh C liver disease.

For those with stable Child-Pugh A disease, intensivists estimated a mean 1-year mortality of 14% and gastroenterologists 33%. For those with Child-Pugh B, intensivists estimated mortality at 26% and gastroenterologists 38%. Individuals with stable Child-Pugh C had an estimated annual mortality of 48% by both intensivists and gastroenterologists.

Respondents were asked to estimate the percentage mortality in each grade of Child-Pugh if the patient was admitted to ICU. For those with Child-Pugh A admitted to ICU, intensivists estimated a mean ICU mortality of 30% and gastroenterologists 32%. For those with Child-Pugh B, intensivists estimated mean ICU mortality of 47% and gastroenterologists 48%. Individuals with Child-Pugh C had an estimated ICU mortality of 74% by intensivists and 65% mortality by gastroenterologists.

3.5.2.6 Aetiology of chronic liver disease

Respondents were asked whether aetiology of liver disease impacted upon their decision to refer or admit a patient to ICU. 45.8% of consultant gastroenterologists and 48.5% of consultant intensivists answered ‘yes’.

If the respondent answered ‘yes’ they were asked to explain how aetiology influenced their decision. Gastroenterologists believed those with alcoholic liver disease had a poorer prognosis than other aetiologies, in particular if the individual continued to drink precluding the suitability for liver transplant. One gastroenterologist explained the significance of recent therapies to successfully treat viral hepatitis and the positive impact on prognosis. Likewise, when intensivists were asked how aetiology influenced their decision a number of individuals believed that alcoholic liver disease would limit options for treatment and potential for transplant. One respondent replied that if the liver disease was “*secondary to substance abuse and continuing then the patient takes responsibility for continuing health or lack of*”. Intensivists made

reference to the modification of risk factors, reversibility of liver disease and potential for ICU rehabilitation.

3.6 Discussion

The results from both surveys indicate that decision-making in the referral and admission of cirrhotic patients to intensive care is multifactorial, with agreement between gastroenterologists and intensivists in the significance of Child-Pugh score measured when the patient is stable. Inconsistencies exist in the impact of underlying aetiology, however it is clear the presenting complaint is pertinent to the decision. Results from Survey 2 suggest that there may be patients who would be accepted for intensive care but who are not deemed suitable by the referring team, whilst intensivists were reluctant to continue care or readmit patients who had not previously survived to home discharge. For stable cirrhosis intensivists estimated a lower mortality for Child-Pugh A and B whilst an increased mortality for Child-Pugh C admitted to the ICU.

3.6.1 Interpretation of findings

3.6.1.1 Criteria for admission to ICU

The findings from this study demonstrate universal agreement between gastroenterologists and intensivists in the value of utilising Child-Pugh score when stable as the most significant factor in their decision as to whether a patient with liver disease is appropriate for intensive care. In contrast Child-Pugh score measured at the time of potential admission was given less significance by both specialties. This result is interesting given that studies have shown that Child-Pugh score and encephalopathy and PT, components of the score, predict mortality of cirrhotic patients in ICU if measured at the time of ICU admission (118, 124). Whilst the score gives a reflection of the severity of liver disease its use may be limited as it does not reflect organ failure in the form of cardiovascular, respiratory or renal dysfunction (129). Many studies demonstrate that scores specific to ICU which reflect the degree of organ failure, are more accurate in predicting ICU mortality than those reflecting the severity of liver disease (section 1.6) (117, 124, 177, 222, 223).

Results from this study suggest that reversibility of either the precipitant factor or liver disease and potential for definitive treatment are perceived as relevant factors by both specialties. Therapeutic advances in both endoscopic and pharmacological treatment for variceal bleeding have led to dramatic improvements in mortality of cirrhotic patients which explains why the majority of consultants in both specialties opted for ICU management of all grades of Child-Pugh cirrhosis with gastrointestinal bleeding (224). A single centre study demonstrated a reduction in mortality from 70% to 32% in Child-Pugh class C patients between 1980 and 2000 (225).

The significance placed upon listing for liver transplantation could be due to various factors and with a 96% 90 day survival following elective transplant, UK survival rates following liver transplantation are high (section 1.5.5) (226). If an individual has been selected for definitive treatment of their liver disease, onus may be placed on specialists to offer ICU management in order that they have optimal chance of survival to transplant. Selection for liver transplant in the UK is stringent with involvement of a multidisciplinary team, assessment of comorbidity, drug and alcohol use plus a thorough physiological and psychological assessment (123, 227). To proceed to listing, patients must be predicted to have a 5 year survival after transplant of over 50% (228). If individuals are assessed when stable and predicted to survive transplantation this information may inform the decision regarding ICU care and help predict if the patient will have reserve to survive critical illness. The MELD score used to determine urgency for transplantation in the USA and the MELD-Na score was utilised by one intensivist in their decision whether to admit cirrhotic patients to ICU (145). Evidence suggests that both serum sodium and MELD score predict survival in those awaiting liver transplantation (149, 229).

Significance was placed on the importance of 6-month abstinence from alcohol by both specialties. Alcohol dependence is associated with increased hospital mortality, sepsis and septic shock (230). Alcoholics develop more complications following ICU admission, with longer hospital stays (231, 232). Within 3 months of abstinence liver function improves, there is reversal of cardiac dysfunction, improvement in immune function and normal cortisol response to stress (233, 234). Consideration of ICU admission must deliberate not only survival but recovery to an acceptable QOL. Critical illness is associated with muscle wasting

and weakness which impact upon rehabilitation (235). In those with liver disease capacity for recovery is further compromised by the skeletal muscle myopathy resulting from alcohol dependence (236). As is evident in the responses to the survey, some clinicians consider alcoholic liver disease as a self-inflicted disease, whereby the patient must take responsibility for the progression of disease. Others may view problematic alcohol intake as a mental health issue. There has been a reluctance in the past to offer treatment, however, national guidelines recommend that patient care should be based on need irrespective of whether the patient's actions have contributed to the cause (204, 237, 238).

The findings from this study demonstrate a difference in the significance placed upon age with respondents placing greater importance on whether an individual was under 30. Whilst the results are unclear whether consultants would be more or less likely to admit younger patients with liver disease, a number of factors are relevant. Age is included in many scoring systems used within critical care to predict hospital mortality (such as APACHE II) and has been demonstrated to play a role in ICU triage decisions (164, 215). Evidence in the general ICU population suggests advanced age is an independent risk factor for death, but the role of premorbid functional status, comorbidity and severity of disease is significant (239-241). The burden of comorbidity and physiological reserve of each individual is a considerable factor in ICU survival and QOL following critical illness (119, 242). Both are difficult to quantify with existing tools such as the Charlson comorbidity index not shown to predict ICU mortality or use of resources (119, 243).

The importance placed upon nutritional status and BMI below 18.5 by both specialties is supported by studies outwith the critical care population, including one meta-analysis which found extremes of weight to be associated with increased mortality and morbidity (244, 245). In a study of 11,326 Canadians through the National Population Health Survey, the adjusted relative risk of death was 1.89 in those with a BMI of under 18.5 and 1.48 in those with a BMI of over 35 when compared to a BMI of 22.5 to 25 (245). Studies suggest that critically ill patients who are underweight have higher mortality and are less likely to return to baseline health following discharge when compared to overweight or obese individuals (246, 247). It is hypothesised that underweight

individuals may lack nutritional reserve to adequately respond to the increased metabolic demand of critical illness (248-250).

Deprivation, sex, employment, smoking and drug use were not given any weighting in the decision to refer or admit a patient by either specialty. This finding is not that surprising with a 2001 Swiss study of 232 intensive care doctors determining socioeconomic status, drug and alcohol use to have little influence on their decision to admit patients to ICU (251). The association of socioeconomic deprivation and poor health has previously been explored (section 1.2.5.3) and whilst socioeconomic status may influence access to healthcare in certain countries such as the USA, the universal access to the NHS removes this barrier in the UK (252). A 2002 cross-sectional study of 46,587 admissions to ICUs in England, Wales and Northern Ireland demonstrated gender differences in ICU admission with certain conditions – however cirrhosis was not considered (253). Few studies exist in the literature which examine the role of substance abuse in the decision to refer or admit a patient to the ICU.

Patient and family wishes were noted to influence the decision to offer intensive care, reflecting other studies which have documented a move towards patient autonomy in decision-making (251, 254). Whilst self-determination of treatment is ideal, conflict will still arise if a patient wishes to seek intensive care but the clinician believes it to be futile. Although it was not noted by any of the respondents, QOL has been demonstrated to have an important role in the decision to offer intensive care in another study performed at the same centre (255). This is further explored in Chapter 7.

Peer standards appear to play a pivotal role with a previous study from the same centre demonstrating that intensivists were keen to seek opinion of their colleagues within the ICU and consensus of opinion was deemed important between the referring gastroenterologist and receiving intensivist (255). It was noted that referring doctors may have prior knowledge of a patient's resilience or their compliance with therapy which may help predict patient approach to ICU rehabilitation. In their editorial on intensive care triage, Levin and Sprung highlighted the persistence of the referring clinician and seniority of doctors involved in the decision as important (217).

3.6.1.2 Aetiology of chronic liver disease

The findings of the initial survey demonstrated that whilst intensivists gave some significance to aetiology of chronic liver disease, referring gastroenterology consultants did not feel aetiology impacted on their decision. This opinion was further explored in the second survey where 48.5% of consultant intensivists and 45.8% of consultant gastroenterologists stated aetiology impacted upon their decision to offer ICU management. The apparent change in attitude by gastroenterologists between surveys is difficult to explain. The first survey was distributed in October 2014 and the second in July 2015 and during this time period there were no landmark studies published regarding aetiology of liver disease and ICU management. It is possible that different consultants responded to each survey or since completing the initial survey, consultant intensivists had reconsidered their opinion.

Respondents of both specialties highlighted prognosis as an important factor, stating that those with alcoholic liver disease had a poorer outcome with ongoing alcoholism impacting upon potential for transplantation. This is contraindicated by a single centre American study of 40 patients with cirrhosis where mortality of critically ill cirrhotics was found to be lower in those with an underlying diagnosis of alcoholic liver disease than other causes of liver disease (115). Furthermore, in those with decompensated cirrhosis secondary to viral hepatitis, recent studies have reported that antiviral therapy is beneficial for those with Hepatitis B and Hepatitis C (256, 257). Certainly, the potential for definitive treatment influences the decision to offer ICU care.

3.6.1.3 Child-Pugh and mortality

With little difference in the management of all grades of Child-Pugh cirrhosis with gastrointestinal bleed, there is disagreement in the level of care offered to individuals with Child-Pugh C cirrhosis and sepsis with the majority of intensivists reluctant to offer ICU admission. This finding was consistent with intensivists estimating a higher ICU mortality for those with Child-Pugh C than gastroenterologists. In a single centre Scottish study of long-term outcomes by the MD student and colleagues (Chapter 6) Child-Pugh C ICU mortality was 50%, which was closer to the 65% estimated by gastroenterologists (258). Both groups

estimated higher ICU mortality of those with Child-Pugh A and B than the study. Whilst agreement existed between specialties for the 1-year mortality of stable Child-Pugh C cirrhotics, gastroenterologists estimated higher mortality for both Child-Pugh A and B cirrhotics. A 2005 systematic review of 118 studies concluded 1-year survival of Child Pugh A, B and C to be 95%, 80% and 45% supporting the estimates of intensivists (53).

In all case studies, intensivists were more likely to offer ICU admission to patients than gastroenterologists were to refer patients. Whilst it is difficult to draw firm conclusions this finding would suggest that in practice certain patients would be offered intensive care by intensivists but may never be referred by their gastroenterology consultant. The 2013 NCEPOD report into management of patients with alcoholic liver disease found that 31% of patients deemed eligible for intensive care were denied escalation of care either by referring clinician or intensivist (109). When ICU admission was deemed appropriate a greater proportion of intensivists would offer multi-organ support rather than limiting treatment to single organ support in comparison to gastroenterologists. This is perhaps a reflection of a view held by many intensivists that critically ill patients should initially be offered multi-organ support to give greatest chance of survival and if multi-organ failure persists after a number of days then treatment should then be limited (204, 255). It could also reflect the belief that if renal failure is present in the context of cirrhosis then prognosis is poor and to offer renal replacement therapy would be futile (259). In every case study, fewer intensivists would support readmission to ICU during the same hospital stay compared to gastroenterologists. A number of studies, including a large prospective multicentre cohort, demonstrated that mortality is higher amongst patients readmitted to ICU and the lack of enthusiasm amongst intensivists to readmit patients may represent a feeling of futility (260, 261). This was mirrored in those patients surviving to home discharge. The majority of consultants in both specialties would consider intensive care for patients with previous ICU admissions on subsequent admissions, however there was a reluctance to offer ICU care to those with reduced functional ability and continued alcohol intake.

3.6.1.4 Future directions

Given the survey design it was necessary to use vignettes to explore clinicians' decision-making. To further investigate themes that have arisen in this chapter it may be valuable to perform a prospective study. This would involve identifying all critically ill individuals with decompensated cirrhosis and exploring the factors used to decide on their escalation of therapy in real-time. This study would facilitate analysis of the factors used to admit or deny ICU admission. Using all routinely available data, specialists involved in making the decision would be asked to estimate mortality for the individual, which could be compared to actual mortality.

3.6.2 Limitations

Sixty-seven Scottish consultant intensivists and 35 consultant gastroenterologists responded to Survey 1, however fewer individuals responded to Survey 2. As the survey was distributed in an identical manner the fall in responses rate could be attributable to response fatigue (221). Response rates to web based surveys differ widely, the response rate is higher than other similar web-based surveys of critical care practice (262, 263). There are no accurate national figures published for the number of consultant intensivists and gastroenterologists in Scotland making it difficult to identify a denominator and thus a response rate. Each ICU in Scotland was contacted directly to confirm the number of consultant intensivists within the department. Confirming the number of gastroenterologists proved challenging as those responsible for liver disease in Scotland encompass hepatologists, gastroenterologists and consultants in general medicine. To establish an approximate denominator, a website was used to identify consultants with an interest in liver disease and in addition all consultant members of the SSG were emailed an invitation to participate (219). These numbers rely on current email addresses and may include those who are no longer practising, who now work outwith Scotland and there is the possibility that newly appointed consultants have been excluded. There were barriers to access clinicians in ICU with the equivalent professional body to the SSG contacted but unable to distribute the survey link to consultant intensivists. Although the response rate was not lower than other similar surveys it is difficult to generalise these results to reflect national practice as it would appear the

majority of consultants did not give their view. As highlighted in the survey design (section 3.4.1) the results of this study may reflect an element of responder bias. It remains unknown how representative those consultants responding to the survey were of current Scottish practice. Few details were recorded about the responder to the survey, thus it was not possible to identify the frequency of which a consultant was required to refer or admit a patient to ICU. It could be that individuals who participated were those who more frequently referred or admitted patients to ICU and thus envisaged greater utility of the results of the survey (264). Performing data collection in the form of structured interviews would facilitate the recording of more detailed data, however, those individuals willing to participate in any method of data collection would be biased towards those who view the subject as relevant and the responder would lose anonymity. In addition, performing structured interviews can introduce desirability bias, leading the respondent to give an answer they perceive to be socially acceptable or the 'correct' answer they believe the interviewer would agree with.

The design of both surveys limits how the results of this chapter can be applied to clinical practice. Whilst the vignettes are designed to mirror common scenarios, the decision to admit or refer a patient is multi-factorial and may well involve the availability of further information.

3.7 Conclusion

This chapter presents the results of 2 surveys exploring the factors involved in the referral and admission of patients with cirrhosis to intensive care. The results demonstrate:

- The only factor given a median rating of 5 by both gastroenterologists and intensivists was Child-Pugh score when stable

- Child-Pugh score at time of ICU referral was given a median rating of 3 by both specialties

- In Survey 1 aetiology of liver disease was given a median rating of 1 by gastroenterologists and 3 by intensivists, however in Survey 2, 45.8% of

gastroenterologists and 48.5% of intensivists felt aetiology impacted upon their decision to offer intensive care

- Only 33.3% of intensivists felt intensive care was appropriate for cirrhotics with Child-Pugh C and sepsis compared to 76.4% of gastroenterologists

- In every vignette more intensivists than gastroenterologists would offer intensive care

- Likewise a greater proportion of intensivists would offer multi-organ support rather than single organ support

- In each vignette where the patient survived their initial presenting complaint but developed a new clinical problem requiring intensive care a greater proportion of gastroenterologists supported continuation of care

- Fewer intensivists supported ICU readmission during the same hospital stay compared to gastroenterologists

- One year mortality for those with stable Child-Pugh A and B cirrhosis was estimated to be higher by gastroenterologists

- ICU mortality of cirrhotics with Child-Pugh C was estimated to be 74% by intensivists and 65% by gastroenterologists

The next chapter of this MD thesis will explore the timing of Child-Pugh scoring and outcome.

Chapter 4 The utility and timing of the Child-Pugh score

4.1 Introduction

In Chapter 3, the study of consultant practice in Scotland reported that Child-Pugh score calculated when a patient was stable, was found to be the only variable given a rating of 5 out of 5 by both intensivists and gastroenterologists in their decision to admit patients with chronic liver disease to intensive care. Conversely, Child-Pugh score calculated at time of referral to intensive care was given a rating of 3 out of 5 by both specialties. This finding is noteworthy as there are no studies within the literature to suggest optimum timing for scoring of Child-Pugh so as to inform decision-making or mortality prediction.

This chapter investigates the timing of the calculation of the Child-Pugh score in patients with chronic liver disease admitted to intensive care.

4.2 Child-Pugh score

The Child-Pugh score has been discussed in detail in Chapter 1 (section 1.6.1.1). The score comprises the 5 clinical variables bilirubin, albumin, PT, ascites and encephalopathy.

4.2.1 Bilirubin

As described in section 1.2.2 one function of the liver is to eliminate substances from the body. Bilirubin is produced in the liver as a product of the metabolism of proteins such as red blood cells and myoglobin (265). Unconjugated water-insoluble bilirubin is transported to the liver attached to albumin (265). Bilirubin is taken up into the hepatic cell membrane where it becomes water-soluble and excreted into bile (265). The majority of measured serum bilirubin is unconjugated (265). Whilst it is used as a marker of liver disease, a raised serum bilirubin level is not specific to chronic liver disease severity and a rise in bilirubin levels may result from haemolysis, post-hepatic obstruction from cholestasis, liver cell injury or inflammation (16). Bilirubin levels may also increase in response to acute processes such as sepsis (266).

4.2.2 Albumin

Albumin is a plasma protein which is produced solely in the liver and utilised in the body as a transport molecule for water-insoluble substances such as bilirubin, hormones and drugs (67, 265). Albumin level indicates the synthetic function of the liver (265). It is required to maintain intravascular oncotic pressure and acts as a buffer within the body. In addition albumin has both antioxidant and immunomodulation properties (267). Liver dysfunction results in decreased albumin synthesis and impaired albumin function, leading to complications such as ascites (267).

Serum albumin concentration is not specific to liver disease, which may affect its reliability within the Child-Pugh score. A reduced level of albumin can result from excess albumin loss in renal disease or secondary to malnutrition (265, 268). In critical illness, albumin is redistributed between the intravascular and extravascular fluid compartments (268). Further, in the acute phase response to inflammation or sepsis albumin synthesis is reduced (268). Intravenous albumin is widely administered to cirrhotic patients, in particular it is given to those undergoing therapeutic paracentesis as a volume expander (69). It has been hypothesised that intravenous albumin administration may prevent endothelial dysfunction, improve response to bacterial translocation and reduce oxidative stress (267).

4.2.3 Prothrombin time

PT is a measure of coagulation performed on citrated plasma by adding calcium and tissue factor (67). With the exception of factor VIII, all coagulation factors are produced in the liver and thus PT indicates synthetic liver function (265). PT measures the extrinsic and common pathways of clotting and a time of 11 to 15 seconds is found in those without impaired coagulation, although this is varies between different laboratories (67). In order to overcome the variability between laboratories, PT can be measured in a ratio to a control sample and reported as the INR (67). An INR in healthy subjects measures between 0.8-1.2 (67). In response to differences between PT and INR, some versions of the Child-Pugh score have been modified to include INR instead of PT.

Whilst PT and INR measure coagulation, neither measure accurately represents an overall view of haemostasis for an individual with chronic liver disease (section 1.4.7). Both PT and INR may be altered by medication such as vitamin K, blood products or anticoagulation, introducing uncertainty into the timing of measurement of the Child-Pugh score.

4.2.4 Ascites

As discussed in detail in section 1.4.1, although ascites is the most common complication of chronic liver disease, it is not specific and may result from other disease processes (68, 69). Assessment of ascites is acknowledged to be subjective despite improved visualisation with the use of ultrasound (section 1.6.1.1).

4.2.5 Hepatic encephalopathy

Hepatic encephalopathy has been explored earlier in the thesis, with the nomenclature and classifications agreed upon at the 1998 World Congresses of Gastroenterology discussed in detail in section 1.4.3 (80). Similar to ascites, the grading of hepatic encephalopathy is subjective. In particular challenges exist in grading those with fluctuations in neurological function or individuals with co-existing neurological disease (section 1.6.1.1).

4.3 Validation and utility of the Child-Pugh score

Chapter 1 described the development of the Child-Pugh score as a modification of an existing scoring system described on a consecutive case series of 38 patients between 1966 and 1972 who underwent transthoracic ligation of oesophageal varices for portal hypertension (141, 269). Despite this small specific case series the Child-Pugh score has been demonstrated to be of value for prognostication in both surgical and medical populations.

Preoperative Child-Pugh score has been shown to predict mortality in those with cirrhosis undergoing both elective and emergency abdominal operations (270). Child-Pugh score was found to be an independent predictor of survival for individuals with known varices given medical prophylaxis to prevent variceal

bleeding (271). In those undergoing TIPS, the Child-Pugh score has been shown to be of equal value to the MELD score in predicting survival (272).

Child-Pugh score has been independently demonstrated to predict mortality in those with ascites and cirrhosis irrespective of underlying aetiology and a small Dutch study showed that a higher Child-Pugh score predicted future episodes of hepatic encephalopathy (273, 274).

Child-Pugh score has been validated for use in multiple aetiologies of liver disease by independently predicting survival in hepatocellular carcinoma and cirrhosis secondary to both Hepatitis C virus and alcohol (275-277). In addition, Child-Pugh score was demonstrated to predict survival in those with primary sclerosing cholangitis, primary biliary cirrhosis and Budd-Chiari syndrome (278-280).

Before 2002 the Child-Pugh score was used by the United Network of Organ Sharing (UNOS) in the USA to prioritise patients requiring liver transplantation (281). It was replaced by the MELD score due to perceived weakness in the subjective measurement of ascites and encephalopathy, lack of inclusion of renal function and inability to differentiate between candidates for transplant, as the Child-Pugh score allocates a maximum score of 3 per variable (145, 281). The MELD score has subsequently been adopted for use in Europe (281). Despite this change in practice, a systematic review published in 2006 demonstrated that the MELD score was not superior to the Child-Pugh score in predicting mortality following liver transplant or for those individuals with cirrhosis on the transplant waiting list (140). One advantage of the Child-Pugh score over MELD is that it can be calculated easily without a computer model (53). In the UK, the UKELD score is used to determine allocation in liver transplantation (281).

In the critical care population multiple scoring systems exist which measure severity of disease and organ dysfunction such as APACHE and SOFA (section 1.6.2). Although scoring systems such as CLIF-SOFA and RFH exist there is no liver-specific scoring system designed for critically ill cirrhotic patients which has been demonstrated to be superior to Child-Pugh score. However, studies of cirrhotics admitted to ICU have demonstrated that non-disease specific scoring

systems appear to have superior predictive value in predicting mortality (116, 140, 177).

There is a paucity of literature examining the changes in the results of scoring systems if measured at a time of stability compared to the score at a time of critical illness. One of the few studies which exists explores a UK population of critically ill cirrhotic patients and found that Child-Pugh score increased by 2.5 points between measurement when stable and on admission to ICU (156). Despite reporting the change in Child-Pugh score this study did not explore any association between the timing of scoring and outcome.

4.4 Study question and aims

4.4.1 When should the established prognostic scoring tool Child-Pugh be measured to inform the decision to admit a patient?

Child-Pugh score has been used throughout the literature in studies of both medical and surgical patients with liver disease. Given the emphasis placed upon stable Child-Pugh score found in Chapter 3 it is postulated that clinicians use the score as a reflection of chronic illness progression, rather than relying upon Child-Pugh score at a time of acute illness when it can be altered by a number of factors. The time point within disease progression at which Child-Pugh score is most useful in predicting mortality for those individuals admitted to intensive care remains unknown.

As Child-Pugh score is used in both acute and chronic illness, it is widely documented within patient case notes. This provides an opportunity to perform a study examining patient survival predicted by Child-Pugh score on admission to ICU and historical Child-Pugh scores.

4.4.2 Aims

- To identify any relationship between ICU and hospital survival and Child-Pugh score measured when a patient is clinically stable

- To identify any relationship between ICU and hospital survival and Child-Pugh score measured when a patient is admitted to ICU

4.5 Methodology

4.5.1 Design

This study was performed by creating a dataset of 134 patients who had been admitted to intensive care between June 2012 and December 2014 with a confirmed diagnosis of cirrhosis. The study incorporated both retrospective and prospective elements as case notes were reviewed retrospectively to determine Child-Pugh score, whilst the ICU score on admission was recorded prospectively at the time of admission by medical staff. Case notes in the ICU at GRI are computerised with medical and nursing staff inputting all clinical variables including observations, laboratory values and medical notes, including past medical history. Individual computerised case notes were reviewed to record clinical reason for admission to intensive care. Admission diagnosis was coded into 6 groups comprising respiratory failure, gastrointestinal bleed, sepsis, encephalopathy and other causes. Child-Pugh score was calculated on ICU admission using recorded clinical variables and each individual was graded into Child-Pugh A, B or C. The aetiology of cirrhosis was recorded as alcoholic or non-alcoholic. Both ICU and hospital survival were recorded.

Existing medical records were reviewed to calculate Child-Pugh score when a patient was deemed clinically stable - prior to hospital admission with critical illness. Firstly, a pre-existing database of known cirrhotic patients reviewed in the outpatient liver clinic was searched to identify patients based on their Community Health Index (CHI) number. This database was designed and implemented by a consultant gastroenterologist at GRI, Dr Stephen Barclay. The database records clinical variables and documented Child-Pugh score for each patient reviewed in the outpatient liver clinic by medical or nursing staff. The last episode recorded at a liver outpatient clinic was used as a stable Child-Pugh score as it was assumed that the patient was not acutely unwell nor requiring hospital inpatient stay.

For those patients not reviewed in the liver outpatient clinic their NHS Greater Glasgow and Clyde electronic patient record was examined (section 2.1.4). This is an electronic system which records secondary care contact and includes outpatient letters, inpatient case notes, laboratory values and radiology reports. It is used throughout NHS Greater Glasgow and Clyde and thus would include any attendances at hospitals across the health board. Any patient contact with healthcare services where blood tests were obtained and comment made on presence of encephalopathy or ascites was recorded. This included outpatient clinic appointments with other specialties or on discharge from hospital admissions. At these points of review, Child-Pugh score was calculated and was labelled as stable as the patient did not require hospital admission or was deemed fit for discharge. If variables within the Child-Pugh score were not measured or recorded then patients were scored '1' as this is the lowest point available for each variable in the Child-Pugh score.

If a patient had no record of contact with secondary care, laboratory values taken by primary care were used to identify a Child-Pugh score. A method of single imputation was used to replace missing values in the assessment of ascites or encephalopathy. Both clinical variables were given values of '1' as there was no record obtainable of these clinical variables. The relationship between Child-Pugh score when stable and on admission to ICU and both hospital and ICU survival was then explored.

4.5.2 Participants

Subjects studied had been admitted for Level 3 care at GRI between June 2012 and December 2014. Demographic and clinical data used within this study were routinely recorded on the electronic patient record (section 2.1.4). All patients over the age of 18 with a diagnosis of cirrhosis were included in the study. The diagnosis of cirrhosis was based upon pre-existing diagnosis, clinical findings consistent with chronic liver disease such as ascites or encephalopathy and radiological findings consistent with cirrhosis (187). Sixteen individuals were readmitted to intensive care and were removed from the dataset.

4.6 Statistical analysis

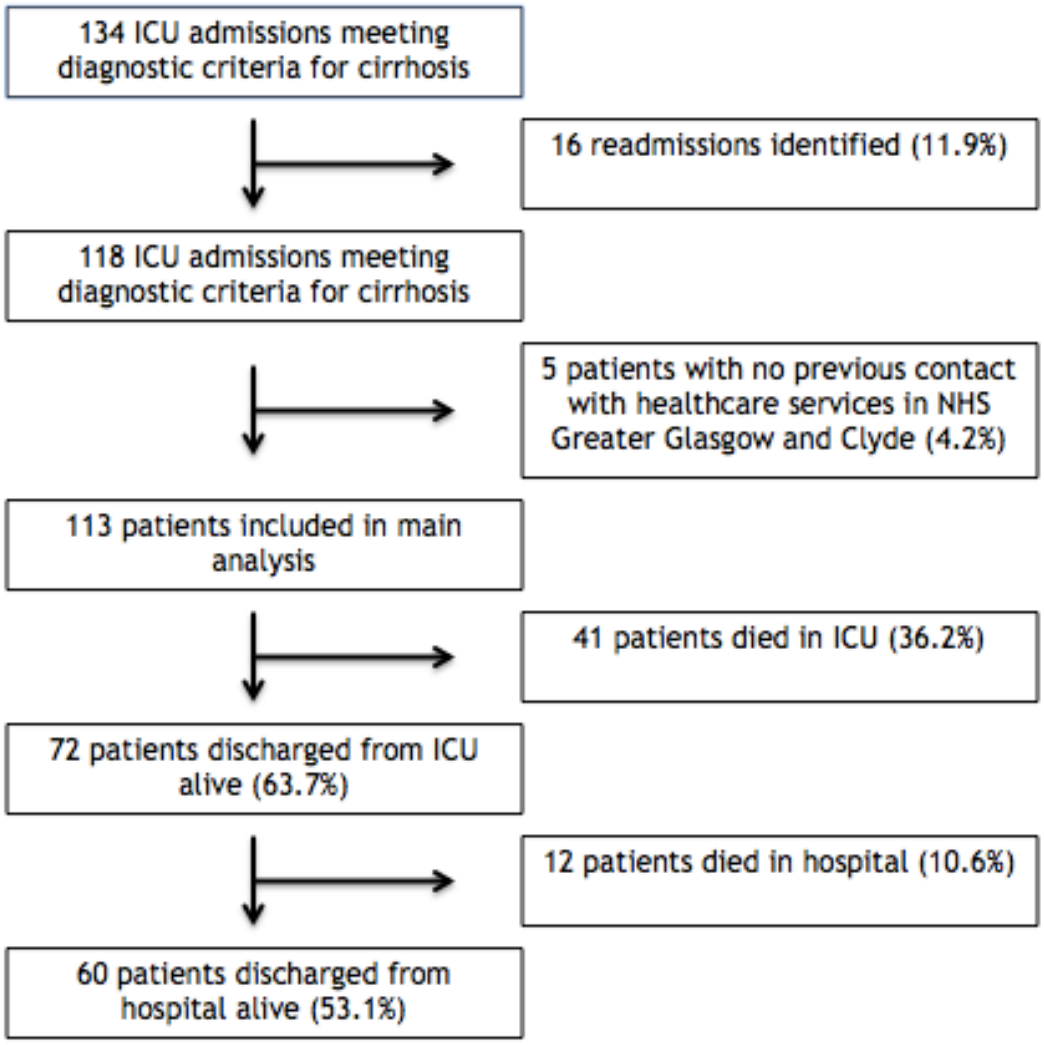
All data was found to be non-parametric data and each factor was described using the median and IQR (179). Bivariate analysis was performed using the chi-squared test to determine whether there was any relationship between Child-Pugh class and survival. Data were then analysed using logistic regression to determine if Child-Pugh score was able to predict ICU or hospital survival. A logistic regression model was used as the outcome variable (survivor or non-survivor) was categorical and the predictor variable (change in raw Child-Pugh score from stable to acute) was continuous. The linearity assumption was assessed by visualising the residuals, which demonstrated a linear trend. The OR was then calculated to determine whether there was a change in the odds of survival for every point score change in raw Child-Pugh score. To reflect similar studies a 95% CI was calculated for each OR. Likewise a logistic regression model used to analyse survival and change in Child-Pugh score on admission to ICU. Similarly the outcome variable (survivor or non-survivor) was categorical and the predictor variable (change in raw Child-Pugh score on presentation to ICU) was continuous.

4.7 Results

4.7.1 Demographics

Figure 4-1 outlines a flowchart of patients admitted to ICU with cirrhosis who were included in the dataset. Individuals who had been readmitted to ICU within the study period and those with no previous recorded contact with healthcare in NHS Greater Glasgow and Clyde and were excluded from further analysis.

Figure 4-1 Flowchart of patient recruitment



Of the 113 patients included in the main analysis, 36 required Level 3 support following respiratory failure, 19 were admitted following a gastrointestinal bleed, 21 had sepsis, 5 required ICU admission secondary to seizures, 5 required admission secondary to encephalopathy and 27 patients required ICU admission for another reason (Table 4-1). For the majority of patients (77.0%) alcohol was the underlying aetiology of their liver disease.

Table 4-1 Survival, demographics and reason for admission of 113 cirrhotic patients admitted to ICU

	All ICU admissions	ICU		Hospital	
Number of Survivors n, (%)	113.0 (100.0)	72.0 (63.7)		60.0 (53.1)	
	All ICU admissions (n=113)	ICU survivors (n=72)	Patients who died in ICU (n=41)	Hospital survivors (n=60)	Patients who survived ICU but died within hospital (n=12)
Age, mean (range)	**52.7 (27.0-85.0)**	53.4 (31.0-85.0)	51.5 (27.0 - 77.0)	52.3 (31.0-85.0)	58.0 (40.0-80.0)
Male gender, n (%)	**82 (72.6)**	**54.0 (75.0)**	28.0 (62.3)	46.0 (76.7)	8.0 (66.7)
SIMD quintile, median (IQR)	**1.0 (1.0-2.0)**	**1.0 (1.0-2.3)**	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.5 (1.0-3.3)
Social deprivation, n (%)	**86.0 (76.1)**	**54.0 (75.0)**	34.0 (82.9)	47.0 (78.3)	7.0 (58.3)
APACHE score, median (IQR)	**23.0 (18.0-29.0)**	**22.0 (18.0-29.0)**	24.0 (18.8-29.0)	21.0 (17.0-27.0)	27.0 (23.5-33.0)
Length of ICU stay (Days), median (IQR)	**5.0 (3.0-13.0)**	**5.5 (3.0-14.0)**	5.0 (3.0-10.0)	5.5 (3.0-14.3)	5.5 (2.0-11.0)
Reason for Admission					
Gastrointestinal bleed, n(%)	19 (16.8)	11 (15.3)	8 (19.5)	9 (15.0)	2 (16.7)
Respiratory failure, n(%)	36 (31.9)	23 (31.9)	13 (31.7)	21 (35.0)	2 (16.7)

Sepsis, n(%)	21 (18.6)	12 (16.7)	9 (22.0)	9 (15.0)	3 (25.0)
Seizures, n(%)	5 (4.4)	5 (6.9)	0 (0.0)	3 (5.0)	2 (16.7)
Encephalopathy, n(%)	5 (4.4)	3 (4.2)	2 (4.9)	3 (5.0)	0 (0.0)
Other, n(%)	27 (23.9)	18 (25.0)	9 (22.0)	15 (25.0)	3 (25.0)
Alcohol Aetiology, n(%)	87 (77.0)	54 (75.0)	33 (80.5)	46 (76.7)	8 (66.7)
Child-Pugh grade on ICU admission					
Child-Pugh A, n(%)	17 (15.0)	13 (18.1)	4 (9.6)	13 (21.7)	0 (0.0)
Child-Pugh B, n(%)	50 (44.2)	35 (48.6)	15 (36.6)	31 (51.7)	4 (33.3)
Child-Pugh C, n(%)	46 (40.7)	24 (33.3)	22 (53.7)	16 (26.7)	8 (66.7)
Child-Pugh grade when clinically stable					
Child-Pugh A, n(%)	49 (43.4)	36 (50.0)	13 (31.7)	30 (50.0)	6 (50.0)
Child-Pugh B, n(%)	49 (43.4)	27 (37.	22 (53.7)	24 (40.0	3 (25.0)

		5)		)	
Child-Pugh C, n(%)	15 (13.3)	9 (12.5)	6 (14.6)	6 (10.0)	3 (25.0)

The median Child-Pugh score recorded when the patient was clinically stable was 7 (IQR 6-8), representing a Child-Pugh Class B. The majority of variables for calculation of Child-Pugh score were measured at outpatient appointments. A total of 51 Child-Pugh scores were calculated at liver outpatient clinic appointments and 13 Child-Pugh scores were calculated from information recorded at outpatient appointments for other specialties. Some 33 patients had Child-Pugh scores calculated from blood results and medical notes at discharge from a hospital inpatient stay. Sixteen individuals had Child-Pugh scores calculated from blood results taken in primary care.

The median time between measurement of Child-Pugh score when clinically stable and on admission to ICU was 127 days (IQR 70-247), with a maximum time of 1381 days. When clinically stable, 49 patients were calculated as Child-Pugh A, 49 patients were calculated as Child-Pugh B and the remaining 15 calculated as Child-Pugh C (Table 4-1).

Using variables measured on ICU admission to calculate the Childs-Pugh score, the documented median score was 9 (IQR 7-11), graded as Child-Pugh Class B. Seventeen patients were Child-Pugh A, 50 patients were Child-Pugh B and 46 were Child-Pugh C (Table 4-1).

Table 4-2 Change in Child-Pugh score and survival

Change in Child-Pugh Score from stable to ICU admission	Number of patients, n (%) (n=113)	ICU Survival n,(%)	Hospital Survival n,(%)
-3	1 (0.9)	1 (100.0)	1 (100.0)
-2	4 (3.5)	4 (100.0)	4 (100.0)
-1	9 (8.0)	6 (66.7)	6 (66.7)
0	22 (19.5)	14 (63.6)	13 (59.1)
1	17 (15.0)	15 (88.2)	14 (82.4)
2	22 (19.5)	12 (54.5)	10 (45.5)
3	14 (12.4)	7 (50.0)	4 (28.6)
4	10 (8.8)	6 (60.0)	2 (2.0)
5	7 (6.2)	5 (71.4)	4 (57.1)
6	3 (2.7)	1 (33.3)	1 (33.3)
7	2 (1.8)	0 (0.0)	0 (0.0)
8	2 (1.8)	1 (50.0)	1 (50.0)

4.7.2 Child-Pugh score and survival

Of the 113 patients included in the analysis, 72 (63.7%) survived to ICU discharge and 60 (53.1%) survived to hospital discharge. ICU and hospital survival for each class of Child-Pugh graded at a period when the patient was clinically stable and

on ICU admission are shown in Table 4-1. ICU and hospital mortality for each change in Child-Pugh grade is presented in Table 4-2. There was no significant difference in either ICU or hospital survival in those with an underlying aetiology of alcoholic liver disease.

Child-Pugh score measured when the patient was clinically stable was not significantly associated with ICU (p= 0.159) or hospital survival (p=0.264). Child-Pugh score measured on admission to the ICU was significantly associated with hospital survival (p=0.003), however, it was not significantly associated with ICU survival (p=0.095).

The change in total Child-Pugh score between the score measured when stable, reflecting the severity of chronic liver disease, and the score measured on admission to ICU was then assessed for change in risk of survival. For an individual patient, every increased point in the total Child-Pugh score from the point of being stable to ICU admission involved a 20% decrease in ICU survival (OR 0.80 CI 0.66-0.95) and a 27% decrease in hospital survival (OR 0.73 CI 0.60-0.87). Thus the greater change in Child-Pugh score from stable to acute presentation to ICU the higher the risk of mortality. This was a multiplicative effect and not additive, thus mortality does not increase linearly with change in Child-Pugh.

When considering the Child-Pugh scale of scores from 5 to 15, for every increased point in total Child-Pugh score on admission to ICU there is a 21% decrease in ICU survival (OR 0.79 CI 0.67-0.92). With every unit increase in raw Child-Pugh score on admission to ICU there is a 28% decrease in hospital survival (OR 0.72 CI 0.60-0.84). For example, a patient with a total Child-Pugh score of 15 would have a 21% decrease in ICU survival and a 28% decrease in hospital survival when compared to a patient with a Child-Pugh score of 14. As before, this was not a linear relationship as the effect was multiplicative.

When considering Child-Pugh score when stable, for every increased point in total Child-Pugh score from 5 to 15 there is a 12% decrease in ICU survival (OR 0.88 CI 0.72-1.09) and a 15% decrease in hospital survival (OR 0.85 CI 0.69-1.05).

4.8 Discussion

4.8.1 Interpretation of findings

4.8.1.1 Timing of Child-Pugh scoring

Whilst the utility of the Child-Pugh score has been extensively investigated, as far as can be established this is the first study in the literature to examine survivorship and the time point when Child-Pugh score should be carried out in the critically ill population. Moreover, the findings from this study suggest that there is a relationship between Child-Pugh score measured on admission to the ICU and hospital survival for critically ill patients with cirrhosis. However, no statistically significant relationship was found between Child-Pugh score measured when a patient was clinically stable and ICU or hospital survival.

On further analysis of the results using a regression model, there appears to be a trend between an increase in mortality and an increase in Child-Pugh score, measured both on ICU admission and when stable. However, as presented in the results, the confidence interval crosses 1 when Child-Pugh is measured when stable. Increasing the sample size would aim to increase the precision of the results and decrease the margins of the confidence interval.

Few studies in the literature discuss different time points for assessment using scoring systems. One paper which discussed outcomes and scoring systems in critically ill cirrhotic patients at 2 non transplant centres in London, measured Child-Pugh at time of critical illness and when individuals were stable (282). In that study the median Child-Pugh scores on admission to ICU and when stable were comparable to our findings, which suggests the population in our study is similar to other UK cohorts. Median Child-Pugh score increased by 2 points in this study and by 2.5 points in the London cohorts (282). This paper reported on a limited number of 137 patients admitted during a 20-month period between 2007 and 2009 (282). Of those patients with cirrhosis, determining a stable Child-Pugh score was only possible in 84 patients and the authors do not detail when or how the stable Child-Pugh score was calculated (282). Similar limitations exist to this this study, with difficulties arising in the grading of hepatic encephalopathy outwith hospital admission. The authors state that they

believe all critically ill patients with cirrhosis have a degree of hepatic encephalopathy and as such equated documentation of a ‘normal’ neurological status to Grade I/II hepatic encephalopathy, allocating this a score of 2 rather than 1 in Child-Pugh grading (282).

The relationship between Child-Pugh score measured on admission to the ICU and hospital survival contradicts the findings from the national survey of Scottish intensivists and gastroenterologists discussed in Chapter 3. That survey found that Child-Pugh score measured when stable was the most significant factor utilised by both intensivists and gastroenterologists in the decision whether to admit patients to ICU. There are a number of potential explanations for the difference in these findings. The relationship of Child-Pugh score measured on ICU admission to hospital survival may reflect the fact that Child-Pugh score encompasses physiological variables known to predict prognosis in acute illness (283). Established scoring tools designed to measure severity of organ dysfunction in the critically ill utilise similar variables, with the SOFA score encompassing bilirubin and neurological status (139). Castera et al. examined variables associated with survival in 243 patients with cirrhosis (118). That study demonstrated that in addition to a requirement for mechanical ventilation, PT, creatinine and encephalopathy measured on admission to ICU were significant variables in predicting mortality.

As the responses to the survey in Chapter 3 are likely to mirror daily practice, the significance placed upon stable Child-Pugh score in decision-making is likely to be multifactorial. It may reflect an understanding that ICU survival is determined by resilience and physiological reserve prior to ICU admission, with Child-Pugh score used as a surrogate indicator (242). The use of stable Child-Pugh score to reflect the severity of chronic disease may also reflect historical cohorts of patients in whom many aetiologies of liver disease were considered irreversible. However, recent advances in the treatment of viral hepatitis and a widening of transplant criteria to include those with alcoholic liver disease, represent an opportunity for reversal of the course of disease for select patients (14). In the majority of patients Child-Pugh score measured when an individual is clinically stable will be lower than when an individual is critically ill. Using a Child-Pugh score to determine ICU admission, a larger proportion of individuals would be offered admission if a stable score was used. Clinicians may argue that

this gives a greater number of patients with chronic liver disease access to ICU and thus improves a patient's chance of survival.

Survivorship in those with cirrhosis is impacted by disease trajectory, with a difference between those patients who have compensated and decompensated cirrhosis (53). As this study examined only two time points in the patient journey, it is impossible to determine the specific course of disease for each patient prior to ICU admission, and whether the Child-Pugh score when stable was associated with compensated or decompensated cirrhosis. However, the results demonstrate that with every increase in point in total Child-Pugh score there is a 20% decrease in ICU survival and 27% decrease in hospital survival, thus the degree of change in the severity of liver disease remains significant irrespective of the Child-Pugh score when stable.

Little evidence exists regarding the change in severity of cirrhosis following ICU survival, however it is known that in other populations of critical illness survivors, such as elderly patients, there is significant decline in function following ICU stay (284). For example, Ferrante et al. found functional trajectory prior to ICU stay to be an independent predictor of mortality in their elderly cohort (284). An observational cohort study of 33,324 Canadian ICU admissions found that whilst death in the first 30 days following ICU admission was determined by acute illness, survival after 90 days following ICU admission was influenced by age and comorbid conditions (285). It may be that long-term survivorship in the cirrhotic cohort could be significantly related to Child-Pugh score when stable and Child-Pugh score could be used as a surrogate marker for chronic comorbidity. Whilst severity and reversibility of disease is an important factor in the decision to admit an individual to ICU, establishing a baseline functional state and the impact of comorbidity might give an assessment of potential resilience. Although the outcome for those who died in ICU or hospital is known, for those who survive it was beyond the scope of this study to investigate progressive Child-Pugh scores. It would be valuable to discover if and when patients return to their baseline Child-Pugh score.

An important finding of this study was that Child-Pugh score on ICU admission was significantly associated with hospital survival but not ICU survival. As Child-Pugh score has been used extensively as a marker of liver disease severity it may

be that the variables measured in Child-Pugh play a greater role in determining long-term survival. Those with a greater degree of liver impairment may be at greater risk of subsequent deterioration prior to discharge, struggle with rehabilitation and are more likely to be denied ICU readmission. Individuals with chronic liver disease are known to have increased endotoxin and cytokine concentrations, predisposing them to ongoing inflammation (286).

4.8.1.2 Individuals without medical history

Five individuals admitted to ICU in this dataset were excluded from analysis as they had no existing clinical information or laboratory values to enable stable Child-Pugh scoring. This may represent a challenging cohort of individuals with advanced yet asymptomatic liver disease who present in decompensated liver disease. This group of patients pose challenges in deciding whether or not to offer intensive care as little is known of their functional state, physiological reserve and engagement or compliance with therapy, factors demonstrated to be important in Chapter 3.

The results of this study suggest that an isolated measurement of the Child-Pugh score on ICU admission can be useful for those with an unknown past history. The results demonstrate a marked increase in both ICU and hospital mortality with each additional point attained on Child-Pugh score. However, this finding would require validation in a larger cohort of patients.

4.8.1.3 Alcoholic liver disease

Alcohol was recorded as the underlying cause of cirrhosis in the majority of the patients included in the dataset although this was not significantly associated with either ICU or hospital survival. This reflects a similar population of ICU admissions with cirrhosis admitted to 2 non-transplant ICUs in London (156). Over the last 30 years UK hospital admission rates for those with liver cirrhosis have increased dramatically by 71% in men and 43% in women (287). Hospital admissions for those with cirrhosis caused by alcohol doubled over a similar period (287). The relationship between Child-Pugh score on admission to ICU and survivorship found in this study must be interpreted with caution as it may not be representative of all aetiologies of cirrhosis with some patients having more

than one aetiology of chronic liver disease. Worldwide, the underlying aetiology of cirrhosis differs with Hepatitis B and C more prevalent than alcoholic liver disease in sub-Saharan Africa and Asia (14).

4.8.2 Limitations

This study examines the timing of Child-Pugh score and the relationship to both ICU and hospital survival. The cohort of patients examined is small and comes from a single centre in Glasgow, as such the results may not be generalisable to other populations worldwide. Given the small number of patients there is potential for a type 2 error. It may be that there is a relationship present between survival and Child-Pugh score when stable which was not detected as the relationship did not reach statistical significance. The confidence intervals presented show that the increase in mortality differs widely for both Child-Pugh score measured when stable and on admission to ICU. Notably, the confidence interval for Child-Pugh when stable crosses 1, suggesting that for some an increase in score can lead to a decrease in mortality. This loss of precision reflected in the width of the confidence intervals is in part due to the small sample size.

The reason for admission to ICU was recorded, however, there may have been more than one underlying diagnosis. The small numbers in this dataset prevented meaningful assessment of any relationship between diagnosis requiring ICU admission and survivorship. With larger numbers it would be possible to analyse each subgroup of admissions. Moreover, it is recognised in the literature that multi-organ failure is associated with increased mortality (129). This study did not record any subsequent diagnoses once patients were admitted to ICU, which may have an impact upon survival and would be of clinical use in determining outcome.

Some studies have criticised Child-Pugh score as the measurement of ascites and hepatic encephalopathy can be subjective and lead to error within calculation. In particular, the grading of hepatic encephalopathy and ascites is challenging in the critically ill patient who may be intubated. The score does not account for changes occurring with treatment, as such the total score may be iatrogenically altered. One example of this is seen in the administration of exogenous albumin

in the critically ill or in those undergoing therapeutic paracentesis which may lead to temporary improvement in Child-Pugh score (267). Further fluid replacement given in the management of acute illness can have a detrimental effect on coagulopathy and drugs administered to facilitate intubation alter neurological status can prevent accurate assessment of encephalopathy. The Child-Pugh score gives equal weighting to each variable, with no consideration for alteration with management. Giving equal weighting may mean that the impact of each variable is either under or over estimated. Specific points in the score may be of greater value in certain clinical situations and it could be argued that in many circumstances the variables are not independent of each other.

Calculation of Child-Pugh score for those admitted to ICU relied upon accurate input of variables by medical staff on admission. The assessment of degree of encephalopathy may become impossible once patients are sedated and ventilated in ICU. This measurement requires precise documentation of a neurological examination of the patient prior to induction of anaesthesia. Laboratory variables scored in Child-Pugh are continuous, however, patients with severe liver disease can only score the maximum 15 points. Durand and Valla describe this as a 'ceiling effect' preventing separation of the most severely unwell patients with deranged bilirubin, albumin or coagulation (288). This limits the clinical use of the score in determining differences in mortality within a Child-Pugh class. In the cohort of patients in this study it may facilitate identification of the characteristics of a subgroup of the Child-Pugh C patients who died. Furthermore, with such high rates of mortality secondary to bacterial infections (section 1.4.8) it would have been useful to note further clinical details of this cohort, such as underlying cause of sepsis or whether any of the patients admitted developed sepsis during their ICU stay.

This study investigated Child-Pugh score when clinically stable. Those patients who had been assessed by liver specialists and included in the chronic liver database were potentially more accurately scored than those patients scored outwith this clinic due to focus on severity of liver disease. The study relied upon medical documentation of clinical findings in patient notes and an assumption that a patient would be clinically stable if fit for discharge. It was acknowledged that patients scored solely on blood tests performed by their

General Practitioner (GP), would potentially receive lower Child-Pugh scores as there was no documentation relating to ascites or encephalopathy available for inclusion. A method of single imputation was chosen to replace missing values for those patients who did not have grade of ascites or encephalopathy recorded in primary care. It is recognised that imputation of values will reduce statistical power and introduce bias to the results. Single imputation was chosen due to the low numbers of individuals with missing values and the likelihood that if ascites or encephalopathy was present in primary care the patient would have most likely been referred to hospital and have an associated admission or clinic review. An alternative method of imputation would be listwise deletion, however, with the limited number of individuals in this dataset it was felt that this would prevent further statistical analysis. Another method to overcome missing values would be to use a complete case analysis and use multiple imputation. A complete case analysis and multiple imputation was beyond the scope of this thesis.

4.9 Conclusion

This chapter discusses the utility and timing of the Child-Pugh score in predicting ICU and hospital survivorship in those with cirrhosis and critical illness. The results demonstrate:

- The median Child-Pugh score measured in this cohort when the patients were clinically stable was 7 (IQR 6-8) which increased to 9 (IQR 7-11) on admission to ICU

- There was no statistically significant relationship demonstrated between Child-Pugh score measured when a patient was clinically stable and ICU or hospital survival

- Child-Pugh score measured when the patient was admitted to ICU was not significantly associated with ICU survival

- Child-Pugh score measured when the patient was admitted to ICU was significantly associated with hospital survival ($p=0.003$)

- With every unit change in Child-Pugh score between the score measured when stable and a score measured on admission to ICU there is a 20% decrease in ICU survival and a 27% decrease in hospital survival

- For every unit increase in total Child-Pugh score on admission to ICU there is a 21% decrease in ICU survival and a 28% decrease in hospital survival

This chapter examined the utility and timing of Child-Pugh score in determining ICU and hospital survival. The following chapter examines the use of a proxy to measure alcohol intake in critically unwell individuals admitted to ICU.

Chapter 5 Use of a proxy to measure alcohol history for patients in intensive care

5.1 Introduction

Previous chapters have discussed the factors involved in deciding whether a patient with cirrhosis will benefit from ICU admission. This chapter discusses one of the preventable aetiologies of chronic liver disease, alcohol and its impact on intensive care and individuals with critical illness. It aims to assess whether a proxy can be used as a reliable source of information to provide an alcohol history on behalf of a critically unwell individual.

5.1.1 Burden of alcohol in Scotland

The 2018 Global status report on alcohol published by the WHO revealed that 13% of men and 4.7% of women in the UK had an alcohol use disorder (289). Further data reported 2.2% of men and 0.7% of women in the UK had alcohol dependence (289). The 2016 Scottish Health Survey reported that approximately 25% of adults drink above the recommended 14 units of alcohol per week in Scotland (290). Moreover, men were twice as likely as women to drink above the recommended weekly limits (290). Data from the Scottish Health Survey 2015 concluded that 82% of Scots were abstinent or drank low levels of alcohol, 15% exhibited hazardous levels of alcohol intake, 2% drank to harmful levels and 1% demonstrated alcohol dependence (291). Men are 1.7 times more likely to die from alcohol-related causes in Scotland than in England and Wales (292, 293). In 2009 it was reported that 5% of deaths in Scotland were linked to alcohol and whilst alcohol-related deaths decreased from the early 2000s to 2010, more recent trends now show an increased mortality from 2012 in 2016 (290, 293).

National data published in 2016 demonstrated that NHS Greater Glasgow and Clyde had the highest rate of alcohol-related hospital admissions in Scotland with alcohol-related mortality rates between 1979 and 2011 higher in Glasgow than the rest of Scotland (294, 295). According to the SIMD, approximately 50% of those who reside in Glasgow live in the 20% of the most deprived areas of Scotland (295). Areas of deprivation are reported to experience a greater number of acute and psychiatric hospital admissions secondary to alcohol-

related problems (294). However, when compared to other UK cities with similar levels of deprivation, such as Manchester or Liverpool, alcohol-related mortality in Glasgow remains significantly higher (295).

There are substantial economic implications caused by alcohol misuse in Scotland and the Scottish Government estimate that alcohol problems cost the NHS over £140 million every year (296). Furthermore alcohol problems cost social work services £80 million and the justice system £268 million annually (297). Loss of earnings secondary to alcohol problems total over £405 million annually with 1.7 million working days lost in Scotland due to alcohol (290, 297). Alcohol problems cost Scotland in excess of £3.6 billion every year (298). Put into context, alcohol problems have a greater financial impact on the health budget than drug misuse, stroke or Alzheimer's disease (297, 299).

In order to ease this socioeconomic burden the Scottish Government aims to reduce the volume of alcohol consumed, modify harmful behaviours surrounding alcohol intake and change the "*cultural focus on intoxication*" (297). Strategies implemented include a reduction in drink-drive limits compared to the rest of the UK and setting a minimum price per unit of alcohol (290, 300). The Alcohol (Scotland) Act 2010, limited discounts in the bulk buying of alcohol, introduced a Challenge 25 age policy and restricted alcohol marketing (290).

5.1.2 The health impact of alcohol

The excessive consumption of alcohol and alcohol withdrawal cause a wide range of physical and mental health disorders and may have considerable impact upon an individual, their family and friends (301). A recent Scottish survey stated that 1 in 2 people reported harm from another individual's drinking (302). One in 10 presentations to the ED in Scotland are linked to alcohol, with 3% of acute hospital admissions in Scotland related to alcohol (297). Worldwide it is estimated that 3.8% of deaths are caused by alcohol with excess alcohol consumption being linked to wide number of acute and chronic diseases in most systems of the body (21). It can also exacerbate existing comorbidities (303). The consumption of alcohol is a direct causative factor in alcoholic liver disease and alcohol-induced pancreatitis (21). A number of different cancers can arise from excess alcohol consumption and include oesophageal, mouth, liver, breast

and colon cancer (21). Furthermore diabetes, epilepsy, ischaemic heart disease and cerebrovascular disease are also linked to excess alcohol intake (21). In the pregnant woman alcohol can cause fetal abnormalities, whilst psychiatric disorders such as depression are commonly caused by alcohol (21). Unintentional or self-inflicted injury such as falls, poisoning, drowning and road traffic accidents can be directly attributed to alcohol (21). The Scottish Trauma Audit Group reported that alcohol was a factor in 26% of males presenting with major trauma in 2015 (304).

5.1.3 The impact of alcohol on critical care

Mental and behavioural disorders are documented as the most prevalent cause of acute hospital admissions related to alcohol in Scotland (294). Thereafter the most common cause of admissions are those related to alcoholic liver disease (294). The number of Scottish hospital admissions due to alcohol withdrawal are relatively low, however, the total is reported to have increased every year since 1997 (294). A recent study in Glasgow reported that 35% of admissions to critical care had an alcohol use disorder, with the number of alcohol-related admissions to critical care increasing (187, 305). The Intensive Care National Audit and Research Centre (ICNARC) database for England and Wales demonstrated that critical care admissions for alcoholic liver disease tripled between 1996 and 2005 (306). The Scottish data between 2005 and 2010 shows that those admitted to ICU with alcoholic liver disease are more likely to have a longer hospital stay and be readmitted than other patients admitted to ICU (4). A systematic review of patients with alcoholic liver disease who were admitted to critical care concluded that mortality of this group ranged from 34-63% (122). Moreover alcohol consumption is associated with an increased mortality within 1 year of discharge from ICU (307). Both the acute and chronic implications of excess alcohol consumption are of considerable concern in critical care. Excess alcohol consumption is independently related to sepsis, prolonged mechanical ventilation, bacterial infection, ARDS and a higher risk of readmission (230, 308-310).

Alcohol withdrawal increases susceptibility for ICU related delirium (311). Approximately 80% of intubated patients develop delirium which may result in excess sedation, inhibit attempts to successfully wean patients from ventilators,

cause long term cognitive impairment and can lead to a reluctance to transfer patients from the ICU to a ward (312). Consequently there is an incentive to prevent and treat delirium effectively to reduce the length of ventilation, the time in ICU and hospital reducing the associated medical and economic costs (313). Furthermore critically ill patients may experience seizures, autonomic hyperactivity and hallucinations as part of an alcohol withdrawal syndrome (314). This causes tachycardia, hypertension, pyrexia, decreased cerebral blood flow, increased oxygen consumption, a respiratory alkalosis and electrolyte disturbances (314). These clinical findings may complicate diagnosis and management of the underlying presentation and thus it is advantageous to promptly identify patients at risk and prevent withdrawal occurring.

5.1.4 Measurement of alcohol intake

Historically, research into excessive alcohol intake concentrated on severe alcohol dependence or alcoholism (315). The focus now has shifted to include hazardous or harmful alcohol intake in an attempt to identify those at risk from the consequences of excess alcohol consumption (186). Widespread use of appropriate screening tools in healthcare settings can help identify patients at risk of alcohol related disorders allowing targeted intervention to reduce potential harm (316). To reduce alcohol use disorders, primary prevention requires national strategies at government level (317). Secondary prevention concerns detection and treatment of individuals with existing hazardous alcohol consumption, which can be undertaken in both the primary and secondary care setting (317). An American study published in 2008 demonstrated that screening for alcohol misuse was as cost effective as other interventions such as screening for hypertension, colorectal cancer, vision or influenza vaccination (318). The study of primary care interventions concluded that the effectiveness of screening relied upon four factors which included adherence with screening, sensitivity of screening tools, the ability of existing strategies in producing behavioural change and how effective behaviour change was in reducing the consequences of pre-existing excessive alcohol consumption (318).

The WHO, National Institute of Alcohol Abuse and Alcoholism (NIAAA) and the American Psychiatric Association (APA) proposed that individuals could be classed into different groups based on their pattern of drinking (Table 5-1) (319).

A systematic review identified that ‘at-risk, hazardous, heavy or problem drinking’ were terms used to describe individuals at risk of consequences from alcohol, either due to volume or pre-existing comorbidities (319).

Table 5-1 Classification of alcohol intake (319)

Category	Organisation	Definition
Moderate alcohol consumption	NIAAA	Men ≤ 2drinks/day Women ≤1 drink/day Over 65 ≤1 drink/day
At-risk alcohol consumption	NIAAA	Men >14 drinks/week or >4 drinks/occasion Women >7 drinks/week or >3 drinks/occasion
Hazardous alcohol consumption	WHO	At risk of adverse consequences from alcohol
Harmful alcohol consumption	WHO	Physical, psychological or socio-economic harm from alcohol
Alcohol abuse	APA	≥1 of the following per year; failure to fulfil major role obligations, recurrent use in hazardous situations, recurrent alcohol-related legal problems, continued use despite social problems caused or exacerbated by alcohol
Alcohol dependence	APA	Alcohol use Disorder ≥3 of the following per year; tolerance, require alcohol to prevent symptoms of withdrawal, time spent obtaining or using alcohol or recovering from its effect, unable to perform significant activities, more alcohol consumption than intended, failure to reduce intake, use despite awareness of physical, psychological or social problems caused by alcohol

5.1.5 Biochemical measures of alcohol intake

Despite the high sensitivity of alcohol screening questionnaires, it is recognised that alcohol history is not always reliable or easily obtainable (320). A number of biochemical markers exist which are objective measures of regular heavy drinking (320). Measurement of blood, breath or urine ethanol levels can

indicate chronic levels of drinking (321). Ethanol levels over 33mmol/L without clinical intoxication or over 65mmol/L at any point indicate increased tolerance and should raise suspicion of chronic alcohol consumption (321).

Gamma-glutamyltransferase (GGT) is a membrane-bound enzyme which catalyses glutathione to peptide acceptors (321). Serum levels of GGT rise in response to a number of conditions including increased alcohol intake and medications making it a non-specific marker of alcohol excess (321). Heavy drinking is indicated by a serum GGT measurement of over 35 units per Litre (units/L) (322). Alcohol consumption can lead to a change in the structure of transferrin and prolonged heavy drinking is indicated by a measurement of carbohydrate-deficient transferrin (CDT) in excess of 20 units/L (322, 323). The liver function tests aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are markers of liver injury with a raised AST to ALT ratio suggestive of alcohol aetiology (321, 324). A multinational study of 120 individuals found the serum biomarkers of alcohol excess; GGT, AST and CDT to be comparable with sensitivity of 33 to 40% and specificity of 85 to 94% (325). A full blood count may indicate excess alcohol intake with macrocytosis noted in 70.3% of alcoholics and a mean corpuscular volume (MCV) over 100 fl in 49.5% of alcoholics in a study of 398 individuals with chronic liver disease (326). Koivisto et al. demonstrated a dose-dependent response in MCV in relation to volume of alcohol intake (327).

At present biochemical measurement of alcohol excess can give some indication of chronic alcohol use but the majority of such measurements lack sensitivity and incur the expense of a laboratory test. A German study comprising 1233 individuals presenting to the ED found that using a questionnaire based approach was superior to biomarkers in identifying individuals with alcohol use disorders (328). Furthermore use of biomarkers in combination with a questionnaire-based screening tool did not show any improvement in sensitivity or specificity (328).

5.1.6 Alcohol screening tools

The following section of this chapter discusses a number of different alcohol screening tools. The tools discussed are the most frequently used questionnaires discussed within the literature and in use clinically.

5.1.6.1 Michigan Alcohol Screening Test

The Michigan Alcohol Screening Test (MAST) was published in 1971 and was the first questionnaire which enabled an individual to self-report current and past alcohol consumption (329, 330). The test can be completed in 5 minutes and consists of 25 dichotomous yes or no questions on problem drinking and behaviour associated with excess alcohol intake (330). A score of 0-3 suggests a problem with alcohol is unlikely, a score of 4 describes a possible problem with alcohol intake and a score of 5 or over suggests that the individual may be a problem drinker (330). As with other alcohol screening tests the results rely on an individual answering truthfully and the MAST will not identify a problem drinker in denial (331). The MAST also fails to distinguish between responses linked to current alcohol consumption from responses concerning previous alcohol behaviour (329). A meta-analysis concluded that the MAST had a reliability of 0.78-0.84 (183).

5.1.6.2 Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers

In 1974 Mayfield et al. published a paper describing 4 interview questions to screen for an alcohol use disorder (332). The questions encompass Cutting down, Annoyance regarding criticism about alcohol use, feelings of Guilt about drinking and whether alcohol was required as a morning Eye-Opener (CAGE) (333). Each positive response scores a point, with a score of 2 or more suggesting alcohol dependence and a maximum score of 4 indicating a likely diagnosis of alcoholism (334). Whilst it is one of the first alcohol screening tools described in the literature, the CAGE questionnaire remains one of the fastest to complete taking approximately 30 seconds (320). The CAGE tool was designed to screen hospitalised patients for alcohol problems and unlike the Alcohol Use Disorders Identification Test (AUDIT) tool it reflects long-term alcohol consumption and its consequences rather than quantifying alcohol intake or the pattern and frequency of alcohol intake (334). A systematic review published in 2000 revealed that sensitivity to detect at-risk drinkers ranges from 14-84% with a specificity of 95-97% (319). In those who drank excessive volumes of alcohol the sensitivity was between 49-69% and specificity of 75-95% (319). A review of reliability studies demonstrated a reliability 0.80-0.95 (335).

5.1.6.3 Alcohol Use Disorders Identification Test

The AUDIT was developed by the WHO in 1987 with the aim of screening individuals for excess alcohol consumption (336, 337) (Appendix 3). In addition to identifying those with alcohol dependence the tool is designed to identify individuals with hazardous and harmful drinking behaviour (336). The AUDIT consists of 10 questions (336, 338). The first 3 questions gauge hazardous alcohol use and cover the frequency and quantity of alcohol consumed (336). The subsequent 3 questions identify symptoms of dependence and include impaired control of drinking, increased salience of drinking and morning drinking (336). The final 4 questions concern harmful alcohol use and cover feelings of guilt, blackouts, alcohol-related injuries and concern from other individuals (338). There is a maximum score of 40, with scores of 8 or above indicating problem drinking (338). Studies have also shown that the tool may perform differently in men and women, with a suggestion that a score lower than 8 be used to indicate problem drinking in women (339). At present the WHO does not advise any differences in interpretation of the AUDIT score based on gender.

The tool has been validated in 6 countries within primary care settings and can be performed in 2 minutes (338). It has been used within an employment setting to assess alcohol problems in the police force and in secondary care settings (339). However, in certain clinical settings such as the ED, Hodgson et al. raised concern that the AUDIT takes too long to complete when faster screening tools are available (315).

The AUDIT is unique in the fact that it concentrates on current alcohol behaviour, it was constructed utilising responses from a multinational sample and identifies hazardous drinking rather than long-term dependence (340). A systematic review of the screening tools available to detect alcohol problems in primary care demonstrated that the AUDIT tool had sensitivities of between 51%-97% and a specificity of between 78%-96% in detecting individuals with at-risk, hazardous or harmful alcohol intake (319). In addition the AUDIT has been proven to have a median reliability of 0.81 (341). The AUDIT remains one of the few tools which aims to not only identify alcohol dependence but detect individuals with ‘at-risk’ drinking behaviour, potentially providing opportunity for early intervention to avoid harm (339).

Few studies exist which examine use of the AUDIT in the ICU population. One American study of outpatient veterans screened individuals using the AUDIT-C - a shorter version of the AUDIT tool, and subsequently followed up this population to determine the incidence of ICU admission (342). It concluded that those with severe alcohol problems were more likely to be admitted to ICU (342). The same group of researchers have investigated use of the AUDIT in those with ARDS (343). Using a lower threshold value of 5 on the AUDIT they found 23% of those with ARDS screened positive for an alcohol use disorder (343).

5.1.6.4 The Fast Alcohol Screening Test

Following criticism that the AUDIT was not used routinely in time pressured clinical scenarios such as the ED, the Fast Alcohol Screening Test (FAST) was developed based on specific questions from the AUDIT (315). The FAST consists of 4 questions and the first question concerns frequency of consuming more than 8 alcoholic drinks for men and 6 for women (315). The second question concerns inability to remember events the night before due to alcohol excess (315). The third questions the frequency that the individual is unable to complete tasks expected of them due to drinking (315). The fourth question asks the individual if anyone has expressed concern regarding their alcohol intake or suggested reduction in alcohol intake (315). Whilst the questions are different, the themes covered are similar to those within the CAGE questionnaire. To increase speed at which FAST can be performed the first question can be used as a filter and eliminate the need for the remaining questions in over 50% of patients (315). The FAST is negative if the individual does not drink more than 8 (for men) or 6 (for women) alcoholic drinks (315). If consumption exceeds this number of drinks on a weekly or daily basis the test is positive (315). Whilst the FAST can be performed in 12 seconds it has not been validated as extensively as the AUDIT nor does it differentiate between hazardous or harmful alcohol intake and alcohol dependence (315).

Despite the number of instruments available no biochemical test or screening tool have been validated to measure the volume of alcohol consumed. Furthermore, to date none of the alcohol screening tools discussed have been validated within the ICU setting. The majority of ICUs in the UK document volume of alcohol consumed, based on patient or relative history, rather than

using a screening tool (344). Accurately gauging alcohol intake is challenging and participation in the use of any assessment tool is compromised if the patient is sedated or ventilated, as is often the case in critical care. Moreover, up to 80% of all intubated patients experience delirium, which also has an association with alcohol withdrawal (312). This may impact upon validity of a history following extubation and self-reporting of alcohol consumption. In any setting, self-reporting of alcohol intake may be inaccurate and the value of an alternative source of information, such as a collateral history can prove to be useful (345, 346).

5.1.7 Proxy studies

A proxy is defined by the Oxford English Dictionary as a "*person authorised to act on behalf of another*" (347). Existing studies have investigated use of a proxy to measure alcohol intake using questionnaires such as CAGE and MAST (348). Chermack et al. found that reported alcohol consumption using the CAGE questionnaire did not differ significantly between patient and proxy in a study of 581 cases (348). Likewise the MAST questionnaire was demonstrated to correlate between partners for those with known excess alcohol consumption in 2 studies (349, 350). Use of a collateral informant to assess alcohol use using the AUDIT has been found to correlate with the patient's own assessment of alcohol intake in the ED (345). Patients enrolled to that study had screened positive for alcohol problems and were predominantly young, educated men (345). There is a paucity of studies which investigate use of a collateral history in the literature, despite routine clinical use and description in national guidelines for patients with an inability to provide an accurate history, such as those with dementia (351).

The use of a collateral informant to provide insight into alcohol history has not yet been investigated within an ICU environment nor where the patient is unable to self-report alcohol history (344). If a proxy is found to be a reliable substitute to provide information on alcohol intake then this method may provide an opportunity to gauge alcohol intake more accurately. This could potentially enable identification and treatment of patients most likely to be at risk of alcohol withdrawal. The findings may empower clinicians to target appropriate alcohol treatment programmes to those patients who require such support.

There is evidence to suggest that ICU admission provides an opportunity to deliver interventions to reduce preventable causes of disease such as cigarette smoking and excess alcohol consumption (352).

5.2 Study question and aims

5.2.1 Can a proxy be used to measure alcohol intake in a patient admitted to intensive care?

Alcoholic liver disease is one of the preventable causes of chronic liver disease and cirrhosis. Prompt recognition and treatment of patients who consume excess alcohol would inform acute medical management and facilitate targeted health intervention. However, obtaining an accurate alcohol history is challenging, particularly if the patient is critically ill. If a proxy is able to supply a reliable alcohol history this would provide valuable information in the intensive care setting.

5.2.2 Aims

- To identify whether intensive care patients' self-evaluation of alcohol intake correlates with that of a proxy evaluation of alcohol intake

- To identify whether frequency, nature and mode of contact between patient and proxy has any influence on the correlation of results

5.3 Methodology

5.3.1 Design

This study was a prospective questionnaire, designed to consist of identical paired questionnaires given to a patient and a proxy at different stages of the patient journey.

Potential proxies were provided with a letter of invitation when they visited their friend or relative in ICU and invited to participate in the study. They were approached by a member of the research team who consisted of the MD student,

the MD supervisors: Dr Joanne McPeake and Dr Tara Quasim, Dr Jill Selfridge or one of the clinical research nurses based at GRI or QEUH.

Potential proxy participants were given an information sheet detailing the research team, the purpose of the study, their involvement, risks and benefits of participation, how information would be stored and how information gathered would be used (Appendix 6). The potential proxy was then approached during the same patient visit after they had read the information sheet.

Following consent, the proxy completed the AUDIT, answering the questions on behalf of the patient using their perception of the patient's alcohol behaviour. The proxy provided further information regarding their relationship to the patient and frequency of contact with the patient. Once extubated and deemed fit to step down from a Level 3 care, the patient was approached by a member of the research team, provided with a letter of invitation to participate in the study and given an information sheet. Following consent the patient was asked to complete the 4 'A's Test (4AT) (Appendix 4) (353). This screening tool was used to exclude patients with severe cognitive impairment or delirium. If the patient did not screen positive on the 4AT they were then asked to complete the AUDIT.

Prior to ethical approval all aspects of the study were reviewed by former patients and members of the public attending an ICU follow-up clinic (354). This included conduct, approach and documentation, ensuring readability and identification of any ambiguity within the questions.

5.3.2 Questionnaires

5.3.2.1 Alcohol Use Disorders Identification Test

The AUDIT tool is described in detail in section 5.1.6. It was selected for use in this study as it is able to detect current or recent detrimental drinking whilst providing insight into an individual's drinking pattern and behaviour (345). Published by the WHO, the AUDIT tool is available for use provided it is not utilised for commercial purposes (336) (Appendix 3). In keeping with other

studies a threshold score of 8 was used within the study to determine problematic drinking (319).

5.3.2.2 The 4 'A's Test

The 4AT is an assessment designed to detect cognitive impairment or delirium (353) (Appendix 4). It measures patient alertness, attention, acute or fluctuating change in mental function and incorporates the abbreviated mental test (AMT) comprising patient age, date of birth, location and current year. If no cognitive impairment or delirium is present a score of 0 will be achieved. A score of 1 to 3 over all questions indicates possible cognitive impairment and a score of over 4 indicates possible delirium or cognitive impairment, with a maximum score of 12. The tool is considered to be useful in assessment of individuals with severe agitation or drowsiness and can be performed in less than 2 minutes. The 4AT tool has been validated in a number of studies including an Italian study of 236 individuals aged over 70 who were admitted to hospital and a study of 111 admissions to an acute stroke unit in GRI - the same site as the present study (353, 355). Permission to use the 4AT questionnaire in this study was granted by the author, Dr Alasdair MacLullich on 5 September 2014.

5.3.3 Participants

Proxies enrolled into the study were recruited following admission of a relative or friend to the GRI or the QEUH ICU. There was no randomisation and any identified proxy of every patient who met the inclusion criteria admitted to the ICU within the data collection period was approached, provided another proxy had not completed the AUDIT questionnaire on behalf of the patient.

Patients were invited to participate in the study when they were deemed fit for discharge from Level 3 care. The initial recruitment was planned over a 9-month period from 07/03/2015 until 07/12/2015. However, due to low recruitment levels, further ethical approval was granted to add a second recruitment site at the QEUH, Glasgow. Recruitment was then extended until 19/07/2016.

Following discussion with a statistician it was decided that the study would require 206 patients to power the study to 99% at a 0.05 significance level. This

would enable differentiation between proxy and patient, in determining whether the patient's alcohol intake was harmful, hazardous or dependent – the three groups of patients classified by the AUDIT. With approximately 750 patients admitted to GRI ICU in 9 months it was initially predicted that sufficient participants would be recruited to power the study.

5.3.4 Inclusion Criteria

- Over 16 years old
- Competent to give consent
- Identifiable proxy over the age of 16
- No cognitive impairment on 4AT
- No delirium on 4AT
- English Speaking

5.3.5 Exclusion Criteria

- Refusal to consent
- Death before discharge from intensive care

5.3.6 Centres

Data collection was initially commenced at the GRI ICU, however, the recruitment target was not met in the single site. Subsequently the QEUH, Glasgow was approved an additional recruitment site. Details of both hospitals are provided in section 2.1.4.

5.3.7 Informed consent

All participants (proxies and patients) were fully informed that they were being asked to participate in a research study. Each was provided with a participant

information sheet (Appendix 6). A signed consent form was obtained and retained by the investigators. Participants who were patients were made aware that their case notes could be accessed by staff involved in the research and independent research monitors in their inspection of documentation. Their GP was also informed of participation in the study. All participants were provided with a telephone number of an independent party to contact should they wish to discuss participation in the research and a telephone number of an investigator should they have any further enquires. It was emphasised to the proxy and patient that any data collected would not inform treatment as it was primarily looking at correlation of results between patient and proxy. Participants were made aware that completion of the AUDIT could prompt either the patient or proxy to assess and address their own alcohol drinking patterns and behaviour.

5.3.8 Confidentiality and data management

In addition to the procedures previously detailed (section 2.1.7) each patient and proxy pair was given a unique identifier within the study in order to link the results of both completed AUDIT questionnaires. This identifier was exclusive to the study and it was not possible to identify the patient from this number. The results of each AUDIT completed, the 4AT assessment and further questions completed by the proxy regarding relationship to the patient were entered into an anonymised data collection sheet for analysis.

5.3.9 Ethics

The study was granted ethical approval by the West of Scotland Research Ethics Committee 3 on 27 January 2015 (REC reference: 15/WS/0014 Chair: Dr Adam Burnel) (Appendix 5). Further ethical approval was granted to add a second site (Queen Elizabeth University Hospital) on 17 November 2015 and to extend the study for 12 months on 18 February 2016.

5.3.10 Statistical Analysis

All data were found to be non-parametric data and as such each factor was described using the median and IQR (179). A Wilcoxon signed-rank test was used to analyse whether the distribution of answers given by the patient and the

proxy significantly differed. As multiple testing was performed on the data a Bonferroni adjustment was made to the p values to reduce the Type I error (182). A Type I error would mean that significant differences between the proxy and patient AUDIT answers could be falsely demonstrated (182). Answers given by patient and proxy were then tested to identify the interrater level of agreement using a weighted Cohen's Kappa. A weighted Cohen's kappa was used as it would assign more significance to greater levels of disagreement between patient and proxy. As a threshold score of 8 has been used to identify those with 'problem drinking' further analysis was performed to assess levels of agreement using this score using a weighted Cohen's Kappa.

5.4 Results

5.4.1 Demographics

One hundred and thirty-one proxies were recruited to the study across the 2 recruitment sites. Of the 131 proxies, only 37 (28.2%) patients were recruited. The low recruitment rate was caused by a range of factors. Thirty-four (26.0%) patients died whilst in ICU and could therefore not be recruited, 31 (23.7%) were discharged from hospital before they were recruited, 13 (9.9%) were transferred to a different hospital prior to discharge, 6 (4.6%) declined to take part in the study, 4 (3.1%) patients did not have capacity to complete the AUDIT following screening with the 4AT. Of the remaining patients, 1 (0.8%) patient was under arrest and therefore could not be recruited and 5 (3.8%) patients remained Level 3 admissions at the end of the recruitment period.

Of the 37 proxy-patient pairs recruited the majority of proxies (35.1%) were the partner of the patient. 29.7% of proxies were the patient's child, 16.2% were parents of the patient, 13.5% of proxies were siblings of the patient and the remaining 5.4% were friends of the patient. The most frequent reported contact with the patient was in person in 27 (73.0%) cases, whilst 8 proxies and patients spoke most frequently by telephone (21.6%) or in 2 (5.4%) cases by text. The majority of proxies (73%) reported contact with the patient on a daily basis, whilst 7 (18.9%) proxies described weekly contact. Only 2 (5.4%) proxies had contact with the patient on a monthly basis, whilst 1 (2.7%) proxy had contact with the patient every 6 months.

5.4.2 Proxy and patient assessment of alcohol

The median total AUDIT score from the proxy assessment was 4 (IQR 0-9). The median total AUDIT patient score was 3 (IQR 0-8). There was no significant difference found between the total score for the AUDIT for proxy or patient (p=0.54). Moderate agreement was demonstrated between patients and proxies when assessing total AUDIT scores, with a kappa statistic of 0.51 ($p=4.67^{-05}$) (Table 5-3).

A score of 8 has been suggested as a threshold for problematic drinking by the AUDIT's authors (336). When scored by the proxy, 13 patients (35.1%) achieved 8 or above on the AUDIT tool, with 10 patients (27.0%) achieving a score of 8 or above on self-reporting. When assessing levels of agreement using a threshold value of 8, a Kappa statistic of 0.67 ($p=4.67^{-05}$) was demonstrated between patients and proxies suggesting substantial agreement between groups (356).

Each group of questions within the AUDIT was subsequently analysed. The initial 3 questions concern hazardous alcohol consumption with the median proxy group score of 3 (IQR 0-6) and the median patient group score of 3 (IQR 0-6). There was no significant difference found between the proxy and patient answers (p=0.61). The second 3 questions concern alcohol dependence symptoms, with the proxy group median of 0 (IQR 0-0) and patient median of 0 (IQR 0-0). There was no significant difference found between the proxy and patient answers (p=0.96). The final 4 questions concern harmful alcohol consumption, with a median proxy group score of 0 (IQR 0-2) and a median patient group score of 0 (IQR 0-2), again there was no significant difference found (p=0.71).

Proxy and patient answers for each question were then analysed in turn. There was no significant difference demonstrated in the answers between proxy and patient (Table 5-2). Differing levels of agreement were noted between individual AUDIT questions. Using a kappa value of 0.41 or above to identify agreement, 5 questions had at least moderate agreement between patient and proxy (Table 5-3).

Table 5-2 Distribution of patient and proxy responses to AUDIT questions

AUDIT Question	Patient median score (IQR)	Proxy median score (IQR)	p value
1. Frequency of alcoholic drink	1 (0-2)	1 (0-3)	0.30
2. Typical number of drinks consumed per day	1 (0-2)	1 (0-2)	0.62
3. Frequency more than 1 drink	0 (0-2)	1 (0-2)	0.33
4. Unable to stop drinking in past year	0 (0-0)	0 (0-0)	0.52
5. Failed to do what was normally expected	0 (0-0)	0 (0-0)	0.72
6. Drink first thing in the morning	0 (0-0)	0 (0-0)	0.58
7. Guilt or remorse following alcohol	0 (0-0)	0 (0-0)	0.80
8. Inability to remember previous night's events due to intoxication	0 (0-0)	0 (0-0)	0.61
9. Someone else injured because of respondents alcohol intake	0 (0-0)	0 (0-0)	0.09
10. Someone else suggesting a reduction in alcohol intake	0 (0-0)	(0-0)	0.32
Total AUDIT score	3 (IQR 0-8)	4 (IQR 0-9)	0.54

Table 5-3 Levels of agreement between patient and proxy responses to AUDIT questions

AUDIT Question	Kappa value	Z statistic	p value
1. Frequency of alcoholic drink	0.79	6.86	6.87^{-12}
2. Typical number of drinks consumed per day	0.56	4.69	2.73^{-06}
3. Frequency more than 1 drink	0.61	5.16	2.42^{-07}
4. Unable to stop drinking in past year	0.28	2.20	0.03
5. Failed to do what was normally expected	0.15	1.23	0.22
6. Drink first thing in the morning	0.21	1.47	0.14
7.Guilt or remorse following alcohol	0.41	3.95	7.70^{-05}
8. Inability to remember previous night's events due to	0.38	3.23	0.01

intoxication			
9. Someone else injured because of respondents alcohol intake	-0.05	-0.33	0.74
10. Someone else suggesting a reduction in alcohol intake	0.59	3.95	7.84^{-05}
Total AUDIT score	0.51	4.08	4.55^{-05}
AUDIT score of 8	0.67	4.07	4.67^{-05}

5.5 Discussion

5.5.1 Interpretations of findings

5.5.1.1 Use of a proxy to provide an alcohol history

This study is understood to be the first study in the literature to examine the use of a proxy in ICU to provide an alcohol history. There is a paucity of research investigating use of a proxy for any history-taking in ICU despite the widespread use of a collateral historian to provide information on behalf of a patient who is often unable to provide their own history due to critical illness, drugs or intubation. However, given the under recruitment in this study the results can only be used to indicate possible associations and as such it is not possible to form firm conclusions.

Furthermore the results of this study demonstrate that there is no significant difference in both levels of agreement and distribution of total AUDIT scores reported by proxy or patient. This suggests that a proxy could be used to provide an accurate reflection of the patient's alcohol intake, which would be useful to

aid recognition and early treatment of alcohol withdrawal. This study supports the findings of previous research, which demonstrated agreement between proxy and patient scores following completion of the AUDIT in trauma patients (345). The study reported by Donovan et al. in 2004 consisted of patients presenting to a single centre American ED and participants were predominantly young, white males (345). Whilst the study recruited good numbers of patients, almost half of the American patients had undergone treatment for alcoholism in the past (345). Unlike the study performed by Donovan et al., the study reported in this chapter recruited patients irrespective of a known or suspected alcohol use disorder.

Due to poor recruitment, no firm conclusions could be made as to whether the type of relationship, frequency of contact and mode of contact between proxy and patient has a role in determining the correlation of AUDIT results. However, studies investigating the use of a proxy in reporting QOL for critically ill patients have found that living in the same household or the type of relationship between proxy and patient did not influence results (357, 358). One Italian paper reported on QOL prior to ICU for 172 patients with critical illness (357). The authors reported similar difficulties in recruitment with exclusion of patients who were unable to co-operate with the questionnaire, concluding that the results would potentially exclude those with the most severe critical illness (357). Of note, the study reported greater concordance in topics covering physical or witnessed impairment rather than emotional impairment (357). This may equate to differences observed between patient and proxy agreement in questions in the AUDIT, reported in this study. Similarly, a UK study of 99 patients admitted to ICU reported agreement between patients and proxies in functional aspects of QOL (358). This study reported significant loss to follow-up with patients excluded due to age, lack of willingness to participate or inability to administer the questionnaire due to timing of discharge (358).

Using a threshold value of 8 scored on the AUDIT, substantial agreement was demonstrated between patient and proxy when identifying the incidence of a suspected problem with alcohol consumption, with 35.1% of proxies identifying a problem and 27.0% of patients self-reporting problem-drinking. These figures are comparable to the incidence of an alcohol use disorder in ICU patients which was reported to be 35% in a study at the same centre (187). Other investigations report the incidence of an alcohol use disorder to be between 16.7%-33% in the

general ICU population (305, 307, 359-361). The choice of a value of 8 in the AUDIT to identify those with problem drinking has been debated within the literature (362). The original AUDIT cut-off score was 11 and a decrease was due in part to a reduction in drink drive limits, however, this differs between countries (362). Further, there remains discussion regarding use for specific cut-off scores for different populations of patients and for alternative uses such as prediction of risk or intervention (362).

Interestingly, the number of proxies who scored a relative or friend as a problem drinker exceeded the number of patients who identified themselves as such. Patients may under-report their alcohol consumption or falsely answer questions regarding their behaviour due to denial of their alcohol intake or reluctance to share sensitive information as they are concerned that this may not be kept confidential or prejudice future medical care (346, 363-365). Over-reporting of alcohol consumption by the proxy may reflect their attitude or a lack of awareness regarding the patient's behaviour (345). The proxy may feel that this is one route to highlight their concerns and a means to seek help for the patient (345).

The distribution of patient and proxy scores were similar for each question across the different subgroups of hazardous alcohol consumption, harmful alcohol consumption and alcohol dependence. Levels of agreement differed between questions, however, at least moderate agreement was identified in half of the questions. The first 3 questions in the AUDIT score cover frequency and quantity of alcohol consumption and showed good levels of agreement, which is perhaps not surprising for objective or witnessed actions. Further, it is reassuring that there was agreement for subjective questions such as guilt after drinking. This finding mirrored that of the previous study of trauma patients (345). Poorer levels of agreement were shown in questions covering dependence symptoms such as impaired control and salience, which are perhaps difficult to assess on behalf of another individual. Poor agreement was demonstrated in questions covering memory problems due to alcohol and morning drinking which may be explained by the fact that these behaviours can be unwitnessed and without explicitly asking the patient a proxy is unable to provide this information. Without a comparative population it is difficult to determine

whether the spread of scores across questions was representative of other critically unwell individuals.

5.5.1.2 Incidence of delirium and cognitive impairment

Prior to recruitment all patients were screened for delirium and cognitive impairment using the 4AT. Of the patients who survived their ICU stay only 4 (8.5%) of the possible 47 approached for recruitment screened positive for cognitive impairment or delirium. With up to 80% of ICU developing delirium this number is perhaps lower than expected (366). As delirium is known to extend ICU length of stay and mortality it would have been useful to identify whether those who died or remained in Level 3 care during the study would have screened positive for delirium whilst in ICU. The low incidence of delirium in our cohort may be explained by the resolution of delirium by the time of testing, a lower incidence of delirium in the study sites or it may be that a large proportion of those with delirium did not survive to ICU discharge.

5.5.2 Limitations

This study suggests that a proxy can be used to provide information regarding alcohol consumption in critically ill patients admitted to ICU. However, these findings are based on the results of a screening questionnaire and due to the study design no clinical information was recorded. Whilst the use of questionnaire based screening tools have been proven to be more sensitive than biochemical results such as GGT, CDT and liver function tests, using such tests may have added to accuracy regarding findings (319).

There was a considerable loss to follow up within this study and, despite the addition of a second site for recruitment, the numbers of patients recruited remained low. A significant number of patients with proxies died prior to completion of the AUDIT. It is well established that the critically ill with alcohol use disorders have a higher mortality and it is possible that the subgroup of patients recruited may have been skewed towards those without an alcohol use disorder (187). Furthermore, as a member of the study team was not permanently present in the ICU or GRI a number of patients were discharged prior to enrolment. This could mean that individuals with a short length of stay

in hospital, potentially those who with fewer chronic co-morbidities were not recruited. In any future study it would be useful to record clinical and demographic data to facilitate analysis of those individuals recruited and seek permission to follow up discharged patients in a postal survey.

Although the AUDIT has been validated in a number of different populations at present this has not included a population of ICU patients. A number of studies conclude that the cut-off score of 8 suggested by the authors should be lowered for females or older patients (339). Without large numbers and demographic data it is not possible to analyse such subgroups within this study. In this study, focussing on levels of agreement between total AUDIT scores and the threshold value of 8 rather than upon individual questions aimed to reduce the error introduced by small numbers of participants. It was acknowledged that a greater number of participants would be required to improve the power of the study and reduce the probability of a type 2 error.

Furthermore, assessment of interrater agreement with small numbers of participants is challenging and introduces the concepts of precision and accuracy in determining utility of a test and in this study, the utility of a proxy (356). The kappa statistic was chosen as it reported precision. It was decided that this would provide information on the magnitude of agreement between patient and proxy, rather than focussing upon the accuracy of agreement for individual questions (356). The kappa statistic is altered by both prevalence of the disease (alcohol use disorder) and bias, both of which are beyond the scope of this thesis, but it is important to acknowledge that any further studies beyond this prospective study would need to address such issues.

5.6 Conclusion

This chapter discusses the results of a prospective study to evaluate the use of a proxy to provide accurate information on alcohol consumption and behaviour for patients admitted to ICU using the AUDIT. The results illustrate:

- Substantial agreement between proxy and patient in the identification of an alcohol use disorder using the AUDIT and predetermined threshold score of 8

- Moderate levels of agreement and no significant difference in the distribution of total AUDIT scores between proxy and patient

- No significant difference between proxy and patient in each of the 3 subgroups of AUDIT questions examining hazardous alcohol consumption, harmful alcohol consumption and alcohol dependence

- 8.5% of ICU survivors approached for recruitment screened positive for cognitive impairment or delirium

This chapter evaluates the use of a proxy to aid identification of ICU patients with alcohol use disorders and identify those at risk of alcohol withdrawal. The next chapter will explore long-term survivorship in critically ill cirrhotic patients.

Chapter 6 The factors associated with long-term outcome of patients admitted to intensive care with cirrhosis

6.1 Introduction

Chapter 4 explored the utility and timing of Child-Pugh score in predicting ICU and hospital outcome in critically ill cirrhotic patients whilst Chapter 5 investigated the use of a proxy to report alcohol history once a patient is admitted to ICU. This chapter investigates the long-term survival of patients with cirrhosis admitted to a UK general intensive care unit.

6.2 Survivorship following admission to intensive care of individuals with cirrhosis

6.2.1 Short-term survival

Short-term survival of critically ill patients with cirrhosis has been discussed in detail earlier in this thesis (section 1.5.7). Short-term outcomes for critically ill cirrhotics have been reported since the 1980s when ICU mortality was stated to be up to 100% in patients with septic shock, severe cirrhosis, acute hepatitis or renal failure (5-7). Both ICU and hospital mortality have improved with the most recent study of short-term outcome in the UK reporting a 31% ICU mortality and 46% hospital mortality (120). However, mortality figures increased in those with liver disease caused by alcohol, compared to those of other aetiologies (120).

The short-term outcome of the critically ill cirrhotic population studied in this chapter are comparable to other contemporary studies and report an ICU mortality of 30% and hospital mortality of 46% (18).

6.2.2 Long-term survival

Whilst both ICU and hospital mortality have been extensively reported, there are fewer studies examining long-term survival of critically ill cirrhotic patients beyond 6 months. The 6-month mortality of those with cirrhosis of any aetiology admitted to a general ICU has been reported as 56% at in a German study (177). A meta-analysis, published in 2017, of 13 studies examining 2523 critically ill

cirrhotic patients reported 6-month mortality at 75.1% (367). Only 3 of the studies included were performed outwith tertiary referral centres, with just 1 of those 3 studies reporting outcome at 1-year. This French study of patients admitted to ICU with severe hepatic encephalopathy reported 1-year mortality at 54% (368). Additionally, 1-year mortality was reported in an American study of 420 critically ill cirrhotics admitted to ICU in a tertiary referral centre offering liver transplantation, demonstrating a 1-year mortality of 69% and a 5 year mortality of 77% (167).

Aetiology of underlying liver disease may influence long-term mortality with a Scottish tertiary liver ICU reporting a 78%, 6-month and 81%, 12-month mortality in those with decompensated alcoholic liver disease (369). A recent study published national Scottish mortality data for those with alcoholic liver disease admitted to ICU (4). The authors reported an ICU mortality of 44% and a 5-year mortality of 79.2% for those admitted between 2005 to 2010 (4). Long-term mortality was greater than other critically ill patients including those admitted with chronic disease such as severe cardiovascular, respiratory or renal disease, where 5-year mortality was reported as 75.3% (4).

6.2.3 Factors known to affect survival

A range of different clinical factors have been shown to predict survival in critically ill cirrhotics. The underlying cause of admission to ICU is known to impact upon long-term survival in cirrhosis secondary to alcoholic liver disease (369). Individuals admitted to a Scottish tertiary ICU with sepsis had a higher mortality than individuals presenting with gastrointestinal haemorrhage or encephalopathy (369). This has been reflected in a number of studies reporting lower mortality in critically ill cirrhotics of any aetiology presenting with upper gastrointestinal haemorrhage (118, 123). Indeed, in the specific subgroup of cirrhotics requiring intensive care due to an upper gastrointestinal haemorrhage, 6-month mortality has been reported to be as low as 50%, with a 92% mortality for cirrhotics requiring Level 3 care for other reasons (118). Admission with severe encephalopathy or sepsis has been widely demonstrated to predict both poor short and long-term survival (118, 123, 367).

Whilst few studies support any demographic associations with survival, one French study of 138 patients reported that age greater than 50 to be predictive of initial ICU mortality (117). Opinion differs regarding the predictive value of the clinical findings of liver disease, with the same study finding no prognostic value in the presence or severity of ascites or varices (117). The study performed by Campbell et al. examining short-term outcomes found that the presence of ascites predicted ICU mortality in a London dataset of patients (18). However, both short and long-term mortality in a separate cohort of cirrhotic patients was associated with the presence of jaundice in combination with a high APACHE III score and requirement for vasopressor (167). Short-term mortality in critically ill cirrhotics has been associated with higher measurements of INR or PT ratio, bilirubin, ALT, creatinine, lower albumin levels and the presence of HRS (18, 116-118, 367, 370).

Severity of acute illness, measured by the number of separate organ failures has been demonstrated to predict in-hospital mortality (117, 127). A number of studies report an association between both short and long-term mortality and higher severity of illness scores such as APACHE II and APACHE III (119, 123, 167). The SOFA score has been demonstrated to predict short-term mortality (367, 370). One recent meta-analysis which examined mortality following ICU admission concluded that Child-Pugh class C and MELD predicted outcome at 6 months (367).

Requirement for interventions such as mechanical ventilation, vasopressors or renal replacement therapy whilst in ICU has been demonstrated to be associated with poor short and long-term survival (118, 119, 123, 127, 167, 367, 370). In the cohort of patients reported in this study a previous investigation demonstrated that lactate was an independent predictor of ICU mortality and a modified scoring system of Child-Pugh + Lactate was proposed (17, 18). Furthermore, a retrospective cohort analysis of critically ill cirrhotics demonstrated that in those who developed renal failure, the degree of renal dysfunction determined both ICU and hospital mortality, as did the presence of septic shock (125).

6.3 Study question and aims

6.3.1 What is the long-term survival of patients admitted to intensive care with cirrhosis?

Multiple studies demonstrate that the short-term survival of patients with cirrhosis admitted to intensive care is improving. However, there are few studies reporting the long-term survivorship of patients with cirrhosis admitted to intensive care outwith tertiary referral centres or beyond 6 months. Information on the long-term outcomes could inform the clinical decision whether to admit patients to ICU and give valuable information to patients who have the capacity to make the decision to undertake intensive treatment.

6.3.2 Aims

In a cohort of critically ill patients with chronic liver disease admitted to a general non-transplant ICU in Glasgow:

- To identify the 12 month survival of those individuals with cirrhosis
- To detect any factors associated with patient survival at 12 months
- To explore the predictive ability of existing scoring systems in determining long-term outcome

6.4 Methodology

6.4.1 Design

This is an observational cohort study of adult patients with liver cirrhosis admitted to GRI ICU between June 2012 and December 2013. The short-term outcomes of this population have already been published (18). The study site has been described in section 2.1.4.

The ICU at GRI utilises electronic patient record systems, enabling clinical data to be collected prospectively at the time of ICU admission. Demographic data collected included age, gender, reason for ICU admission and aetiology of liver

disease. Postcode of each patient was recorded which enabled calculation of the SIMD (40). For the purpose of this study if a patient lived in one of the 20% most deprived areas they were considered to be socially deprived (40).

6.4.2 Participants

Participants were diagnosed with cirrhosis if they had a documented positive liver biopsy or clinical features of cirrhosis such as evidence of portal hypertension, ascites or encephalopathy or oesophageal varices (18). Patients displaying signs of liver cirrhosis on ultrasound were also included. All diagnoses of liver cirrhosis were checked by a second independent clinician who was a consultant intensivist at GRI.

6.4.3 Ethics

This research was approved by the West of Scotland Research Ethics Committee on 20 March 2012 (REC reference; 12/WS/0039 Chair; Dr Gregory Ofili).

6.4.4 Statistical analysis

Bivariate analysis was performed to determine whether there were any relationships between measured variables and survival at 12 months. Normally distributed data were assessed using the independent t-test and presented as mean and standard deviation. Data found to be non-parametric were assessed using the Mann-Whitney U test and described as median and IQR. Proportions were compared using the Chi-squared test for association.

Multivariate analysis was then performed to examine the relationship between multiple variables and mortality at 12 months. As mortality is a categorical variable a stepwise backward multivariate logistic regression model was used to assess the relationship between independent clinical variables and mortality.

Survival analysis was performed to determine the survival of this population of critically ill cirrhotics. The variable of interest was time until death. Cumulative survival was plotted against days of survival following ICU admission. In order to determine patient survival following ICU admission, data were analysed using Kaplan–Meier curves. Three curves were plotted to reflect survival of Child-Pugh

Class A, Class B and Class C. Using each Kaplan-Meier curve it was possible to estimate survival at any time point from ICU admission. A log rank test was used to determine whether there was a statistically significant difference in survival between each Child-Pugh class.

ROC curves were then plotted for different scoring systems used within critical care and chronic liver disease. To ascertain the performance of each scoring system for this population the AUC for each ROC curve was calculated (200).

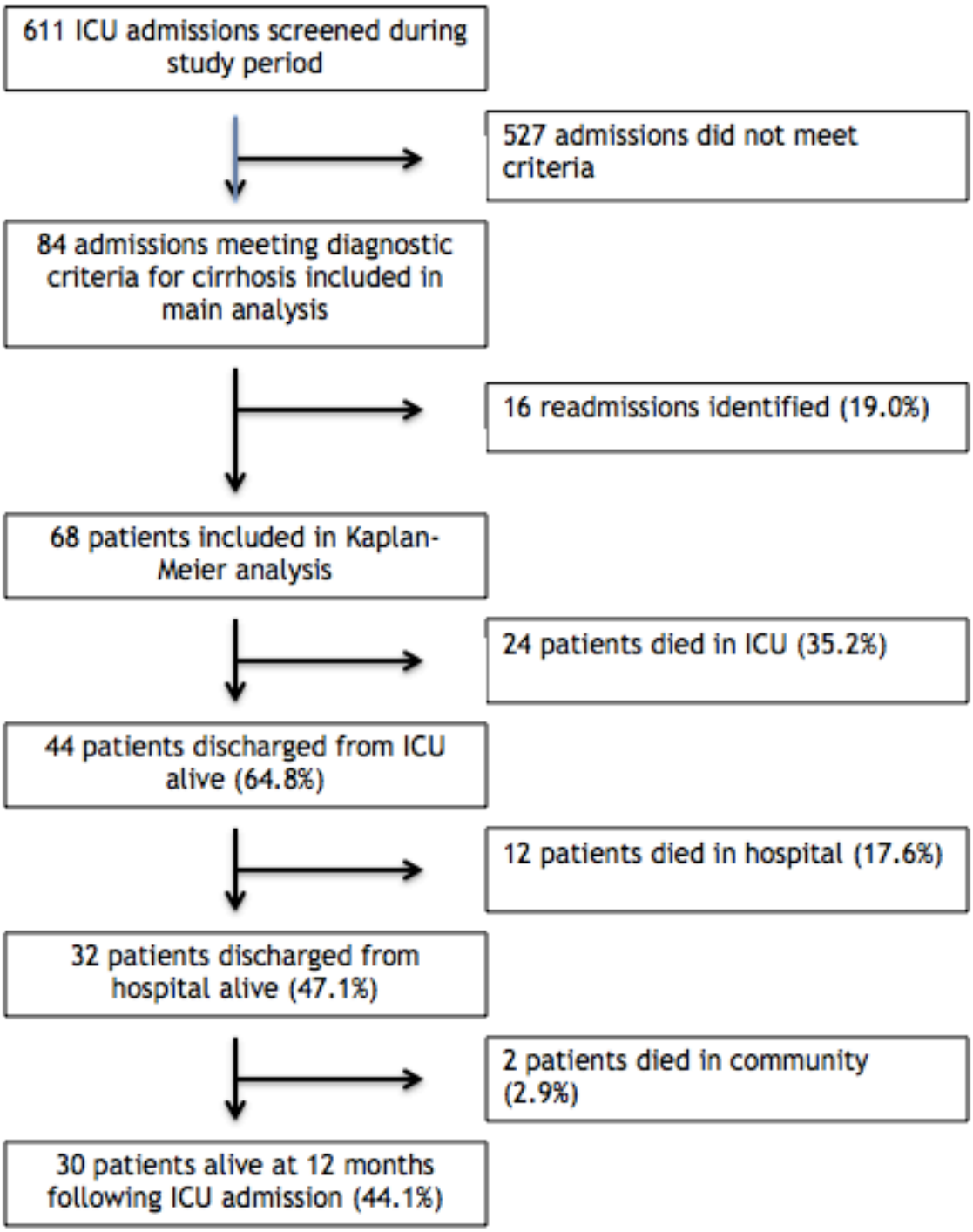
6.5 Results

6.5.1 Demographics

Between June 2012 and December 2013 there were 611 admissions of critically ill patients to GRI ICU. Of these admissions, 84 (13.7%) were identified with cirrhosis (Figure 6-1). Of those with cirrhosis the mean patient age was 50.2 years (+/-11.2) and 59 (70.2%) were male (Table 6-1). Fifty-six (66.7%) individuals with cirrhosis lived in an area of social deprivation. Liver disease secondary to excessive alcohol intake was the most common cause of cirrhosis in this cohort and was found in 70 (83.3%) admissions.

In 68 (81.0%) individuals included in the study this was their first admission to ICU (Figure 6-1). The remaining 16 (19.0%) were readmissions to the unit within the same hospital stay and were excluded from survival analysis. No patient had previously been admitted to this ICU on a previous hospital admission. The mean ICU length of stay was 5 days (IQR 1-12.8) (Table 6-1).

Figure 6-1 Flowchart of patient recruitment



At the time of arrival to the ICU, 58 admissions (69.0%) were receiving mechanical ventilation, with pneumonia the most common diagnosis in 19 (22.6%) of all admissions with cirrhosis. ICU admissions were of varying aetiologies as outlined in Table 6-1.

Table 6-1 Demographics and clinical variables of 68 cirrhotics admitted to a general ICU

	All admissions (n=68)	Survivors at 12 months (n =30)	Non-survivors at 12 months (n=38)	p value
Age (mean +/- SD, range)	51.2 +/- 11.5, (29-80)	48.5 +/- 10.3, (29-64)	53.3 +/- 12.0, (32-80)	0.125
Male gender, n (%)	45 (66.2)	21 (70.0)	24 (63.2)	0.738
SIMD quintile, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.633
Social deprivation, n (%)	56 (82.4)	25 (83.3)	31 (8.6)	1
Alcohol-related disease, n (%)	55 (80.9)	24 (80.0)	31 (81.6)	1
Ventilated on admission, n (%)	52 (76.5)	25 (83.3)	27 (71.1)	0.369
ICU admission reason				0.141
Pneumonia/ARDS, n (%)	23 (33.8)	10 (33.3)	13 (34.2)	
GI Haemorrhage, n (%)	10 (14.7)	5 (16.7)	5 (13.2)	
Sepsis, n (%)	5 (7.6)	0 (0.0)	5 (13.2)	
Encephalopathy, n (%)	4 (5.9)	2 (6.7)	2 (5.3)	
GI perforation, n (%)	3 (4.4)	0 (0.0)	3 (7.9)	
Trauma/Burns, n (%)	5 (7.6)	3 (10.0)	2 (5.3)	
Decompensated cirrhosis, n (%)	3 (4.4)	0 (0.0)	3 (7.9)	
Seizures, n (%)	4 (5.9)	3 (10.0)	1 (2.6)	
Other[a], n (%)	7 (11.9)	4 (13.3)	3 (7.9)	
Drug related, n (%)	3 (4.4)	3 (10.0)	0 (0.0)	
Pancreatitis, n (%)	1 (1.5)	0 (0.0)	1 (2.6)	
Length of ICU stay (Days), median (IQR)	4.5 (1.0-12.0)	4 (1.25-12.0)	5 (1.0-8.8)	0.323
Sodium (mEq/L), median (IQR)	136.5 (132.0-142.0)	139.0 (135.0-142.8)	133.0 (131.0-140.0)	0.035
Potassium (mEq/L), median (IQR)	3.8 (3.5-4.4)	3.8 (3.5-4.2)	3.9 (3.5-4.7)	0.418
Urea (mmol/L), median (IQR)	8.1 (4.0-12.3)	6.0 (3.5-11.2)	9.2 (4.4-14.1)	0.112

	All admissions (n=68)	Survivors at 12 months (n =30)	Non-survivors at 12 months (n=38)	p value
Lactate (mmol/L), median (IQR)	2.0 (1.4-2.7)	1.5 (1.1-2.1)	2.4 (1.7-5.3)	0.003
Bilirubin (µmol/L), median (IQR)	47.5 (19.8-111.3)	25.5 (14.0-57.0)	74.0 (40.8-206.0)	<0.001
Creatinine (µmol/L), median (IQR)	81.0 (57.0-151.8)	71.5 (57.0-109.0)	131.5 (60.8-192.3)	0.080
White cell count ($\times 10^{-9}$/L), median (IQR)	12.4 (7.8-17.3)	13.5 (8.1-17.3)	10.4 (7.6-17.2)	0.422
Albumin (g/L), median (IQR)	20.5 (17.0-26.0)	24.0 (19.3-28.0)	18.0 (16.0-22.5)	0.001
PT ratio, median (IQR)	1.5 (1.2-2.1)	1.3 (1.1-1.5)	1.8 (1.5-2.5)	<0.001
Platelet count ($\times 10^{-9}$/L), median (IQR)	103.5 (75.8-164.3)	133.5 (93.8 – 186.8)	90.5 (59.3 - 132.3)	0.009
PaO_2/FiO_2 ratio (kPa), median (IQR)	21.8 (12.5-36.4)	29.3 (15.1-40.0)	18.0 (11.7-32.3)	0.342
Glasgow coma score, median (IQR)	10.0 (3.0-14.0)	9.0 (3.0-11.0)	11.0 (3.0-15.0)	0.333
Ascites, n (%)	27 (39.7)	7 (23.3)	20 (52.6)	0.012
Encephalopathy, n (%)	24 (35.3)	9 (30.0)	15 (39.5)	0.800

[a] Other includes urinary tract infection, renal failure, respiratory failure (not secondary to infection and does not meet criteria for ARDS), acute cholecystitis, biliary obstruction, diabetic ketoacidosis and post-cardiac arrest

6.5.2 Factors predictive of long-term survival

Following bivariate analysis, a number of factors were associated with survival at 12 months (Table 6-1). They included increased arterial lactate (p=0.003), serum bilirubin concentration (p<0.001), PT ratio (p<0.001), serum albumin (p=0.001), ascites (p=0.012), serum sodium concentration (p=0.035) and platelet count (p=0.009). No significant association was found between 12-month survival and an underlying aetiology of alcohol or social deprivation.

As readmission to ICU during the same hospital stay is both a subjective and multifactorial decision this was removed from further analysis. Multivariate

analysis revealed age (OR 1.09, 95% CI 1.03-1.15, p=0.002), arterial lactate on admission (OR 1.57, 95% CI 1.12-2.20, p=0.01), serum bilirubin on admission (OR 1.01, 95% CI 1.00-1.02, p=0.015) and PT ratio on admission (OR 4.82, 95% CI 1.38-16.82, p=0.014) were all significantly associated with long-term survival (Table 6-2).

Table 6-2 Factors predictive of mortality at 12 months following logistic regression analysis

	Odds ratio	95% confidence interval	p value
Age (years)	1.09	1.03, 1.15	0.002
Lactate (mmol L^{-1})	1.57	1.12, 2.20	0.010
PT ratio	4.82	1.38, 16.82	0.014
Bilirubin (µmol $L^{-1)}$	1.01	1.00, 1.02	0.015

6.5.3 Scoring systems and survival prediction

A number of existing scoring systems for survival prediction in critical illness and chronic liver disease were applied to this population. They included APACHE II, SOFA, CLIF-SOFA, SOFA-Lactate, Child-Pugh, MELD, UKELD, RFH and Child-Pugh + Lactate. All scoring systems were found to predict mortality at 12 months, with statistically significant values ($p<0.001$). The p value for Child-Pugh score was slightly higher but remained statistically significant (p=0.001). There were no significant differences between the scoring systems based upon 95% confidence intervals. Only two scoring systems had AUC of over 0.80, the threshold for clinical use. They were MELD (AUC=0.82, 95% CI 0.74-0.91) and Child-Pugh + Lactate (AUC=0.80, 95% CI 0.71-0.90) (Table 6-3).

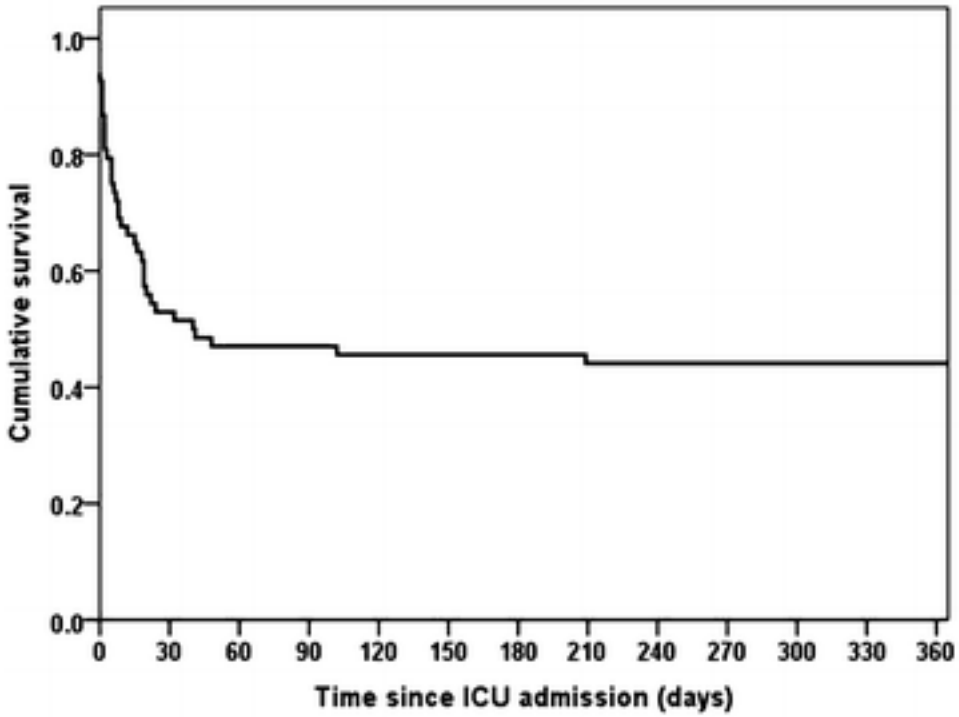
Table 6-3 Utility of scoring systems predicting 12-month outcome in patients with cirrhosis admitted to a general ICU

	Area under ROC curve	95% Confidence Interval
APACHE II	0.763	0.662, 0.864
SOFA	0.748	0.642, 0.855
CLIF-SOFA	0.782	0.684, 0.880
SOFA-Lactate	0.769	0.667, 0.871
Child-Pugh	0.718	0.609, 0.828
MELD	0.823	0.735, 0.911
UKELD	0.778	0.675, 0.882
RFH	0.779	0.679, 0.879
Child-Pugh + Lactate	0.804	0.712, 0.896

6.5.4 Long-term survival

Following removal of readmissions to ICU, the survival of 68 ICU admissions with cirrhosis was analysed. Twenty-four (35.2%) patients did not survive to ICU discharge and a further 12 (17.6%) died prior to hospital discharge. Following hospital discharge a further 2 (2.9%) patients died. Cumulative mortality at 12 months following ICU admission was 55.9% (Figure 6-2).

Figure 6-2 Kaplan-Meier curve of the survival of 68 patients admitted to a general ICU with cirrhosis



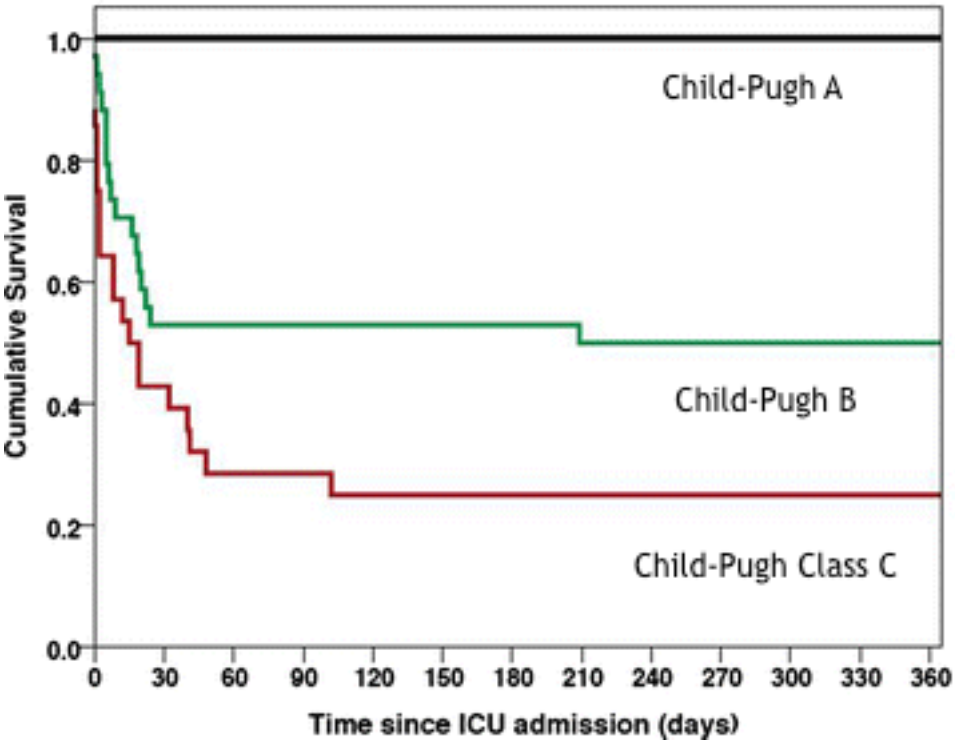
6.5.5 Child-Pugh and survivorship

Sixty-eight patients were grouped into Child-Pugh Class A, B and C based on their clinical and laboratory findings measured on arrival to ICU. Six (8.8%) patients were found to be Child-Pugh Class A, whilst the majority were Class B (34 patients, 50.0%) and Class C (28 patients, 41.2%) (Table 6-4). Kaplan-Meier curves for 12-month survival for each Child-Pugh Class were plotted and a significant difference (p=0.002) was found between the different grades (Figure 6-3). Mortality at 12 months was 0.0% for those in Child-Pugh Class A on ICU admission, 50.0% for those in Child-Pugh Class B and 75.0% in Child-Pugh Class C.

Table 6-4 Child-Pugh score on admission to ICU and survival

	Child-Pugh A (n=6)	Child-Pugh B (n=34)	Child-Pugh C (n=28)	p value
Alive at ICU discharge	6 (100.0%)	24 (70.6%)	14 (50.0%)	0.015
Alive at hospital discharge	6 (100.0%)	18 (52.9%)	8 (28.6%)	0.002
Alive at 12 months post admission	6 (100.0%)	17 (50.0%)	7 (25.0%)	0.001

Figure 6-3 Kaplan-Meier survival curve stratified by Child-Pugh class on ICU admission



6.6 Discussion

6.6.1 Interpretation of findings

6.6.1.1 Long-term mortality

This investigation represents one of the few studies in the literature that examines long term outcomes beyond 6 months in critically ill cirrhotics admitted to ICU and is the only UK study published from a non-transplant centre. In comparison to other studies, this cohort of patients had high levels of social deprivation and the majority had an underlying aetiology of alcoholic liver disease.

Recent studies in the literature suggest that both short and long-term survival for critically ill cirrhotics is improving. The ICU mortality in this study is comparable to other recent UK studies reporting ICU mortality to be 31-38% (120, 156). However, in our study only 41.2% were classified Child-Pugh C. In similar studies in the literature which examine the outcome of critically ill cirrhotics the incidence of Child-Pugh C is between 53-89% when scored on ICU admission (156). This may mean that the patients in our cohort had less severe

disease and as such lower mortality would be expected. Moreover, the mortality found in the present cohort is lower than the ICU mortality of patients with alcoholic liver disease admitted to all ICUs in Scotland between 2005 and 2010 (4). The higher mortality outlined by Lone et al. incorporated outcomes from all critical care units in Scotland, including a tertiary referral centre offering liver transplantation and excluded cirrhotics of non-alcoholic aetiologies (4). Our study did not show any association between survival and an underlying aetiology of alcoholic liver disease. This finding may have occurred due to the high incidence of underlying alcoholic liver disease in this cohort or reflect other research which fails to demonstrate a link between aetiology of alcohol and mortality (367).

Hospital mortality in this cohort is comparable to the conclusions of a meta-analysis of 13 studies published in 2017 (367). However, a recent large UK study of 31,363 ICU admissions of patients with cirrhosis demonstrated lower hospital mortality of under 50% (120). Without examining the details for each hospital death it is not possible to deduce the reasons behind the mortality differences. It would be helpful to explore whether cirrhotics who died in hospital were denied readmission to ICU, given limits to future intervention and whether mortality was due to acute illness or secondary to complications of chronic liver disease (117). Readmission to ICU was associated with survival in this cohort and there are a number of potential explanations for this finding. Firstly, there are no data to expose the number of discharges who deteriorated following ICU discharge and who were not readmitted to ICU due to perceived futility by clinicians or patient refusal, as explored in Chapter 3. Secondly, readmissions can incorporate patients who have potentially reversible complications from an intensive care stay such as the PICS (4). Thirdly, those who are readmitted have had a period of assessment in ICU, as such there is medical insight into disease reversibility and the physiological reserve of a patient which is lacking in the initial decision to admit a patient (117).

The 12-month mortality of 55.9% reported in this cohort of patients is consistent with other studies which conclude that the long-term survival of critically ill cirrhotics admitted to general ICUs is improving (367, 370). The overall improvement in mortality for critically ill patients is likely in part to medical advances, which include lung protective ventilation and prompt antibiotic

administration (371-373). Specific to cirrhotic patients are the improvements in use of interventions such as endoscopy and TIPS and efficacious use of pharmacological agents such as Terlipressin (129). It has been hypothesised that improved ICU survival may be due to changes in patient selection criteria, denying ICU admission to those least likely to survive (117). The improvement in survival may be due to trends in earlier referral to critical care or the introduction of goal-directed therapy (374).

In this study, mortality following hospital discharge decreased suggesting that cirrhotic patients who recover from their acute illness have good long-term survival. This finding reflects other contemporary studies in the literature (117, 371). It has been suggested that patient selection criteria for ICU admission may influence such results, with critical care offered only to those with good premorbid functional state or good physiological reserve with an improved chance of recovery (371).

6.6.1.2 Factors predictive of long-term mortality

Factors found to predict long-term mortality in this cohort of patients were age, serum lactate, bilirubin and PT ratio. Previous studies have demonstrated the predictive value of age in determining short and long-term mortality of critically ill patients, including those with cirrhosis (117). Age is incorporated into widely accepted and validated scoring systems used to measure disease severity and predict hospital mortality in the critically ill, such as APACHE II (163). It is now hypothesised that survival following ICU admission is predicted by different factors in two distinct phases (285). Short-term survival is determined by the acute illness and severity of organ failure, whilst age, chronic comorbidity and frailty have greater roles in predicting long-term survival (117, 285, 375). This may account for the predictive value of serum bilirubin and PT ratio found in this study, as both are recognised markers of severity of chronic liver disease. Indeed the significant association between liver function and long-term outcome has been recognised in a meta-analysis of 13 studies of cirrhotic patients published in 2017 (367).

Hyperlactataemia can result from excess lactate production due to tissue hypoxia and anaerobic metabolism or reduced clearance, evident in chronic liver

disease (376, 377). Raised serum lactate has been shown to correlate with mortality in those with sepsis, acute kidney injury and acute liver failure (377-380). Furthermore, serum lactate has been demonstrated to predict short-term mortality in cirrhotic patients (129, 154). However, this is the first study in the literature to find an association between serum lactate measured on ICU admission and long-term mortality. It may be that those individuals with raised lactate on admission to ICU represent a subgroup of patients with more severe chronic liver disease with reduced clearance of lactate.

6.6.1.3 Scoring systems to predict long-term mortality

All scoring systems analysed performed well in predicting long-term mortality and there was no significant difference between those designed for use in the critically ill population and those specific to liver disease. Both MELD and Child-Pugh+Lactate were found to have an AUC over the pre-determined threshold, although this is of limited use in clinical application (18, 142). A recent meta-analysis of studies exploring outcomes in critically ill cirrhotics concluded that scores incorporating measures of liver function such as MELD and CLIF-SOFA predicted mortality at 6 months (367).

When our cohort of patients was split into Child-Pugh group on admission there were statistically significant differences in long-term outcome. Whilst all patients graded Child-Pugh class A were alive at 12 months following admission, studies show the majority of patients with cirrhosis admitted to ICU are Child-Pugh class B or C (129, 156). Child-Pugh grading does not identify which patients within each class have the highest risk of short or long-term mortality. The limitations of Child-Pugh scoring have been discussed in detail in Chapter 4 and the ‘ceiling’ effect described in the literature fails to discriminate the severity of liver disease within the Child-Pugh class C patients (288). Those patients scoring a maximum of 15 points in their Child-Pugh score may experience further deterioration in their liver function, which would not be recognised by a change in Child-Pugh score. Results outlined in Chapter 4 found that the change in raw Child-Pugh score measured when a patient was clinically stable and at the time of ICU admission was associated with survival. Chapter 4 further discussed how the components of Child-Pugh score such as albumin and PT ratio may reflect critical illness rather than severity of liver disease (117).

The Child-Pugh+Lactate score, which was described in earlier work by our research group, had an AUC over the predefined threshold for clinical use (201). However, as previously explored in this thesis, this includes measurement of ascites and encephalopathy, which introduce subjectivity (18, 142). The MELD score was also demonstrated to have reached the threshold for clinical use in our study but its design in listing for liver transplantation does not facilitate classification of patients nor is it designed for use in critical illness (156).

6.6.2 Limitations

Whilst the conclusions of our study are limited to a small sample of patients from a single centre, it is one of the few studies to report survival at 12 months in patients admitted to a centre which does not offer tertiary hepatology services or liver transplantation. This study showed that those readmitted to ICU during the same hospital episode had improved survival. With no assessment of the criteria used to inform the decision to readmit it was not possible to conclude what factors were deemed relevant in this decision. As with the majority of similar studies within the literature, the number of critically ill cirrhotic individuals who were not referred or readmitted to ICU is unknown. It would be useful in any future study to determine the characteristics and survival of critically ill patients who were not admitted to ICU based on futility.

Within the group of patients admitted to ICU there was no consistent record of the proposed level of escalation of care, such as whether a patient would be offered renal replacement therapy. It is known that cirrhotics with renal failure have a poorer prognosis and it would be valuable to ascertain whether certain patients were not offered further intervention whilst in the ICU (127, 128).

To ascertain the performance of each scoring system on this population area under the ROC curves were utilised. Whilst it was beyond the scope of this thesis, the ROC curves could have been analysed further to identify cut-off values and be used as a ‘rule out’ test to determine survival. An alternative method would be to evaluate likelihood ratios to compare test performance. It has been suggested in the literature that likelihood ratios give greater insight into the ‘rule in’ or ‘rule out’ abilities of a test and are easier to interpret

clinically (137). Further, to test across ROC curves a DeLong or Venkatraman test could be utilised, however, this was beyond the scope of this thesis.

Whilst long-term mortality is an important outcome to measure when deciding whether to admit a patient to ICU, the morbidity of a patient following ICU survival is also of great importance. Individuals are known to experience physical and psychological deterioration following ICU stay (381). It would have been useful to know the QOL in those ICU survivors on admission to ICU, however, gaining baseline QOL prior to ICU admission is challenging. QOL is further explored in Chapter 7. In addition, inclusion of the comorbidities of critically ill cirrhotics would have been useful to determine whether concurrent chronic disease impacted upon long-term survival.

6.7 Conclusion

This chapter discusses the long-term survival of patients with chronic liver disease admitted to a UK general intensive care unit. The results illustrate:

- An ICU mortality of 35.2%, which is in keeping with contemporary studies, but lower than historical cohorts

- A decrease in mortality following hospital discharge suggesting that cirrhotic patients who recover from their acute illness have good long-term survival, with lower mortality at 12 months (55.9%) following ICU admission than many previous studies

- Long-term mortality was predicted by age, serum lactate, bilirubin and PT ratio

- No association with an underlying aetiology of alcoholic liver disease and long-term outcome

- Statistically significant differences in long-term outcome between different grades of Child-Pugh cirrhosis

- No statistically significant difference in scoring systems when used to predict long-term outcome

This chapter has explored long-term mortality as a primary outcome following ICU admission. However, the long-term morbidity and QOL experienced by patients following critical illness is of equal importance and is examined in the next chapter.

Chapter 7 Quality of life and sleep disturbance in critical illness survivors

7.1 Introduction

This chapter discusses QOL and insomnia in critical illness survivors, pertaining, in particular to those admitted to critical care with cirrhosis.

7.2 Quality of life

7.2.1 Defining quality of life

The WHO defined QOL in 1995 as an individual's "*perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*" (382). Defining QOL is complex with both subjective and objective facets (383). The WHO proposed 6 areas to be considered in measurement of QOL; physical functioning, psychological status, level of independence, social roles and relationships, environment and spirituality (382). However, other areas have been argued to impact upon QOL including work, usual activities and role functioning (384-386). QOL also encompasses negative aspects such as pain, dependence on medication, death and positive aspects such as role functioning, mobility and happiness (387). This research concerns health related QOL, focussing upon the impact of disease on an individual (388). A global assessment of health encompasses health status, level of function and QOL (388).

Measurement of QOL can be discriminative at a single time point, or evaluate changes over a period of time (388). Tools designed to measure QOL can provide an overall summary of health or focus upon a specific disease, patient cohort or functional domain (388). Assessment of QOL provides clinicians with invaluable information on the impact of a disease or treatment and can help predict both patient outcome and future health resource utilisation (389).

7.2.2 Quality of life following critical care admission

As the numbers of individuals surviving critical care increase, there has been a shift in focus towards the QOL of those who do survive (381, 390, 391). Critical

care survivors have subsequent high mortality and morbidity as a consequence of both their critical illness and the intensive treatment strategies required for survival (381). Whilst there is considerable variability, a significant proportion will suffer physical, psychological and cognitive deterioration following critical care admission (392). The term 'postintensive care syndrome' (PICS) was introduced in 2012 by expert consensus at the Society of Critical Care Medicine conference (393). PICS incorporated any new or worsening physical, psychological or cognitive impairment following critical illness (393). There was an appreciation of the impact of critical illness on caregivers with the term PICS-F adopted to describe this group of individuals (393).

Assessing change in QOL is challenging in the ICU population as many individuals will be admitted to critical care unexpectedly, with few studies measuring QOL prior to admission (381). Accurately assessing QOL in hindsight incurs challenges with risk of recall bias and change in patient perception (394). An American proxy study reported that use of a proxy to measure pre-hospitalisation QOL did not correspond well with patient responses in those admitted to critical care with respiratory failure (395).

Whilst many studies focus on QOL in those with specific diseases, studies reflecting the overall population of critical care survivors show QOL following critical care discharge is lower than the age and sex matched general population (396). In the majority of studies, critical care survivors show significantly lower scores across all domains contributing to QOL including physical and social functioning, mental health and role limitation (396-402). Despite the reduction in QOL noted following discharge for a large proportion of patients, one study noted 35% of critical care survivors had an improvement in QOL compared to their pre-admission baseline (397). Whilst deterioration in QOL may not persist for all survivors, few studies demonstrate any long-term improvements in both general and mental health (390, 398, 399, 403).

Measurement of QOL in subpopulations of critically ill survivors has demonstrated marked differences based upon underlying aetiology of disease. A 2010 systematic review of studies pertaining to QOL following intensive care revealed those admitted with ARDS, trauma and septic patients had the most

significant impairment to QOL in comparison to individuals surviving cardiac arrest, pancreatitis, acute kidney injury or oesophagectomy (404).

Studies have identified a number of demographic and clinical factors believed to influence QOL. Age impacts upon the deterioration in QOL, with older individuals perceiving less loss to QOL or adapting more successfully to the change in health or function, particularly if they are less socioeconomically deprived and have an established social network (405-407). However, as Montuclard et al. note in their study of 1888 critical care survivors aged over 70, there remains a selection bias in older individuals offered intensive care (405). Those with substantial comorbidity and poor existing QOL less likely to gain admission to the ICU. Pre-existing co-morbidity is known to influence both ICU and hospital survival (408). Change to QOL in critical care survivors is influenced by both pre-existing disease and functional status prior to hospital admission (406, 409, 410). Severity of injury in trauma patients requiring critical care is known to determine QOL, in addition to any surgical complications (411-413). Outwith the trauma population, severity of illness does not appear to influence change in QOL for critical care survivors (399, 414). It remains unknown which features of the critical care admission have the greatest influence on QOL. A number of studies have found that increasing length of mechanical ventilation and duration of stay predict QOL (406, 413, 415-417). However, this is not the case in studies focussing on ARDS patients (418, 419) where QOL is most influenced by the degree of pulmonary impairment, cognitive impairment and development of posttraumatic stress disorder rather than length of mechanical ventilation or stay (418, 419).

7.2.3 Quality of life in liver disease

In the literature QOL is described in patients with chronic liver disease, however, there are few studies of critical illness survivors with liver disease. A 2001 American study of 353 outpatients with chronic liver disease found their QOL was comparable to individuals with chronic obstructive pulmonary disease or congestive cardiac failure and lower than the general population (420). A 2001 Italian multicentre study measured QOL in 544 individuals with cirrhosis during hospital admission, following resolution of any acute illness or at outpatient appointment (421). In this population QOL was affected by

complications of disease such as pruritus, cramps and ascites, physical health, severity of liver disease and the number and type of medications (421). Aetiology of the liver disease was not found to affect QOL (421). Despite other studies, it remains unclear if the underlying aetiology of chronic liver disease can influence QOL (422). There is discussion within the literature of the effect on QOL of anxiety due to chronic viral disease or the emotional impact of ongoing alcohol intake (421). Subsequent QOL studies in those with liver disease in the USA, Spain, Sweden and Germany largely support the findings of Marchesini et al. and have concluded hypoalbuminaemia, anaemia and comorbidities also contribute to a reduction in QOL (420, 423-426). However, in results that conflict with the Italian study, a study of 203 individuals attending a German tertiary referral centre reported that severity of liver disease as measured by Child-Pugh did not correlate with QOL (425). It has been hypothesised that individuals diagnosed with chronic disease adapt their expectations for QOL with disease progression which they term 'response shift' (427).

In the Marchesini et al. study, individuals with liver disease scored lower in all domains measured by the 36-Item Short Form Survey (SF-36) and Nottingham Health Profile (NHP) QOL questionnaires, with the exception of pain, when compared with the normal Italian population (421). The greatest differences were observed in the physical and emotional role limitation and general health (421). Córdoba et al. in their study of Hepatitis C, noted some deterioration in all domains of the SF-36 except emotional role and mental health (423). Younossi et al. also found as the severity of liver disease increased, the physical and disease-specific domains of the SF-36 declined but mental health did not deteriorate (420). Despite small differences between studies in the significance of certain domains measured to assess QOL in those with chronic liver disease and cirrhosis, there is universal agreement in the deterioration of QOL as compared to the normal population.

7.2.4 Sleep and quality of life

Sleep fulfils an important role in in the cognitive, psychological and physiological recovery of a critically unwell individual (428, 429). Within the ICU, sleep can be disrupted by environmental factors such as light and noise coupled with patient

factors including underlying medical disease, existing sleep disorders and the psychological upset caused by critical illness (429). Survivors of critical illness are known to have impaired sleep patterns, although the underlying cause of this is likely to be multifactorial (428). Few long-term studies examine changes to sleep patterns in critical care survivors. However, it is hypothesised that persistent insomnia is related to age and pre-existing comorbidities rather than events during the ICU stay (430). Adequate quantity and quality of sleep is an important contributor to QOL, with insomnia proven to reduce QOL (431, 432).

Orwelius et al. investigated sleep disturbance in a population of 497 Swedish critical care survivors at 6 and 12 months following hospital discharge (430). Compared to a reference group taken from a Swedish public health survey, the critical illness survivors described problems falling asleep, impaired quality of sleep and frequent wakening (430). The authors excluded patients over the age of 74 as these individuals were not present in the reference group (430). It was reported that up to 38% of critical care survivors had sleep disturbance at 12 months following discharge, compared to a prevalence of between 16-19% in a reference cohort (430). The group of survivors reported reduced QOL in domains of pain, mental health, physical limitations, general health and vitality (430). This study was limited to patients and a reference group from a specific area of Sweden and as the authors identify, the choice of reference group used in the study prevented comparison by comorbidity (430). Given the methods used by the authors, an element of recall bias may be present when patients reported sleep history (430). A Portuguese study of 464 critical care survivors from 10 ICUs found 41% had ongoing sleep disturbance and decreased QOL in all domains measured at 6 months following ICU discharge (433). Whilst QOL and sleep disturbance was measured by a postal questionnaire, some patients were also engaging with critical care by attending an ICU follow-up clinic. One questionnaire used within the Portuguese study to measure recollection, stress and sleep disturbance was designed by one of the authors and had not been tested for face or content validity, as such the answers may be subject to bias (433). Léger at al. found that those in the general population suffering from severe insomnia also described greater pain, impacting upon QOL (434).

Whilst sleep disturbance has been investigated in survivors of critical illness, there appear to be a lack of studies in those admitted to critical care with

cirrhosis. Outwith the critical care population, an association between sleep impairment and chronic liver disease is well recognised (435). Sleep disturbance is reported to be more prevalent in those with cirrhosis compared to the general population or those with other chronic diseases such as renal failure (436). In the UK general population the prevalence of insomnia is reported to be between 10-48% (437, 438). An American study of insomnia in 3445 individuals with chronic illnesses including previous myocardial infarction and diabetes found 16% had severe insomnia and 34% had mild insomnia (439). Changes in sleep may herald the development of hepatic encephalopathy, however, sleep disturbance is frequently reported in cirrhotics without hepatic encephalopathy and is thought to result from changes to circadian rhythm (436). In those without encephalopathy the prevalence of sleep disturbance is reported to be around 35% (436). Specific aetiologies of chronic liver disease are linked to fatigue, such as primary biliary cirrhosis and Hepatitis C (435). Furthermore, sleep disturbances may occur as a side-effect of treatment such as antiviral medications (435).

7.2.5 Questionnaires used to measure quality of life

Questionnaires exist which have been used to measure QOL in studies of critical care patients admitted to intensive care (Table 7-1). There is no gold standard questionnaire specifically designed for, or utilised within, this population to measure QOL. In response to this the 2002 Brussels Roundtable event gathered expert opinion to discuss survival after intensive care and it was recommended that QOL should be measured using either the 36-Item short form survey (SF-36) or the Euroqol Five Dimensions (EQ-5D) (391).

There has been a recent move towards the use of core outcome sets (COS) in critical care research. A COS consists of an agreed set of tools for outcome measurement in a population and should guide any future research in a particular field (440). A study investigating the use of a COS in physical rehabilitation after critical illness published after the study within this thesis, supports the use of the SF-36 and the EQ-5D in measuring QOL in survivors of critical illness (441). Further a COS published for research into survivors of acute respiratory failure recommended that either the EQ-5D or SF-36 should be used to measure QOL (442).

Table 7-1 Questionnaires to measure QOL

Questionnaire	Year	Country	Domains
EuroQol Five Dimensions (EQ-5D) **(384)**	1990	Europe (UK, Netherlands, Sweden, Finland, Norway)	5 Domains • Mobility • Self-care • Activity • Social Relationship • Pain • Mood
36-Item Short Form Survey (SF-36) **(385)**	1992	USA	8 Domains • Vitality • Physical Function • Bodily Pain • General Health Perception • Physical role functioning • Emotional role functioning • Social role functioning • Mental Health
Nottingham Health Profile (NHP) **(443)**	1981	UK	Part 1 – 6 Domains • Mobility • Pain • Sleep • Energy • Emotion • Social Isolation Part 2 – 7 Domains • Occupation • Housework • Social Activity • Sex life • Home life • Hobbies • Holidays
Sickness Impact Profile (SIP) **(386)**	1981	USA	12 Domains • Work • Recreation • Emotion • Alertness • Sleep • Home management • Self-care • Eating • Ambulation • Mobility • Communication • Social Interaction

7.2.6 EuroQol Five Dimensions

The EQ-5D consists of a descriptive system in which respondents rate each of the 5 domains by severity and an EQ VAS – a visual analogue scale. There are three current versions of the EQ-5D – the EQ-5D-3L, EQ-5D-5L and EQ-5D-Y. In the EQ-5D-3L respondents rate each of the 5 domains into one of 3 levels of severity - ‘ 1 - no problems’ ‘ 2 - some problems’ or ‘ 3 - extreme problems’, in the EQ-5D-5L there are 5 levels of severity and the EQ-5D-Y was designed for use in children. The rating of each domain results in a number which when combined with the ratings for all 5 domains provides a 5 digit number which defines the respondent’s current state of health. The EQ VAS provides a vertical scale from 0 ‘the worst health you can imagine’ to 100 ‘the best health you can imagine’ and respondents are asked to place a mark on the scale.

The EQ-5D-3L and the EQ VAS were used for this study, with permission from the EuroQol research foundation. The project was registered on the EuroQol Research Foundation Website.

In addition to the COS recommendation, this questionnaire provided a number of advantages (442). The EQ-5D has been validated in a UK population, it is straightforward, enabling self-reporting and brief to complete, with the advantage of a visual analogue scale should participants be unable to understand individual questions.

7.2.7 Measurement of insomnia

With a paucity of studies investigating insomnia in critical care survivors, there are no recognised tools specifically designed to enable self-reported measurement of quality of sleep in this population. Existing studies have used the Basic Nordic Sleep Questionnaire, the 15D instrument of health-related QOL and the Insomnia Severity Index (ISI) (430, 444, 445). The ISI was used in this study due to previous use in critical care survivors, ease of use and because it is designed take less than 5 minutes to complete and less than 1 minute to score (445).

The ISI was designed to enable self-measurement of insomnia and the impact that sleep disturbance has on the respondent (445). The questionnaire reflects the recognised diagnostic criteria for insomnia outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) produced by the American Psychiatric Association. The questionnaire has 5 domains examining severity of insomnia, sleep satisfaction, interference with daily function, how noticeable sleep impairment is to those in contact with the respondent and how worried the respondent is about their sleep impairment (445). Each domain is scored from 0 to 4 with a maximum score of 28 (445). A score of 15 indicates clinical insomnia whilst a score of 22 suggests a diagnosis of severe clinical insomnia (445).

7.3 Study question and aims

7.3.1 What is the long-term quality of life of patients who survive intensive care?

With improvements in survival, QOL following intensive care stay is considered to be one of the most important long-term outcomes. Sleep is known to contribute to QOL but research into sleep disturbance following ICU discharge is lacking. Moreover, little is known about the QOL and sleep in the subgroup of critical illness survivors with cirrhosis. Determining the long-term QOL and prevalence of insomnia in survivors of critical illness could inform patients about recovery following discharge and facilitate targeted interventions if QOL or sleep were found to be impaired.

7.3.2 Aims

In a cohort of ICU survivors:

- To identify the long term QOL
- To identify factors which predict a reduction in QOL
- To explore any relationship between QOL and cirrhosis
- To determine the prevalence of insomnia

- To identify factors which predict long term sleep disturbance

- To explore any relationship between long term sleep disturbance and cirrhosis

7.4 Methodology

7.4.1 Design

This observational cohort study was performed by postal distribution of 2 questionnaires – the EQ-5D and the ISI (384, 445). The EQ-5D and ISI questionnaires were delivered together in May 2015.

A postal questionnaire was chosen as it enabled the participants to complete the questionnaires at a convenient time, whilst telephone or face-to-face interviews may have improved response rates this was not possible due to time constraints. Email addresses are not stored with the hospital medical records so distribution via the internet was not feasible. To improve the response rate, respondents were supplied with a stamped addressed envelope and both a reminder and questionnaires were posted 6 weeks later to individuals who had not returned the original questionnaire (446). Participant information sheets and questionnaires were short, examined for readability and straightforward to complete (446). Study information outlined the purpose of the study and that any information would be used for non-commercial research (446). Prior to ethical approval, both the participant information sheet and questionnaires were reviewed by former patients and members of the public attending an ICU follow-up clinic (354). This review ensured both the readability and clarity of documentation, whilst confirming that aspects of the study including conduct and subject matter were appropriate.

7.4.2 Participants

Participants had been admitted for Level 3 care at the GRI (section 2.1.4) between June 2012 and December 2013. Clinical and demographic data for this prospective cohort had been recorded, analysed and published for a study which investigated whether alcohol use disorders were associated with long term

survivorship outcomes in intensive care survivors and published in Critical Care in 2015 (187). Of this cohort 34.4% had been identified as having an alcohol use disorder. The study for this thesis concerned only the survivors of this cohort (irrespective of whether they had an alcohol use disorder or not) and assessed the different outcomes of QOL and insomnia.

All patients in the existing database were screened using NHS Greater Glasgow and Clyde electronic patient record to ensure that they were alive, identify a fixed address and determine issues related to consent before the postal survey was distributed. Those excluded from the study included those with no fixed address recorded, address within prison or a medical condition incompatible with informed consent such as those with severe learning difficulties or dementia.

Previous studies at this centre have defined deprivation as the lowest 2 deciles of the SIMD (SIMD 1 and 2) and to facilitate comparison the same definition was utilised in this investigation (187).

7.4.3 Ethics

This research was approved by the East of Scotland Research Ethics Service on 22 May 2015 (REC reference: 15/ES/0084, Chair: Dr Carol Macmillan).

There were a number of ethical issues in this study identified by the MD student. Correct identification of the participant's address relied upon accurate medical records and whilst the letter was addressed to the former patient there was no guarantee that the letter would not be opened by another individual. To reduce potential for harm no clinical or demographic information was included on the patient information with the exception of a statement that the individual had been a former patient. A contact telephone number for the research team was provided should the recipient have wished to discuss the research in further detail.

7.4.4 Statistical analysis

Bivariate analysis was performed to determine whether there were any relationships between measured variables, the presence of cirrhosis, QOL or insomnia. Normally distributed data were assessed using the independent t-test and presented as mean and standard deviation. Data found to be non-parametric were assessed using the Wilcox and the Kruskal-Wallis tests and described as median and IQR. Proportions were compared using the Chi-squared test and Fisher's exact test for association.

A boxplot was used to demonstrate the distribution of Health Utility Scores for those with and without clinical insomnia. It enabled comparison between the 2 populations and identification of outliers.

Multivariate analysis was performed to examine the relationship between multiple variables and 16 incomplete records were removed during this analysis. Two prediction models were created; one for health utility score (HUS) to predict QOL and another for insomnia. ANOVA was used to compare both forwards and backwards stepwise linear regression models to assess the relationship between clinical variables and health utility scores. An R^2 value was used to assess how well the final prediction model fitted the data. As insomnia was measured as a categorical variable a logistic regression model was used to assess the relationship between independent clinical variables and insomnia. Results were expressed in terms of OR and 95% CI. The Wald statistic was used to determine how well the data fitted the final model.

A Fisher's exact test for count data was used to examine for a difference in the proportions of those with cirrhosis and without cirrhosis and the prevalence of clinical insomnia.

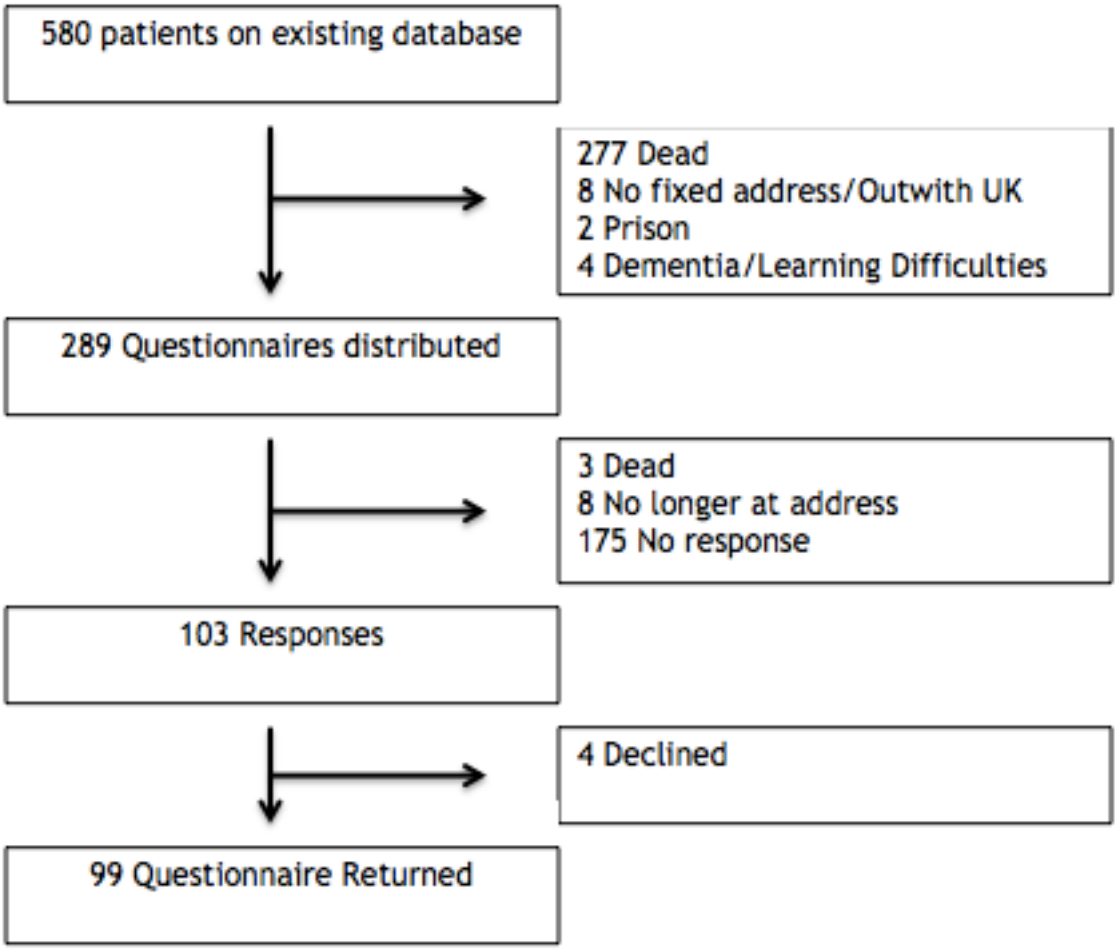
7.5 Results

7.5.1 Demographics

Five hundred and eighty patients were screened using NHS Greater Glasgow and Clyde electronic patient record from the existing database (section 7.4.2) (Figure 7-1). Two hundred and seventy-seven individuals had died since inclusion

in the database, 8 had no fixed address or lived outwith the UK making them ineligible for a postal questionnaire. Two patients were in prison and 4 patients were noted to have a medical condition, which could impact upon informed consent, making them ineligible on ethical grounds. Two hundred and eighty-nine ICU survivors were therefore sent out both the EQ5 questionnaire and ISI questionnaire (Figure 7-1). Eight survivors were no longer at their recorded address and the questionnaires were returned and 4 survivors responded but declined participation. Three patients had died which had not been noted on their medical records and 175 individuals did not respond to the questionnaires. Ninety-nine respondents returned their questionnaires completed, which was a response rate of 37.1%.

Figure 7-1 Flowchart of participant recruitment



The median time for questionnaire completion following ICU discharge was 862 days (IQR 719-954) (Table 7-2). Respondents ranged in age from 22 to 85, with a mean age of 55.8 years. Male gender accounted for 55.6% of respondents and

49.5% of respondents resided in the lowest 2 deciles of the SIMD and were considered socially deprived (Table 7-2).

In the initial database of 580 admissions, 34.4% were noted to have an alcohol use disorder, with 17.0% assessed as harmful or hazardous intake of alcohol and 17.4% noted to be alcohol dependent (187). Of the 99 respondents to this study, 32.3% had an alcohol use disorder with 13.1% noted to have harmful or hazardous alcohol use and 19.2% were considered to be alcohol dependent at the time of ICU admission.

The majority of respondents (65.7%) had been admitted to ICU with a surgical diagnosis, with the remaining 34.3% admitted with an underlying medical diagnosis. Direct admission from the ED accounted for 34.3% of respondents, whilst 27.3% were referred from the ward, 25.3% from theatre and 13.1% from another hospital. On admission the median APACHE II score was 17.5 (IQR 14.0-22.3). 52.5% of respondents had been diagnosed with sepsis during their ICU admission, with 19.2% diagnosed with septic shock. Only one respondent did not receive mechanical ventilation during their ICU admission, with the remaining 98 survivors receiving mechanical ventilation for a median duration of 3 days (IQR 2.0-7.0). The median length of stay in the ICU was 4 days (IQR 2.0-9.0) and the median hospital length of stay was 22 days (IQR 9.5-44.5).

Fifteen individuals with a diagnosis of cirrhosis were identified within the cohort of respondents (Table 7-2). This group had a mean age of 49 years (34-64), 11 were male (73.3%), 8 respondents (53.3%) were deprived and resided within the lowest 2 deciles of the SIMD. There was a significant difference in the prevalence of alcohol use disorders between respondents with cirrhosis on ICU admission and those without ($p=<0.01$). On admission to ICU, 66.7% of respondents with cirrhosis had an alcohol dependency, compared to 10.7% of respondents without cirrhosis. Of respondents with cirrhosis on ICU admission, the median APACHE II score was 20 (IQR 16.0-23.5) and the median duration of mechanical ventilation was 5.5 days (IQR 2.0-12.5). There was a significant difference in the number of days those with cirrhosis required inotrope therapy compared to those without cirrhosis ($p=0.01$). Respondents with cirrhosis on ICU admission had a longer ICU length of stay ($p=0.02$) and hospital length of stay ($p=0.04$).

Table 7-2 Demographics of 99 respondents to EQ5 and ISI questionnaires

	All patients (n=99)	Cirrhosis on admission to ICU (n= 15)	No cirrhosis on admission to ICU (n=84)	p value
Age, mean (range)	55.8 (22.0-85.0)	49.3 (34.0-64.0)	56.9 (22.0-85.0)	0.03
Male gender, n (%)	55.0 (55.6)	11.0 (73.3)	44.0 (52.4)	0.22
SIMD decile, median (IQR)	2.0 (1.0-7.0)	1.0 (1.0-6.5)	2.0 (1.0-7.0)	0.45
Social deprivation, n (%)	49.0 (49.5)	8.0 (53.3)	41.0 (48.8)	1
Alcohol, n (%)				<0.01
No use/low use	67.0 (67.7)	4 (26.7)	63.0 (75.0)	
Harmful/hazardous use	13.0 (13.1)	1 (6.7)	12.0 (14.3)	
Dependency	19.0 (19.2)	10 (66.7)	9.0 (10.7)	
Source of ICU Admission, n (%)				0.45
Emergency Department	34.0 (34.3)	9 (60.0)	25.0 (29.8)	
Ward	27.0 (27.3)	4 (26.7)	23.0 (27.4)	
Theatre	25.0 (25.3)	1 (6.7)	24.0 (28.6)	
Other Hospital	13.0 (13.1)	1 (6.7)	12.0 (14.3)	
Admitting specialty, n (%)				0.45
Medical	34.0 (34.3)	11.0 (73.3)	23.0 (27.4)	
Surgical	65.0 (65.7)	4.0 (26.7)	61.0 (72.6)	
APACHE II score, median (IQR)	17.5 (14.0-22.3)	20.0 (16.0-23.5)	17.0 (14.0-22.0)	0.19

	All patients (n=99)	Cirrhosis on admission to ICU (n= 15)	No cirrhosis on admission to ICU (n=84)	p value
Sepsis, n (%)	52.0 (52.5)	7.0 (46.7)	45.0 (53.6)	0.45
Septic shock, n (%)	19.0 (19.2)	2.0 (13.3)	17.0 (20.2)	0.79
Days ventilated, median (IQR)	3.0 (2.0-7.0)	5.5 (2.0-12.5)	3.0 (2.0-5.0)	0.13
Renal replacement therapy (RRT), n (%)	12.0 (12.1)	3.0 (20.0)	9.0 (10.7)	0.56
Days RRT, median (IQR)	3.0 (1.6-6.8)	1.0 (1.0-7.5)	4.0 (2.0-6.0)	0.40
Inotrope therapy, n (%)	48.0 (48.5)	8.0 (53.3)	40 (47.6)	0.90
Days inotropes, median (IQR)	2.5 (2.0-4.0)	4.5 (3.8-6.5)	2.0 (2.0-3.0)	0.01
ICU length of stay (Days), median (IQR)	4.0 (2.0-9.0)	9.0 (3.0-14.5)	3.0 (2.0-8.0)	0.02
Hospital length of stay (Days), median (IQR)	22.0 (9.5-44.5)	38.0 (21.0-64.0)	17.5 (9.0-41.0)	0.04
Length of time to follow up (Days), median, IQR	862.0 (719.0-954.0)	898.0 (724.0-989.5)	859.5 (715.2-924.8)	0.34

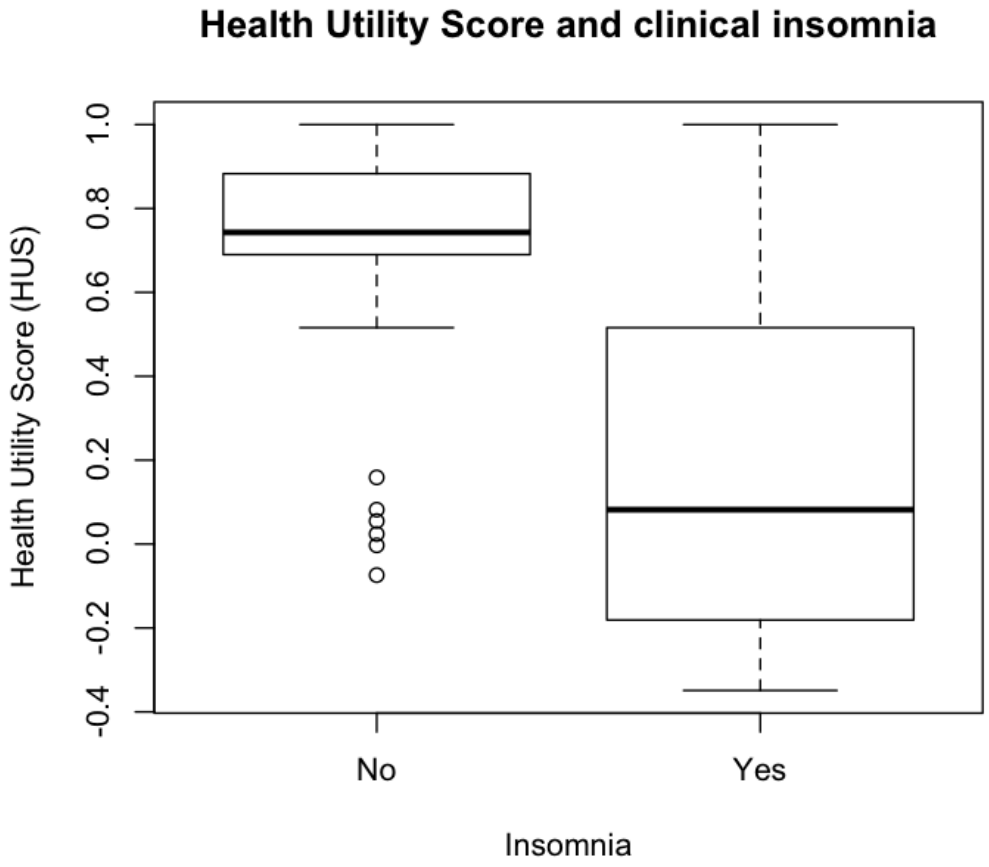
7.5.2 Quality of life

The median health utility score (HUS) reported by the respondents was 0.66 (IQR 0.08 to 0.81). Sixteen respondents (16.2%) indicated an HUS of less than 0, which denotes a QOL less than or equal to death. In those respondents diagnosed with cirrhosis on admission to ICU the median HUS was 0.62 (IQR 0.05 to 0.71). Two of these respondents (13.3%) reported a HUS of less than 0.

The median HUS in patients with clinical insomnia was 0.08 (IQR -0.18 to 0.52) and 0.74 (IQR 0.69 to 0.88) in those without clinical insomnia, which was a

significant difference (p<0.001). Increased ISI score was associated with low HUS (p<0.001) and the distribution of scores for those survivors with and without clinical insomnia is shown in Figure 7-2.

Figure 7-2 Boxplot to show the distribution of Health Utility Scores in 99 critical care survivors for those with and without clinical insomnia



In this group of ICU survivors poor HUS was associated with smoking (p=0.003) and the presence of social deprivation (p=0.02). Furthermore, a low HUS was associated with the following clinical factors; requirement for mechanical ventilation (p<0.001), inotrope therapy (p=0.02), renal replacement therapy (p=0.03), length of stay in ICU (p<0.001) and length of stay in hospital (p=0.01). There was no association between a diagnosis of liver cirrhosis and HUS in this cohort (p=0.46).

Multivariate analysis was performed following the removal of 16 questionnaires as they were only partially completed. ISI score (p<0.01), length of stay in hospital (p=0.03) and requirement for renal replacement therapy (p=0.04) were

independently associated with a lower HUS. Although smoking (p=0.09) and inotrope therapy (p=0.16) were not significantly associated with a lower HUS on multivariate analysis, a prediction model for HUS in this cohort inclusive of ISI score, hospital length of stay, renal replacement therapy, smoking and inotrope therapy was significant ($p<0.05$, adjusted $R^2=0.59$) (Table 7-3).

Table 7-3 Model to predict health utility score

	Non-adjusted model			Adjusted model		
Factor associated with HUS	Estimate	p value	95% Confidence Interval	Estimate	p value	95% Confidence Interval
Smoker	- 0.1173	0.08	-0.2513,1.6571	-0.1079	0.09	-0.2327,0.0169
Presence of social deprivation	0.0314	0.63	-0.0990,1.6174	-	-	
Admission under medical specialty	0.0008	0.44	-0.0013,2.9405	-	-	
Duration of mechanical ventilation (Days)	- 0.011	0.56	-0.0481,2.6295	-	-	
Use of Inotrope Therapy	- 0.0918	0.17	-0.2232,3.9580	-0.089	0.16	-0.2138,0.0361
Use of Renal Replacement Therapy	- 0.1756	0.07	-0.3644,1.3176	-0.1836	0.04	-0.3602,0.007
ICU length of stay (Days)	0.0009	0.60	-0.0260,4.4518	-	-	
Hospital length of stay (Days)	-0.0018	0.05	-0.0035,3.1646	-0.0018	0.03	-0.0034-0.0002
Total Insomnia Severity Index Score (ISI)	- 0.0287	<0.01	-0.0367,2.0628	-0.0281	<0.01	-0.0351-0.0211

7.5.3 Prevalence of insomnia

The median ISI score amongst all respondents was 10 (IQR 4-18) (Table 7-4). Forty-one survivors had an ISI score of 7 or less, with the remaining 58 survivors scoring between 8 and 28. Thirty-seven respondents (37.4%) reported clinical insomnia.

Of the 15 respondents with cirrhosis, the median ISI score was 18 (IQR 7-22) compared to a median score of 9 (4-17) in those without cirrhosis. This difference was not statistically significant.

Eight respondents (53.3%) with cirrhosis on ICU admission had clinical insomnia, compared to 29 (34.5%) respondents without cirrhosis. Those with cirrhosis were found to have an increased incidence of clinical insomnia (OR 2.15 CI 0.61-7.74) although this difference was not statistically significant (p=0.27).

Table 7-4 Prevalence of self-reported insomnia in 99 critical care survivors

	All respondents (n = 99)	Respondents with cirrhosis (n = 15)	Respondents without cirrhosis (n = 84)	p value
Median ISI score (IQR)	10 (4-18)	18 (7-22)	9 (4-17)	0.11
No insomnia (ISI 0-7), n (%)	41 (41.1)	5 (33.3)	36 (42.9)	
Sub-threshold insomnia (ISI 8-14), n (%)	21 (21.2)	2 (13.3)	19 (22.6)	
Moderate insomnia (ISI 15-21), n (%)	24 (24.2)	4 (26.7)	20 (23.8)	
Severe insomnia (ISI 22-28), n (%)	13 (13.1)	4 (26.7)	9 (10.7)	
Clinical insomnia, n (%)	37 (37.4)	8 (53.3)	29 (34.5)	0.27

7.5.4 Severity of insomnia

Analysis of the responses revealed the majority of respondents reported dissatisfaction with sleep (86.8%), early morning wakening (65.7%) and belief that their poor sleep impacted upon their ability to perform daily activities (60.6%) (Table 7-5). Over half of respondents indicated that other individuals had noticed problems with their sleep (66.7%) and most respondents had problems staying asleep (50.4%), difficulty falling asleep (58.5%) and were worried about sleep problems (53.5%). Fifty-two respondents (52.5%) reported sleep disturbance on more than 3 nights per week.

Respondents with cirrhosis reported more severe insomnia symptoms in all of the categories covered by the ISI, however, no significant differences were found (Table 7-5). In particular, 73.3% of those respondents reported sleep disturbance on more than 3 nights per week, compared to 48.8% of those without cirrhosis.

Table 7-5 Self-reported insomnia and cirrhosis in 99 critical care survivors

Self-reported insomnia symptom	All respondents (n = 99)	Respondents with cirrhosis (n = 15)	Respondents without cirrhosis (n = 84)
Dissatisfaction with sleep			
None n (%)	12 (12.1)	1 (6.7)	11 (13.1)
Mild/Moderate n (%)	42 (42.4)	5 (33.3)	37 (44.0)
Severe/Very Severe n (%)	44 (44.4)	9 (60.0)	35 (41.7)
Early wakening			
None n (%)	19 (19.2)	3 (20.0.)	16 (19.0)
Mild/Moderate n (%)	39 (39.4)	4 (26.7)	35 (41.7)
Severe/Very Severe n (%)	26 (26.3)	6 (40.0)	20 (20.2)
Impact on activities of daily living			
None n (%)	28 (28.3)	2 (13.3)	26 (31.0)
Mild/Moderate n (%)	28 (28.3)	7 (46.7)	21 (25.0)
Severe/Very Severe n (%)	32 (32.3)	6 (40.0)	26 (31.0)
Notability of sleep problem			
None n (%)	33 (33.3)	2 (13.3)	31 (36.9%)
Mild/Moderate n (%)	35 (35.4)	6 (40.0)	29 (34.5)
Severe/Very Severe n (%)	31 (31.3)	7 (46.7)	24 (28.6)

Self-reported insomnia symptom	All respondents (n = 99)	Respondents with cirrhosis (n = 15)	Respondents without cirrhosis (n = 84)
Difficulty staying asleep			
None n (%)	26 (26.3)	2 (13.3)	24 (28.6)
Mild/Moderate n (%)	22 (22.2)	3 (20.0)	19 (22.6)
Severe/Very Severe n (%)	28 (28.2)	7 (46.7)	21(25.0)
Difficulty falling asleep			
None n (%)	34 (34.3)	3 (20.0)	31(36.9)
Mild/Moderate n (%)	34 (34.3)	6 (40.0)	28 (33.3)
Severe/Very Severe n (%)	24 (24.2)	5 (33.3)	19 (22.6)
Worry about sleep problem			
None n (%)	45 (45.5)	5 (33.3)	40 (47.6)
Mild/Moderate n (%)	30 (30.3)	5 (33.3)	25 (29.8)
Severe/Very Severe n (%)	23 (23.2)	5 (33.3)	18 (21.4)
Sleep disturbance			
Never (0 nights/week)	24 (24.2)	2 (13.3)	22 (26.2)
Occasional (1-3 nights/week)	22 (22.2)	2 (13.3)	20 (23.8)
Frequent (>3 nights/week)	52 (52.5)	11 (73.3)	41 (48.8)

7.5.5 Factors which predict long term sleep disturbance

In this study, clinical insomnia in ICU survivors was associated with smoking (p<0.001) and social deprivation (p=0.001). Clinical insomnia was associated with longer duration of mechanical ventilation (4 days versus 2.5 days, p=0.04) and longer length of stay in the ICU (5 days versus 3 days, p=0.02). Bivariate analysis revealed no association between severity of insomnia and inotrope requirement, vasopressor use or severity of illness on ICU admission. There was no association between a diagnosis of liver cirrhosis and clinical insomnia in ICU survivors (p=0.27). Following multivariate analysis smoking was associated with a threefold increased odds of clinical insomnia (OR 3.74 95% CI 1.27,11.4; p=0.02).

Table 7-6 Adjusted logistic regression model for insomnia

Factor associated with insomnia	Odds ratio	95% Confidence Interval for the Odds ratio	p value
Smoking	3.74	1.27,11.4	0.02
Presence of social deprivation	2.90	0.97,8.95	0.06
Duration of mechanical ventilation (Days)	1.18	0.85,1.69	0.33
ICU length of stay (Days)	0.93	0.67,1.26	0.64

7.5.6 Comorbidities

In addition to liver cirrhosis, which was of particular relevance to this thesis, other pre-existing comorbidities were noted for each respondent (Table 7-7). Hypertension was the most common comorbidity (25.3%) whilst other co-morbidities evident were mental health problems (19.2%), diabetes (12.1%) and obesity (11.1%). The median number of comorbidities was 1 (IQR 0-2), however, 3 patients were noted to have 5 pre-existing conditions and 1 patient had 6 pre-existing conditions recorded on admission to the ICU. In this group the number of comorbidities was found to be significantly associated with clinical insomnia (p=<0.01) and HUS (p=0.03). An association was found between poorer QOL in

ICU survivors and diagnoses of mental health problems (p=0.01), peripheral vascular disease (p=0.03) and cerebrovascular disease (p=0.03).

Table 7-7 Prevalence of comorbidities in 99 critical care survivors

Disease	n(%)
Hypertension	25 (25.3)
Mental Health	20 (20.2)
Diabetes	12 (12.1)
Obesity	11 (11.1)
Chronic Obstructive Pulmonary Disease	10 (10.1)
Rheumatological/Dermatological Disease	8 (8.1)
Ischaemic Heart Disease	7 (7.1)
Cerebrovascular Disease	7 (7.1)
Pancreatitis	7 (7.1)
Malignancy	7 (7.1)
Asthma	6 (6.1)
Thromboembolism	5 (5.1)
Inflammatory Bowel Disease	5 (5.1)
Atrial Fibrillation	4 (4.0)
Peripheral Vascular Disease	2 (2.0)
Hepatitis C Virus	2 (2.0)
Hepatitis B Virus	1 (1.0)

7.6 Discussion

As far as can be established, this is the first report into insomnia and long-term QOL in critical illness survivors in the UK. Long-term QOL reported in this study is comparable to similar studies performed in the UK, however, a notable number of individuals in this cohort rated their QOL as comparable to, or worse than death. Poor long-term QOL was found to be associated with smoking, social deprivation, mechanical ventilation, inotrope therapy, renal replacement therapy, ICU length of stay and hospital length of stay. In this cohort of respondents clinical insomnia was associated with smoking, social deprivation, longer duration of mechanical ventilation and longer ICU length of stay. In addition, the number of pre-existing comorbidities was associated with both poor QOL and insomnia. Although the number of individuals with cirrhosis was small the results suggest there may be a relationship between a diagnosis of cirrhosis and an increased incidence of clinical insomnia, although this relationship was not found to be significant.

7.6.1 Interpretation of findings

7.6.1.1 The impact of cirrhosis on long-term quality of life and sleep

In this study, QOL in those with liver cirrhosis was comparable to the general population of survivors, with no relationship found between cirrhosis and QOL. Given the small numbers of patients with cirrhosis in this cohort it is not possible to draw firm conclusions as to whether QOL is different in those critically ill survivors with cirrhosis. This finding was not expected as the relationship between chronic liver disease and impaired QOL is documented within the literature. One explanation may be that the remaining population of critical care survivors without cirrhosis had other reasons for an impaired QOL, such as the significant number of comorbidities demonstrated or the presence of PICS. The results may be explained by other factors, such as change in functional status, which were not explored within this study.

Whilst this study identified the presence of liver cirrhosis, no information was recorded on disease trajectory or the severity of liver disease either on admission to critical care or at the time of completion of the questionnaires.

Outwith the critical care population the link between impaired QOL and life-threatening complications of cirrhosis such as ascites, encephalopathy and variceal haemorrhage are established in the literature (421). One Dutch study of 179 outpatients with cirrhosis concluded that an impaired QOL was not evident in all cirrhotics but was noted in those with subclinical hepatic encephalopathy (447). It may be that those who responded to the questionnaire had less severe disease or a lack of complications.

This study demonstrated a relationship between length of stay and QOL when analysing the data from all respondents. It would be interesting to examine this further in a larger group of critically ill cirrhotic patients given they had longer length of both ICU and hospital stay.

When considering sleep disturbance, those with cirrhosis reporting insomnia had a notably higher prevalence of clinical insomnia with reduced ability to perform daily tasks when compared to the whole cohort of respondents. It is challenging to determine whether the daytime fatigue and lethargy reported are manifestations of cirrhosis or as a result of sleep disturbance (448). Furthermore, sleep disturbance may result from iatrogenic causes linked to cirrhosis such as diuretic use or indicate the development of hepatic encephalopathy (448). It is interesting that the relationship between cirrhosis and insomnia was not reflected in a decreased QOL for this cohort as the link between sleep disturbance and QOL is established (435).

7.6.1.2 Long-term QOL in critical care survivors

This study reports long-term QOL for critical care survivors in a cohort of patients admitted to a general ICU in Scotland. Published HUS values are available which provide tables of values based upon age and sex matched population (449). It is challenging to compare the mean HUS found in this study with a population 'norm' for the UK as our cohort is heterogeneous. However, HUS in this study is similar to the findings reported in a population of critical illness survivors in Aberdeen 12 months following ICU discharge where HUS was reported to be 0.666 (392). It is concerning that QOL was rated as worse than, or equal to, death by a considerable number of individuals in this study. This may represent poor recovery from critical illness and the impact on functional level,

however, without baseline data it is not possible to identify if this poor QOL existed prior to ICU admission and the change in the trajectory of QOL following discharge.

It has been proposed that QOL in critical care survivors has an iatrogenic component and is dependent upon events within the ICU stay. The relationship between QOL and duration of mechanical ventilation in this cohort is consistent with other studies in the literature (404). However, the relationship found in this study between QOL and inotrope therapy and renal replacement therapy suggests that multiple factors within the ICU stay play a role in determining QOL. It could be suggested that QOL is most impaired in those with a greater severity of illness, however, as there is no association with APACHE II or the incidence of sepsis this is unlikely in this cohort. Korkeila et al. examined the relationship between renal replacement therapy in ICU and long-term QOL in 62 ICU survivors (450). In contrast to our results, respondents reported good QOL at 6 months (450). The authors note that ICU mortality in those requiring renal replacement therapy is influenced by the underlying aetiology of the renal failure, whether it is in the context of multi-organ failure and the reversibility of renal function (450). Recording such information in our cohort would give further insight into this finding.

Patient factors prior to ICU admission are known to affect QOL. Individual socioeconomic status has been demonstrated to impact upon self-rated QOL in the general population so it is unsurprising that this is replicated in critically ill survivors (451). The association of smoking and QOL is explored in studies of the general population; those with poor QOL are reported to be more likely to begin smoking and less likely to succeed with cessation (452, 453).

Assessment of the QOL of a patient prior to admission to ICU would provide insight into the impact of pre-existing comorbidity (454). QOL following ICU can be influenced by a deterioration in pre-existing comorbidity or by the development of a new comorbidity, such as PICS, as a consequence of their admission. Individuals with PICS report weakness secondary to myopathy and neuropathy, impaired hormonal balance, susceptibility to infection and immobility (455). Furthermore, they experience longstanding physical and psychological symptoms which can affect QOL (456).

7.6.1.3 Sleep disturbance in critical care survivors

Whilst studies examining sleep disturbance in critical care survivors exist this study adds to only a small number of reports into long-term changes to sleep following ICU discharge. The prevalence of long-term sleep disturbance in this population of critical care survivors is comparable to that reported by a Swedish study of 497 ICU survivors (described in section 7.4.2) and a cohort of 143 UK ICU survivors interviewed 3 months after ICU discharge (430, 457). These figures are higher than those reported in healthy volunteers studied at the Glasgow Science Centre (10%), individuals with dementia (12.5%) and individuals diagnosed with cancer (30.2%), implying that survivors of critical illness have high rates of insomnia (458-460). In this study insomnia was not measured until follow up, but a previous study of 179 Australian critical care survivors 6 months after ICU discharge found that sleep quality had deteriorated following ICU stay (444). Whilst there was some potential for recall bias, the patients enrolled in their study completed the initial ISI questionnaire during their ICU stay so the time interval was minimal (444). This Australian study was performed at a tertiary referral centre in Sydney and participants included those admitted to general, cardiothoracic and neurological ICUs for more than 2 nights and as such the results may lack generalisability (444). Unlike the study described in this chapter, the Australian cohort identified and excluded those with known sleep disorders which may have influenced results (444).

Sleep deprivation and disturbance are recognised in the critically ill population however, the association observed between ICU length of stay, duration of mechanical ventilation and severity of insomnia is complex (428, 461). In a similar manner to QOL it is unlikely that this solely represents individuals who are most unwell as there is no association between insomnia and APACHE II, sepsis, inotropic support or renal replacement therapy. There may be an underlying iatrogenic component contributing to the prevalence of insomnia in this cohort. Whilst the total amount of time spent sleeping does not differ from the healthy population it is believed that around 50% of sleep in patients admitted to intensive care occurs during the daytime (461). Sleep is frequently interrupted with reduced rapid eye movement sleep and slow-wave activity (428, 461, 462). Mechanical ventilation disrupts normal sleeping patterns, with one study based in an American burns unit reporting that patients were

awakened up to 63 times per hour (463). In a small single-centre study of 15 critical illness survivors who received mechanical ventilation, chronic sleep-related breathing problems were demonstrated including hypoxaemia at night when compared to healthy volunteers (464). Use of sedation within the ICU may have an effect on sleep and QOL following discharge (428). Sedation can prolong the duration of mechanical ventilation and ICU length of stay (465). Sedative medications including benzodiazepines and opioids can reduce REM and slow-wave activity sleep (428). Furthermore it has been postulated that high sedation use can increase psychological morbidity following ICU discharge, although a single-centre randomised controlled trial of 137 patients failed to demonstrate significant results (466).

The relationship between insomnia and smoking demonstrated in this cohort is established in the literature, with previous studies highlighting the association between smoking, difficulty initiating sleep and sleep fragmentation outwith the critical care population (467, 468).

Many of the factors which contribute to poor sleep such as pain, anxiety and depression also impact upon QOL. This makes it challenging to assess whether sleep disturbance causes poor QOL in critical care survivors or merely occurs as a result of the same factors. Sleep disturbance may occur in survivors and form part of a diagnosis of post-traumatic stress disorder (PTSD) or depression - impairing domains of QOL such as performing daily activities (469). The prevalence of both conditions is high in survivors of critical illness with PTSD reported in up to 64% of survivors whilst up to 33% are diagnosed with depression (470-472).

7.6.1.4 The role of pre-existing comorbidity

The results of this study support the established relationship between the number of comorbidities and both QOL and clinical insomnia. This is comparable to the findings of a Swedish multicentre study which reported that QOL was heavily influenced by pre-existing comorbidity which was discussed earlier (section 7.2.2) (409). The same group reported on sleep disturbance following ICU stay and similarly found that comorbidity was the major determinant of sleep (430). A 2018 study of 240 individuals admitted to ICU in Edinburgh

investigated the role of comorbidity, concluding that pre-existing comorbidity influenced QOL in the year following critical illness (410). However, there appears to be a paucity of literature examining the impact of specific comorbidities on both QOL and insomnia in survivors of critical illness. This prevents direct comparison with the results of this study, which demonstrated association between QOL and the co-morbidities of mental health problems, peripheral vascular disease and cerebrovascular disease. The association with mental health problems described in these findings is not unexpected given that anxiety and depression are one component of the EQ-5D (384). Likewise, persistent cognitive impairment experienced by critical care survivors will exacerbate pre-existing cerebrovascular disease and likely impair functional status and QOL (473).

7.6.2 Limitations

Assessment of both long-term QOL and insomnia is subjective and as such it would have been useful to have baseline scores for each individual prior to ICU admission to determine change in these parameters. Studies have utilised retrospective patient reports of QOL and sleep, but it must be recognised that these are vulnerable to bias. In particular studies with subjective measures are susceptible to 'response shift' whereby changes in patient perception following illness may alter how they would have previously answered the question (394). Recall bias may influence results with individuals unable to accurately score previous QOL or sleep. This may mean that survivors of critical illness over or underestimate their QOL or sleep disturbance as they are unable to accurately compare it to previous experience. Alternative methods to assess premorbid QOL and sleep include use of a patient proxy. A UK study of 88 proxy-patient pairs 6 months after ICU discharge showed consistencies when assessing the physical aspects of QOL, which can arguably be assessed objectively (358). Interestingly, proxies were found to underestimate the negative emotional impact on patient's QOL but overestimate the physical aspects (358). However, use of a proxy is not supported by all studies with an American study of 136 patients who had been admitted to ICU with an acute lung injury demonstrating only moderate agreement between patients and their proxies (395). Use of age and sex-matched controls would have been useful to gain perspective on the relevance of results.

This was a single–centre study and all respondents to this study were former patients at GRI ICU. As discussed in the literature review (section 1.2.5.4), the hospital is based in an area of high deprivation and as such results may differ in a more affluent population and as such they may not be generalisable (40). Higher rates of insomnia are reported by those in lower socioeconomic groups, who are also reported to have lower QOL (474, 475).

The response rate of 37.1% is comparable to other postal surveys of quality of life critical care survivors, including one study in the same centre conducted in 2008 (392, 476, 477). This may represent a response bias whereby the results are skewed. Those who responded to the study may be most affected by their experience and envisage greater gain from study participation. Conversely those who did not respond may represent a group most affected by sleep disturbance and poor QOL who feel unable to engage with follow up.

Due to the retrospective nature of the patient's ICU admission, clinical data during the ICU stay is limited to the data recorded during admission. As such there is no record of the volume of sedation used or quality of sleep during stay, factors which would have been of particular value when assessing long term insomnia. It would be useful to measure the choice and quantity of medication used within the ICU stay and explore any relationship to long-term sleep disturbance. As previously discussed (section 7.6.1.2) sedation can prolong duration of ICU stay and mechanical ventilation and change sleep quality. If such information was recorded it may be possible to identify and address specific factors linked to long-term sleep disturbance.

Delirium during ICU admission is known to impact on long-term outcomes. However, when this cohort of patients were admitted to the ICU, screening was not routinely undertaken or recorded (478). All ICU patients admitted to the study site are now screened daily for delirium using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (479). This would facilitate investigation of the duration and type of delirium to determine any long-term effects on QOL or sleep disturbance. Further, it would allow greater focus of resources on preventing delirium or minimising any long-term complications.

Prevalence of comorbidity was based upon retrospective records from the ICU admission, which was reliant upon the admitting doctor accurately documenting past medical history from the patient, family and existing medical records. It was therefore not possible to stratify the severity or impact of each comorbidity on each individual respondent. The study was limited to comorbidities present on ICU admission, however, respondents may have developed new comorbidities as a consequence of their critical illness or in the time since their admission. Whilst the presence of an alcohol use disorder on admission to ICU was documented for each respondent, the level of alcohol consumption at the time of response to the questionnaires was unknown, which may have impacted upon the results. As the questionnaires were distributed by post it was not possible to screen individuals for cognitive impairment. Cognitive impairment is recognised in survivors of critical illness, influencing not only on the individual's ability to execute complex tasks such as reliably completing questionnaires but also ongoing QOL (480).

7.7 Conclusion

This chapter presents the results of a questionnaire based study examining long-term QOL and sleep disturbance in a cohort of critical care survivors, exploring a subpopulation of individuals with cirrhosis. It is one of the few studies in the literature to investigate long-term sleep disturbance in critical care survivors. The results demonstrate:

- 53.3% of those with liver cirrhosis had clinical insomnia, compared to a prevalence of 34.5% in those respondents without cirrhosis

- The relationship between clinical insomnia and cirrhosis was not found to be statistically significant

- No relationship was demonstrated between QOL and a diagnosis of cirrhosis

- QOL is lower in survivors of critical illness with clinical insomnia

- 16.2% of respondents indicated that their QOL was less than or equal to death

- Poor QOL was associated with smoking and social deprivation

- Poor QOL was associated with the following clinical factors; mechanical ventilation, inotrope therapy, renal replacement therapy, length of stay in ICU and length of stay in hospital

- Insomnia in ICU survivors was associated with smoking

- Insomnia was associated with longer duration of mechanical ventilation and longer ICU length of stay

- The number of comorbidities was found to be significantly associated with QOL and clinical insomnia

- A relationship was reported between poorer QOL in ICU survivors and diagnoses of mental health problems, peripheral vascular disease and cerebrovascular disease.

This chapter has discussed the long-term QOL of critical care survivors, examining the prevalence of sleep disturbance. The influence of comorbidity on long-term QOL was demonstrated, although no relationship was found between QOL or insomnia and an underlying diagnosis of cirrhosis. This was despite a significant number of respondents documented to have excess alcohol consumption on admission to ICU. The next chapter provides a summary of the research in this thesis and future avenues of research for the MD student.

Chapter 8 Summary and future directions

8.1 Introduction

This chapter comprises a summary of the main results and findings of the research studies undertaken in this thesis. This is followed by a discussion of the application the research outcomes to daily clinical practice. Avenues for further research are also explored.

8.2 Summary of results and findings

This research primarily focussed on the impact of chronic liver disease on critically ill patients. The main findings of each chapter are outlined below.

8.2.1 Chapter 1

The narrative literature review describes the anatomy and function of the liver in order to understand the significant impact of liver dysfunction on body homeostasis. Knowledge of the multi-systemic effects of liver disease facilitates greater appreciation of the clinical manifestations and requirements for support during critical illness. Chapter 1 discusses the processes of pathophysiological deterioration in the development of cirrhosis and the reversible and often preventable nature of such changes. It highlights the role that the clinician can play in the trajectory of disease. The epidemiology of chronic liver disease is discussed, focussing upon the role of deprivation and the particular challenges faced in both Glasgow and Scotland. The current demand on existing liver services and critical care is examined whilst the projected need for service expansion highlights the importance of this body of research in determining which critically ill cirrhotic patients are admitted to critical care, how such patients are managed during their stay and the support required following discharge.

8.2.2 Chapter 2

Chapter 2 introduces the methodological considerations taken in research design throughout this study. It describes the concepts used to decide on the most appropriate techniques to answer the study questions. Issues of rigour were

explored to ensure that appropriate and reliable data were collected to help sustain the quality of the research. Statistical considerations were then discussed to explain the choice of data analysis.

8.2.3 Chapter 3

In this chapter the decision-making criteria used by both gastroenterologists and intensivists were explored using the outcomes of 2 national surveys of practice in Scotland. The ethical dilemmas posed in withholding or offering intensive care treatment were discussed with a review of the literature pertaining to this clinical decision. The results of the surveys confirmed the multifactorial nature of the decision to provide intensive care to an individual. However, they highlighted inconsistencies between specialties. In particular intensivists placed greater emphasis on the aetiology of chronic liver disease, potentially reflecting attitudes towards specific causes of disease. This may represent an awareness by gastroenterologists of the medical advances in the successful treatment of aetiologies such as viral hepatitis. Both specialties stressed the importance of reversibility and the significance of a patient's attempts to improve health as a result of the abstinence of alcohol consumption. One significant finding was the difference in potential escalation of therapy with intensivists more likely to offer intensive care and multi-organ support as compared to gastroenterologists. Finally, emphasis was placed on the Child-Pugh score when a patient was considered to be clinically stable by both specialities, despite a lack of evidence to support when this score should be measured to indicate survival.

8.2.4 Chapter 4

In response to the findings of the previous chapter, Chapter 4 explored the timing and utility of Child-Pugh score with consideration of the impact of critical illness on each component of the Child-Pugh score. This chapter focussed on the Child-Pugh score on ICU admission, the Child-Pugh score when the patient was clinically stable and short-term mortality. This chapter found that Child-Pugh score measured at time of ICU admission, rather than when stable, was significantly associated with hospital mortality, which contradicted the survey findings in Chapter 3. However, the degree of change in Child-Pugh score between measurement when stable and on admission to ICU was relevant. It

would prove valuable to increase the sample size and re-survey the respondents to explore the reasons behind the significance placed upon stable Child-Pugh score and whether it was used as a surrogate marker for chronic disease severity.

8.2.5 Chapter 5

This chapter reported a prospective study examining the use of a proxy to report an alcohol use disorder in critically ill patients. Alcohol consumption has been highlighted as a preventable cause of chronic liver disease and abstinence can reverse the development of cirrhosis. Whilst the recruitment numbers were disappointing the results suggested that a proxy could be used as a reliable historian in the identification of an alcohol use disorder. To validate the results of this study it would be useful to perform a similar investigation, in a different location, to help address the problems with recruitment.

8.2.6 Chapter 6

The short-term survival of critically ill cirrhotics has been extensively reported in the literature, with a vast improvement in survival over the last 4 decades. However, wider research into long-term survival is limited and this study reported survival at 12 months for a cohort of cirrhotic patients admitted to a general ICU in the UK. The majority of these patients were socially deprived with an underlying aetiology of alcoholic liver disease. Long-term survival following ICU stay was reported, the findings of which are consistent with other studies. In this cohort Child-Pugh class (when measured on admission to ICU) was demonstrated to stratify patients into 3 distinctive groups for long-term survival. These findings further highlighted the challenges in the decision to determine those patients considered suitable to be admitted to the limited critical care resources available.

8.2.7 Chapter 7

Whilst survival rates are improving, recognition of the long-term sequelae of an ICU stay have a significant impact on the survivors of critical illness. A subgroup of survivors with cirrhosis were studied to identify any relationship between

cirrhosis and QOL or insomnia. This chapter investigated the long-term QOL and prevalence of sleep disturbance and found that for some survivors their QOL was worse than, or equal to death. QOL in those with liver cirrhosis was comparable to the general population of survivors, with no relationship found between cirrhosis and QOL. The subgroup of survivors with cirrhosis had an increased incidence of clinical insomnia compared to the general population of survivors although this relationship was not statistically significant. QOL and sleep disturbance were found to be influenced by pre-existing factors such as prevalence of comorbidity and events during an ICU stay such as mechanical ventilation and length of stay. These findings highlighted the lasting significance of events that occur during the management of critical illness and raised awareness of the potential difficulties some patients face in recovery.

8.3 What does this research add to existing literature?

The findings of this thesis add to the existing body of literature surrounding the critically ill patient with chronic liver disease.

- This thesis reports the first national Scottish survey investigating decision-making regarding admission of individuals with chronic liver disease to critical care. It exposes inconsistencies between specialties, in particular the significance placed upon underlying aetiology of chronic liver disease and proposed levels of escalation of organ support

- As far as it has been ascertained this the first study to investigate the time point at which Child-Pugh score is used by a specialist to inform their decision to offer critical care to a patient. Child-Pugh score measured when a patient is clinically stable is used by the majority of specialists surveyed in Scotland

- This is the first study to investigate the relationship between short-term survivorship and timing of Child-Pugh score. Although this is a small study, there appears to be a trend to suggest mortality increases with an increase in Child-Pugh score, measured both on ICU admission and when stable. However, statistical significance was only demonstrated between Child-Pugh score measured on ICU admission and hospital mortality.

- This is one of only a few studies reporting long-term outcome of a group of cirrhotic patients admitted to a general ICU in the UK. It has demonstrated the ability of Child-Pugh class (when measured on admission to ICU) to stratify patients into 3 distinctive groups for survival. Further it is the first study in the literature to report an association between serum lactate measured on ICU admission and long-term mortality

- As far as can be established, this is the first report into insomnia and long-term QOL in critical illness survivors in the UK. The findings reveal QOL is lower in survivors of critical illness with clinical insomnia with a significant number of ICU survivors reporting that their QOL is less than or equal to death. The number of pre-existing comorbidities was found to be significantly associated with both QOL and clinical insomnia

- The number of individuals with cirrhosis was small but the results suggest there may be a relationship between a diagnosis of cirrhosis and an increased incidence of clinical insomnia, although this relationship was not found to be significant

- This is the first study recorded in the literature to investigate the use of a proxy in reporting an alcohol history for a critically ill patient and found substantial agreement between proxy and patient in the identification of an alcohol use disorder using the AUDIT, using a threshold score of 8

8.4 Recommendations for clinical practice

The findings of this thesis have a number of impacts upon clinical practice.

Firstly, it should prompt clinicians to evaluate their decision-making when deciding to escalate a patient to critical care. It should empower both intensivists and referring clinicians to engage in discussion regarding admission to ICU, particularly for those with severe chronic liver disease. Further this research should prompt discussion and the education of trainee doctors in the allocation of finite critical care resources.

Secondly, it highlights the challenges faced in determining chronic disease severity for those with comorbidity who develop critical illness. The limitations of existing scoring systems to predict mortality in liver disease are highlighted throughout this thesis. The findings should encourage development of systems to effectively determine chronic liver disease trajectory. Clinicians should support anticipatory care planning to ensure intensive care is not offered to those patients for whom it would be futile.

Thirdly, the findings of this research can be used to further inform patients and their families about the likely long-term survival and recovery from critical illness. This supports the concept of realistic medicine, sharing decision-making about treatment with patients (481). The results can be used to support the argument for further support in delivering structured long-term rehabilitation for patients recovering from critical illness (354).

Finally, these findings should prompt thinking about the use of a proxy in critical illness to provide information on the medical history for a patient. The use of a proxy is widely practiced in medicine with limited evidence of its utility or reliability. These results provide some reassurance that this is a valid method to be used for the collection of an alcohol history for a critically ill patient, although further research would be beneficial.

8.5 Future directions

This thesis has explored the complexity surrounding the decision to admit a patient with advanced chronic liver disease to critical care and reports the outcome of those who are admitted to critical care. However, the number and characteristics of those individuals with critical illness who are not admitted to critical care remain unknown. It would be useful to identify this cohort of patients and determine the reasons for non-admittance to critical care together with their outcomes.

There is also limited research that investigates the patient journey prior to admission. It remains unanswered as to whether critical illness is predictable in those with chronic disease and a study plotting the trajectory of disease severity in those with chronic liver disease would be beneficial. Likewise monitoring the

recovery of critically ill cirrhotics could help determine whether individuals return to baseline liver function and physiological reserve. Any future research in chronic liver disease would need to determine whether patients were admitted to critical care with ACLF or a chronic decompensation.

With a movement towards publishing outcomes from large datasets and the increased use of electronic patient records it is likely that long-term survival following critical care admission will be reported on a national level in Scotland. However, reporting at a population level would support the call for increased critical care resources and help inform health policy.

Appendices

Appendix 1: Survey 1 of criteria used by gastroenterologists and intensivists used to refer or admit patients to ICU

Appendix 2: Survey 2 of criteria used by gastroenterologists and intensivists used to refer or admit patients to ICU, distributed using www.surveymonkey.com

Appendix 3: WHO Alcohol Use Disorders Identification test Questionnaire

Appendix 4: 4AT Questionnaire

Appendix 5: Ethical approval for study investigating use of a proxy to measure alcohol history for patients in intensive care

Appendix 6: Participant consent form and information leaflet for the study investigating use of a proxy to measure alcohol history for patients in intensive care

Appendix 7: EQ-5D Questionnaire and registration

Appendix 8: ISI Questionnaire

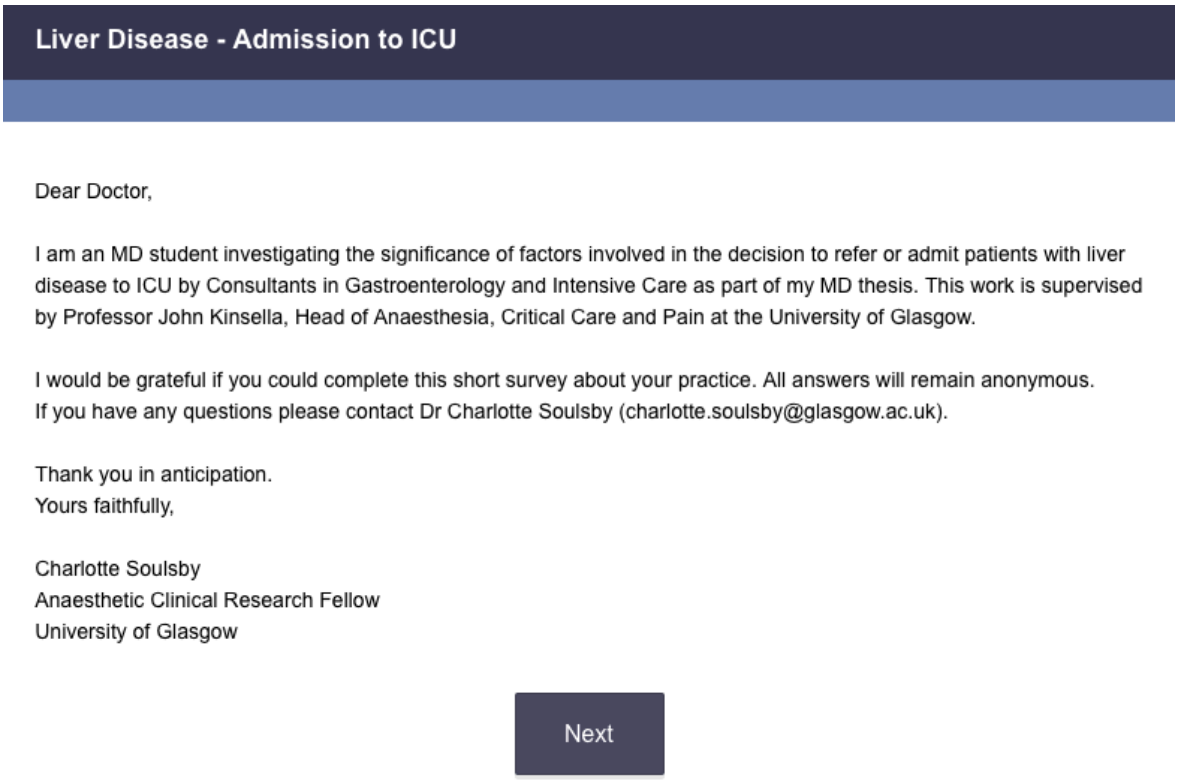
Appendix 9: Ethical approval for study to explore quality of life in survivors of ICU

Appendix 10: Participant consent form and information leaflet for the study exploring quality of life in survivors of ICU

Appendix 11: Rstudio version 1.0.136: Screen shots

Appendix 1

Survey 1 of criteria used by gastroenterologists and intensivists used to refer or admit patients to ICU, distributed using www.surveymonkey.com



Liver Disease - Admission to ICU

Dear Doctor,

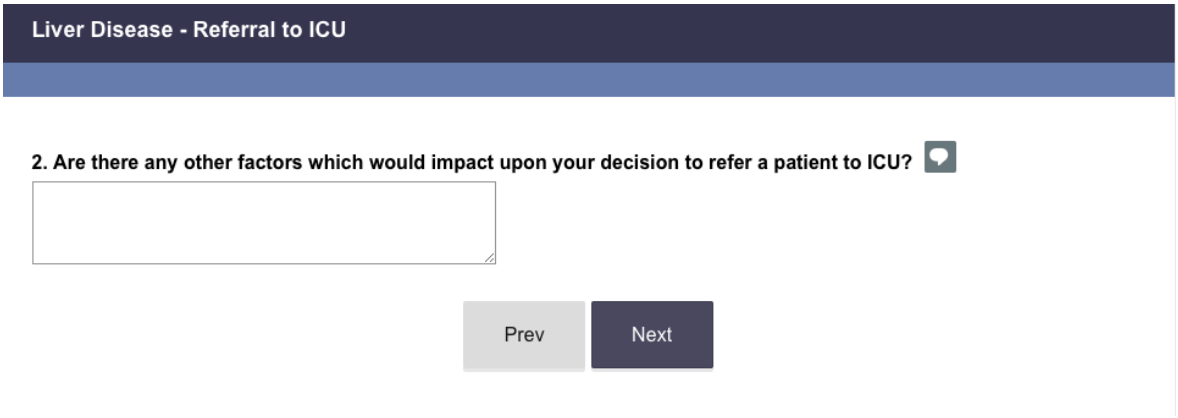
I am an MD student investigating the significance of factors involved in the decision to refer or admit patients with liver disease to ICU by Consultants in Gastroenterology and Intensive Care as part of my MD thesis. This work is supervised by Professor John Kinsella, Head of Anaesthesia, Critical Care and Pain at the University of Glasgow.

I would be grateful if you could complete this short survey about your practice. All answers will remain anonymous. If you have any questions please contact Dr Charlotte Soulsby (charlotte.soulsby@glasgow.ac.uk).

Thank you in anticipation.
Yours faithfully,

Charlotte Soulsby
Anaesthetic Clinical Research Fellow
University of Glasgow

Next



Liver Disease - Referral to ICU

2. Are there any other factors which would impact upon your decision to refer a patient to ICU?

Prev Next

Liver Disease - Referral to ICU

* **3. Which of the following grades of Child-Pugh cirrhosis would you refer with gastrointestinal bleeding to ICU?**

	Yes	No
Child-Pugh A	○	○
Child-Pugh B	○	○
Child-Pugh C	○	○

Liver Disease - Referral to ICU

* **4. Which of the following grades of Child-Pugh cirrhosis would you refer with sepsis to ICU?**

	Yes	No
Child-Pugh A	○	○
Child-Pugh B	○	○
Child-Pugh C	○	○

Appendix 2

Survey 2 of criteria used by gastroenterologists and intensivists used to refer or admit patients to ICU, distributed using www.surveymonkey.com

Liver Disease - Admission to ICU Case Studies for Intensivists

Dear Doctor,

I am an MD student investigating the significance of factors involved in the decision to refer or admit patients with liver disease to ICU by Consultants in Gastroenterology and Intensive Care as part of my MD thesis. This questionnaire further investigates issues surrounding ICU referral and admission raised by a questionnaire sent out in October 2014. It does not require you to have completed the first questionnaire.

Our findings suggested:

- Universal agreement between Gastroenterologists and Intensivists that Child score when stable is the greatest significance on their decision to refer, or admit, a patient to ICU
- Intensivists placing importance on the aetiology of liver disease, whilst Gastroenterologists felt it did not play any part in their decision
- Agreement between specialties in referral and admission of Child Pugh A, B and C with upper gastrointestional bleeding
- The majority of intensivists would not accept a Child Pugh C with sepsis, yet most Gastroenterologists would refer to ICU

The findings were presented at the ISICEM in Brussels and the Scottish Society of Gastroenterologists. The results can be read in full at http://www.ccforum.com/content/19/S1/P384.

In response to these findings I have written three short case studies exploring level and length of support offered to patients in ICU and re-referral to ICU. In addition there are two short questions on mortality of liver disease and aetiology.

I would be grateful if you could complete this short survey, which should take no longer than 5 minutes. All answers will remain anonymous.
If you have any questions please contact Dr Charlotte Soulsby (charlotte.soulsby@glasgow.ac.uk).

Thank you in anticipation.
Yours faithfully,

Charlotte Soulsby
Anaesthetic Clinical Research Fellow

A 55 year old woman presented to the ED with abdominal pain, diarrhoea and vomiting. Her haemoglobin was 77 g/l, white cell count 16 x10^9/L, platelets 43 x10^9/L and PT ratio 3.5. Urea was 14 mmol/L, creatinine 338 mmol/L, potassium 3.4 mmol/L and sodium 126 mmol/L. Liver function tests revealed a bilirubin of 401 mmol/L, AST 139 U/L, ALT 30 U/L, Alk Phos 101 U/L and an albumin of 15g/L. She was an obese Type 2 diabetic with a ten year history of alcohol excess and continued to drink a litre of vodka a day. At a recent outpatient liver clinic she was classified as a Child-Pugh B. She was admitted under general medicine and commenced on intravenous fluids and tazocin. Blood cultures taken on admission subsequently revealed a gram negative bacteraemia.

Over the following two days she deteriorated and was reviewed due to increased oxygen demands. Her respiratory rate was 26, oxygen saturations 92% on 15L oxygen. Respiratory examination revealed a stony dullness to percussion on the left and on abdominal examination shifting dullness was elicited, suggestive of ascites. Chest x-ray confirmed a left sided pleural effusion. Blood tests were repeated. Haemoglobin was 82 g/l, white cell count 14 x10^9/L, platelets 25 x10^9/L and PT ratio 2.4. Urea was 19 mmol/L, creatinine 430 mmol/L, potassium 3.1 mmol/L and sodium 123 mmol/L. Liver function tests revealed a bilirubin of 348 mmol/L, AST 152 U/L, ALT 29 U/L, Alk Phos 121 U/L and an albumin of 12g/L. Her Child-Pugh score is C.

* **1. Would you admit this patient to ICU?**

- ○ Yes
- ○ No

2. If yes, would you offer

- ○ Single Organ Support Only
- ○ Multi-organ support

Liver Disease - Admission to ICU Case Studies for Intensivists

She is admitted to intensive care and requires intubation and renal replacement therapy. After 8 days respiratory function improves and she is discharged back to the medical ward.

* **3. If she deteriorates again would you re-admit to ICU?**

- ◯ Yes
- ◯ No

Liver Disease - Admission to ICU Case Studies for Intensivists

She is discharged home but continues to consume a litre of vodka a day. Her functional ability is reduced after her hospital stay.

* **4. If she is readmitted again would you re-admit to ICU?**

- ◯ Yes
- ◯ No

A 35 year old man presented to the ED following multiple episodes of haematemesis over a day. In resus he is noted to by tachycardic (HR 124) with a BP 107/64. His respiratory rate is 18 and saturations are 98% on room air. He is noted to be confused and has another episode of haematemesis in the ED. His bloods show a Haemoglobin of 101 g/l, white cell count 11 $x10^9$/L, platelets 79 $x10^9$/L and PT ratio 2.3. Urea was 5.7 mmol/L, creatinine 50 mmol/L, potassium 4.4 mmol/L and sodium 136 mmol/L. Liver function tests revealed a bilirubin of 125 mmol/L, AST 202 U/L, ALT 52 U/L, Alk Phos 123 U/L and an albumin of 21g/L. His Child-Pugh score is C.

He has a known history of alcohol excess and was admitted 6 months earlier under gastroenterology with jaundice and ascites. During that admission he was noted to have oesophageal varices on CT. On that admission his Child-Pugh score was C.

You decide the patient requires emergency upper GI endoscopy and he requires placement of a Sengstaken tube for a variceal bleed.

* **5. Would you admit this patient to ICU?**

- ◯ Yes
- ◯ No

6. If yes, would you offer

- ◯ Single organ support only
- ◯ Multi-organ support

He is admitted to intensive care, the Sengstaken tube is removed uneventfully and the variceal bleed resolves. Whilst still in intensive care he develops sepsis.

* **7. Would you continue to offer ICU care?**

- ◯ Yes
- ◯ No

He is successfully discharged from intensive care back to the ward. However, two weeks later he deteriorates again, with signs of recurrent sepsis.

* **8. Would you re-admit to ICU?**

- ◯ Yes
- ◯ No

* **9. If he was readmitted again with gastrointestinal bleeding would you re-admit to ICU?**

- ◯ Yes
- ◯ No

* **10. If he was readmitted again with sepsis would you re-admit to ICU?**

- ◯ Yes
- ◯ No

A 64 year old man presented to the ED with a six day history of shortness of breath and malaise. On examination he was tachycardic (HR 107) and hypotensive (BP 77/51). He was tachypnoeic, with a respiratory rate of 30 and oxygen saturations of 92% on 15L oxygen. Respiratory examination revealed left sided basal crepitations. His GCS 15. Examination was otherwise unremarkable.

His bloods show a Haemoglobin of 130 g/l, white cell count 17 $x10^9$/L, platelets 487 $x10^9$/L and PT ratio 1.2. Urea was 13 mmol/L, creatinine 113 mmol/L, potassium 5.4 mmol/L and sodium 127 mmol/L. Liver function tests revealed a bilirubin of 9 mmol/L, AST 28 U/L, ALT 17 U/L, Alk Phos 122 U/L and an albumin of 22g/L. Chest x-ray shows left basal consolidation. His Child-Pugh score is B.

He is an obese Type 2 Diabetic with peripheral vascular disease and has had a previous stroke. He has been diagnosed with non-alcoholic fatty liver disease at a gastroenterology clinic following abnormalities on an ultrasound scan and was classified as a Child-Pugh A.

He is diagnosed with severe community acquired pneumonia and his blood pressure shows limited improvement with fluid challenges. He is commenced on a vasopressor. His respiratory rate is now 35 and his oxygen saturations have dropped to 88% on 15L oxygen.

* **11. Would you admit this patient to ICU?**

- ◯ Yes
- ◯ No

12. If yes, would you offer

- ◯ Single Organ Support Only
- ◯ Multi-organ support

After four days of ventilation his respiratory function improves and he is suitable for extubation. He now develops renal failure.

* **13. Would you continue to offer ICU care?**

- ◯ Yes
- ◯ No

He does not require any renal replacement and his renal function improves. Following extubation he is discharged to the ward. A week later his respiratory function deteriorates, with a suspected hospital acquired pneumonia.

* **14. Would you re-admit to ICU?**

- ◯ Yes
- ◯ No

He is successfully discharged home and re-presents with sepsis six months later.

15. Would you re-admit to ICU?

- ◯ Yes
- ◯ No

Appendix 3

WHO Alcohol Use Disorders Identification test Questionnaire

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
   Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

Domains and Item Content of the AUDIT

Domains	Question Number	Item Content
Hazardous Alcohol Use	1	Frequency of drinking
	2	Typical quantity
	3	Frequency of heavy drinking
Dependence Symptoms	4	Impaired control over drinking
	5	Increased salience of drinking
	6	Morning drinking
Harmful Alcohol Use	7	Guilt after drinking
	8	Blackouts
	9	Alcohol-related injuries
	10	Others concerned about drinking

Appendix 4

4AT Questionnaire

4AT

Assessment test for delirium & cognitive impairment

(label)

Patient name:

Date of birth:

Patient number:

Date: **Time:**

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	**0**
Mild sleepiness for <10 seconds after waking, then normal	**0**
Clearly abnormal	**4**

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	**0**
1 mistake	**1**
2 or more mistakes/untestable	**2**

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December."
To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	**0**
	Starts but scores <7 months / refuses to start	**1**
	Untestable (cannot start because unwell, drowsy, inattentive)	**2**

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	**0**
Yes	**4**

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

GUIDANCE NOTES Version 1.2. Information and download: **www.the4AT.com**

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment.* Item 4 requires information from one or more source(s), eg. your own knowledge of the patient, other staff who know the patient (eg. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

Appendix 5

Ethical approval for study investigating use of a proxy to measure alcohol history for patients in intensive care

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Dr Tara Quasim
Room 2.71 New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
Glasgow
G4 0SF

Date 19th February 2015
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Dr Quasim

Study title:	**Investigation into the use of a proxy for alcohol history for patients in intensive care using the Adult Use Disorders Identification Test (AUDIT).**
REC reference:	**15/WS/0014**
IRAS project ID:	**162929**

Thank you for your letter 12th February 2015 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Liz Jamieson, wosrec3@ggc.scot.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

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.

Conditions of the favourable opinion

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

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

Sponsors are not required to notify the Committee of approvals from host organisations

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

Ethical review of research sites

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

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter for Amendments]	1	12 February 2015
IRAS Checklist XML [Checklist_14012015]		14 January 2015
Other [CV J McPeake]	1	14 January 2015
Other [CV Professor John Kinsella]	1	14 January 2015
Other [4AT Validated Questionnaire]	1	14 January 2015
Other [Participant Consent Form]	2	12 February 2015
Other [GP Letter]	2	12 February 2015
Other [Proxy Consent Form]	2	12 February 2015
Other [Proxy Frequency and Nature of Relationship]	2	12 February 2015
Other [Proxy Information Sheet]	2	12 February 2015
Other [Participant Information Sheet]	3	12 February 2015
Other [Study Protocol]	3	12 February 2015
REC Application Form [REC_Form_14012015]		14 January 2015
Summary CV for Chief Investigator (CI)	1	14 January 2015
Summary CV for student	2	14 January 2015
Validated questionnaire [WHO AUDIT Screening Tool]	1	14 January 2015

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

User Feedback

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

HRA Training

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

15/WS/0014	**Please quote this number on all correspondence**

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

Yours sincerely

Liz Jamieson
REC Manager
On behalf of Dr Adam Burnel, Chair

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: *Joanne McGarry*
Elaine O'Neil, NHS Greater Glasgow and Clyde R&D

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
(former Royal Hospital for Sick Children Yorkhill)
Dalnair Street
Glasgow G3 8SW
www.nhsggc.org.uk

Dr Tara Quasim
Room 2.71 New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
Glasgow
G4 0SF

Date 8th March 2016
Your Ref
Our Ref
Direct line 0141 232 1805
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Dr Quasim

Study title:	**Investigation into the use of a proxy for alcohol history for patients in intensive care using the Adult Use Disorders Identification Test (AUDIT).**
REC reference:	**15/WS/0014**
Amendment number:	**AM01**
Amendment date:	**18 February 2016**
IRAS project ID:	**162929**

Thank you for your email of 18 February 2016, notifying the Committee of the above amendment.

The amendment covered an extension to the study for a further 12 months.

The Committee does not consider this to be a "substantial amendment"as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Notice of Minor Amendment [Email re Extension to Study]	AM01	18 February 2016

Statement of compliance

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

15/WS/0014:	**Please quote this number on all correspondence**

Yours sincerely

Liz Jamieson
REC Manager

Copy to: *Ms Joanne McGarry, NHS R&D Greater Glasgow & Clyde*

Appendix 6

Participant consent form and information leaflet for the study investigating use of a proxy to measure alcohol history for patients in intensive care

University Department of Anaesthesia

Level 2, New Lister Building

Glasgow Royal Infirmary

Glasgow

G4 0SF

Subject number:

Use of a proxy for alcohol history for patients in intensive care using the Alcohol Use Disorders Identification Test (AUDIT)

Consent Form

Please initial the BOX

I confirm that I have read and understand the information sheet dated 06/02/2015 (version 3) for the above study and have had the opportunity to ask questions ☐

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. ☐

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 the research. I give my permission for the research team to have access to my records. ☐

I confirm that my General Practitioner will be informed of my involvement in the above study ☐

I agree to take part in the above study ☐

| --- | --- | --- |
Name of Participant	Date	Signature
Name of Researcher	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes

University Department of Anaesthesia,
Level 2, New Lister Building
Glasgow Royal Infirmary
Glasgow
G4 0SF

NHS
Greater Glasgow and Clyde

Use of a proxy for alcohol history for patients in intensive care using the Alcohol Use Disorders Identification Test (AUDIT)

Participant Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by Dr Charlotte Soulsby, Joanne McPeake, Dr Tara Quasim, Dr Malcolm Sim and Professor John Kinsella from the Department of Anaesthesia, Pain and Critical Care Medicine in Glasgow Royal Infirmary and the University of Glasgow.

What is the purpose of the study?

The purpose of the study is to assess whether a family member or friend can be used to provide reliable source of information about alcohol intake for patients who are unable to give the information themselves whilst they are inpatients in intensive care. At present, there is no proven method for assessing alcohol intake in intensive care patients, with many units recording units of alcohol consumed. Accurately reporting volume of alcohol is difficult and patient participation is difficult when they are sedated or ventilated.

Why have I been invited?

You have been invited to take part in this study as you have been a patient in the Intensive Care Unit in the Queen Elizabeth University Hospital, Glasgow.

Do I have to take part?

No. It is up to you to decide. We will describe the study and go through this information sheet, which we will then be given to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not

affect the standard of care you receive or your future treatment. If you do decide to take part, your General Practitioner (GP) will be informed of your involvement.

What does taking part involve?

Many patients who have been discharged from intensive care are confused. You will be asked to complete a short questionnaire consisting of six questions to assess if you are confused prior to you completing the second questionnaire consisting of ten questions on alcohol habits and drinking patterns. During your stay in Intensive Care your next of kin was asked to complete the same questionnaire on alcohol intake, answering on your behalf. If you do not wish to take part the information that they have provided will be destroyed.

What happens to the information?

Your identity and personal information will not be recorded and the results of the questionnaire will be kept anonymous. In order to link the answers from both alcohol questionnaires it will be necessary to give each pair of questionnaires completed by a patient and their respective relative or friend the same unique identifying number which will not correspond to any identifiable information. Participation in this study will not be recorded in your medical notes.

What are the possible benefits of taking part?

It is hoped that by taking part in this research you will be providing a way for medical staff to assess alcohol intake in individuals who are not able to provide this information themselves. This enables them to consider the problems associated with excess alcohol intake and withdrawal.

Are there any risks?

There should be no risks associated with completion of the questionnaires. It may lead you to consider your own drinking behaviours and patterns. If your responses suggest that you have hazardous or harmful levels of alcohol consumption or alcohol dependence you will be given the contact details for your local Addaction Alcohol Behaviour Change (ABC) or community addiction team (CAT). It will be your decision if you wish to contact either organisation for advice and support on how to reduce your alcohol consumption.

Who has reviewed the study?

This study has been reviewed by the **West of Scotland Research Ethics Committee.**

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep.

Contacts:

Dr Charlotte Soulsby, Clinical Research Fellow, University of Glasgow. Telephone (0141) 2018631

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact:

Professor John Kinsella

University Department of Anaesthesia

New Lister Building

Glasgow Royal Infirmary

Glasgow

(0141) 2018630

Thank you for your time and cooperation

Appendix 7

EQ-5D-3L Questionnaire and Registration

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

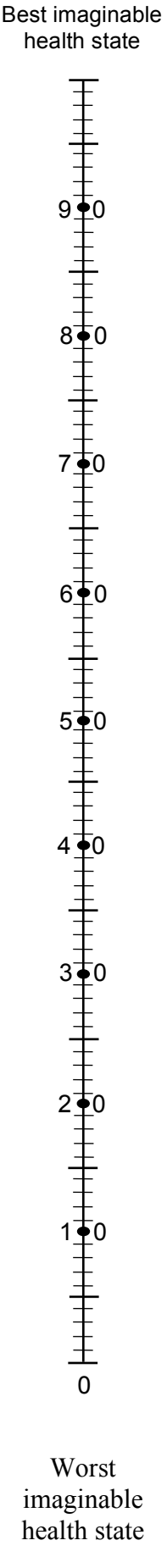
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Mandy van Reenen
To: charlotte.soulsby@glasgow.ac.uk
EQ-5D registration

10 February 2015 10:42
Inbox - StaffGlas

MV

Dear Ms. / Mr. Charlotte Rebecca Soulsby,

Thank you for registering your research at the EuroQol Research Foundation's website.

As the study "Follow up of ICU Survivors" you registered involves low patient numbers (60) you may use the EQ-5D-5L instrument (Paper version) free of charge. Please note that separate permission is required if any of the following is applicable:

- Funded by a pharmaceutical company, medical device manufacturer or other profit-making stakeholder;
- Number of respondents over 5000
- Routine Outcome Measurement;
- Developing or maintaining a Registry;
- Digital representations (e.g. PDA, Tablet or Web)

Please find attached the English (United Kingdom) EQ-5D-5L version (word format). A brief user guide is downloadable from the EuroQol website (www.euroqol.org).

Please note that over the next months the first value sets associated with the EQ-5D-5L system will be published. It will take time before 5L value sets will be available for most countries. Please check our website to see which 5L value sets are currently available. In the meantime, the EuroQol Research Foundation has developed a "crosswalk" between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system, resulting in interim value sets for the new EQ-5D-5L descriptive system. Please find all information about the crosswalk from EQ-5D-5L data to the EQ-5D-3L value sets online at the EuroQol website (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html).

Kind regards,

Mandy van Reenen
Communications Officer
EuroQol Research Foundation
T: +31 88 4400190
E: vanreenen@euroqol.org
W: www.euroqol.org

Appendix 8

Adapted Insomnia Severity Index Questionnaire

Please respond to these questions in relation to your sleep OVER THE LAST MONTH, even if you do not have a sleep problem currently

1. Please rate the severity of any problem(s) sleeping

	None	Mild	Moderate	Severe	Very Severe
a) Difficulty falling asleep	0	1	2	3	4
b) Difficulty staying asleep	0	1	2	3	4
c) Problem waking up too early	0	1	2	3	4

2. How many nights per week were you bothered by problems sleeping?

None	1	2	3	4	5	6	7

3. How satisfied/dissatisfied are you with your current sleep pattern?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very dissatisfied
0	1	2	3	4

4. To what extent do you consider your sleep problem, if you have one, to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood etc.)

Not at all interfering	A little	Somewhat	Much	Very much interfering
0	1	2	3	4

5. If you are having problems with your sleep, how noticeable to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all	A little	Somewhat	Much	Very much

noticeable				noticeable
0	1	2	3	4

6. How worried/distressed are you about your current sleep pattern?

Not at all worried	A little	Somewhat	Much	Very much worried
0	1	2	3	4

7. How many nights a week are you using prescribed medication for your sleep?

None 1 2 3 4 5 6 7

8. How many nights a week are you using over-the-counter medication for your sleep?

None 1 2 3 4 5 6 7

Appendix 9

Ethical approval for study to explore quality of life in survivors of ICU

East of Scotland Research Ethics Service *(EoSRES)* **Research Ethics Service**

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Miss Joanne McPeake
University of Glasgow
Level Two, New Lister Building, Room 2.73
10-16 Alexandra Parade
Glasgow G31 2ER

Date: 22 May 2015
Your Ref:
Our Ref: **DL/15/ES/0084**
Enquiries to: Mrs Diane Leonard
Direct Line: 01382 383871
Email: diane.leonard@nhs.net

Dear Miss McPeake

Study title: **A study to explore quality of life in survivors of ICU**
REC reference: **15/ES/0084**
IRAS project ID: **172758**

Thank you for your letter of 18 May 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

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

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.

Conditions of the favourable opinion

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

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

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.
There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

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

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

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

Ethical review of research sites

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

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
IRAS Checklist XML [Checklist_05052015]		05 May 2015
Other	1	18 May 2015
Other [Reminder Letter]	3	22 May 2015
Participant consent form [Consent Form]	2.0	20 April 2015
Participant information sheet (PIS)	3	18 May 2015
REC Application Form [REC_Form_05052015]		28 April 2015
Research protocol or project proposal [Study Protocol]	2.0	20 April 2015
Summary CV for Chief Investigator (CI) [CV Joanne McPeake (1.0 20/4/15)]	1.0	21 July 2014

Document	Version	Date
Summary CV for student [CV Dr Soulsby]	1.0	20 April 2015
Summary CV for supervisor (student research) [CV Tara Quasim]	1.0	20 April 2015
Validated questionnaire [Validated Questionnaire]	1.0	20 April 2015
Validated questionnaire [EQ-5 questionnaire]		

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

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

15/ES/0084	Please quote this number on all correspondence

Yours sincerely

for Dr Carol Macmillan
Chair

E-mail: eosres.tayside@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Emma- Jane Gault, University of Glasgow
Dr Charlotte Soulsby

Appendix 10

Participant consent form and information leaflet for the study exploring quality of life in survivors of ICU

VERSION 2
(20/04/2015)

STUDY TITLE: A study to explore the quality of life in survivors of ICU

CONSENT FORM

I confirm that I have read and understand the information sheet dated 18/05/2015 (VERSION 3) for the above study and have had the opportunity to ask questions ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

Where it is relevant to the research project, I understand that sections of my ICU medical notes may be looked at. I give my permission for the research team to have access to my records. I understand that all the information extracted will be anonymised. ☐

I agree to take part in the above study. ☐

| --- | --- | --- |
| Name of Participant | Date | Signature |

| --- | --- | --- |
| Name of Witness | Date | Signature |

1 copy to the patient, 1 copy to the researcher, 1 original for the patients' notes

STUDY TITLE: A study to explore the quality of life in survivors of ICU

Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by doctors and nurses from the intensive care unit at Glasgow Royal Infirmary. This project is also contributing to an education qualification for Dr Charlotte Soulsby, an intensive care doctor. The degree is a MD (a postgraduate research qualification). The educational supervisor is Dr Tara Quasim.

What is the purpose of the study?

We are aware that people can find it a struggle to get back to their previous quality of life after an illness that requires admission to an Intensive Care Unit. We want to find out if there are any gaps in the service we provide from Intensive Care.

This letter contains 2 questionnaires. The first is called the EQ5D which provides us with a measure of your current quality of life. The second questionnaire, called the Insomnia Severity Index, seeks to understand information about your sleeping patterns. The data will be stored anonymously so it cannot be traced back to an individual. This research is important as we would ideally like to continue to provide a rehabilitation package after a stay in the Intensive Care Unit but we need to know what you felt were the important issues.

Why have I been invited?

You have been invited to take part in this study as you have previously been a patient in the Intensive Care Unit at Glasgow Royal Infirmary.

Do I have to take part?

It is up to you to decide. We will describe the study in this information sheet and if you have any further queries or would prefer a telephone, or face-to-face interview, please contact Miss Evelyn Selfridge (0141 2018502) and she will direct your call or query to me. You will be asked to sign a

consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason. This would not affect the standard of care you receive or your future treatment.

What does taking part involve?

It involves you filling out these 2 questionnaires and returning them in the stamped addressed envelope provided. It will take approximately 5 minutes to complete. As stated earlier, if preferred we can conduct a telephone or face to face interview. The researchers will also look at your medical notes while you were in the ICU.

What happens to the information?

Your identity and personal information will be completely confidential. The information obtained will remain confidential and stored within an encrypted USB stick and on a central, secure IT back up. All paper information will be kept in a locked filling cabinet. Once you have completed the questionnaires, or declined to participate in the study, all personal information will be erased and therefore you will not be able to be identifiable. The data are held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission.

What are the possible benefits of taking part?

There are no direct benefits for you but it is hoped that by taking part in this research, you will provide valuable information regarding quality of life after Intensive Care and allow us to determine what, if any, issues we can provide more help with for future patients. If completing these questionnaires causes any feelings of upset or distress, please contact the details below (Miss Joanne McPeake). We can then refer you to our ICU follow up service to deal with these issues directly.

Who has reviewed the study?

The East of Scotland Research Ethics Service REC1, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records be made available for scrutiny by monitors from NHS Greater Glasgow and Clyde, whose role is to check that research is properly conducted in the interests of those taking part are adequately protected.

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone not closely linked to the study, please contact Professor J Kinsella

Contacts:

Professor J Kinsella
Level 2, Room 2.70
New Lister Building

Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018630

Supervisors

Miss Joanne McPeake
Level 2, Room 2.73
New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018634

Dr Tara Quasim
Level 2, Room 2.71
New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018505

Student

Dr Charlotte Soulsby
Level 2, Room 2.73
New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018634

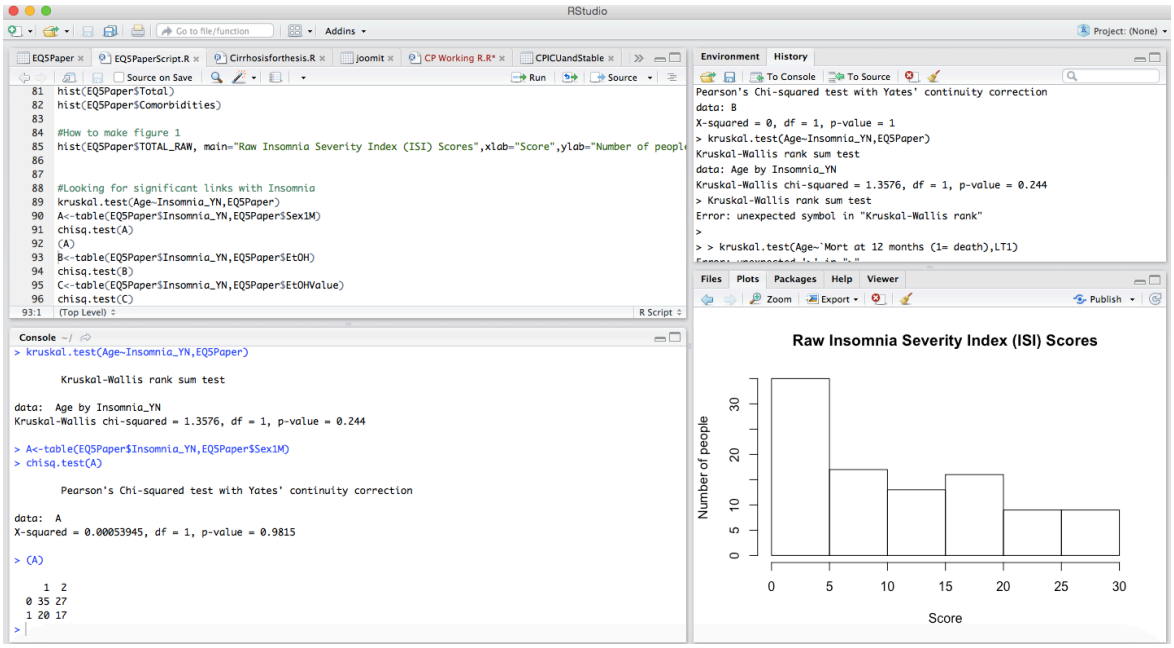
If you have a complaint about any aspect of the study?

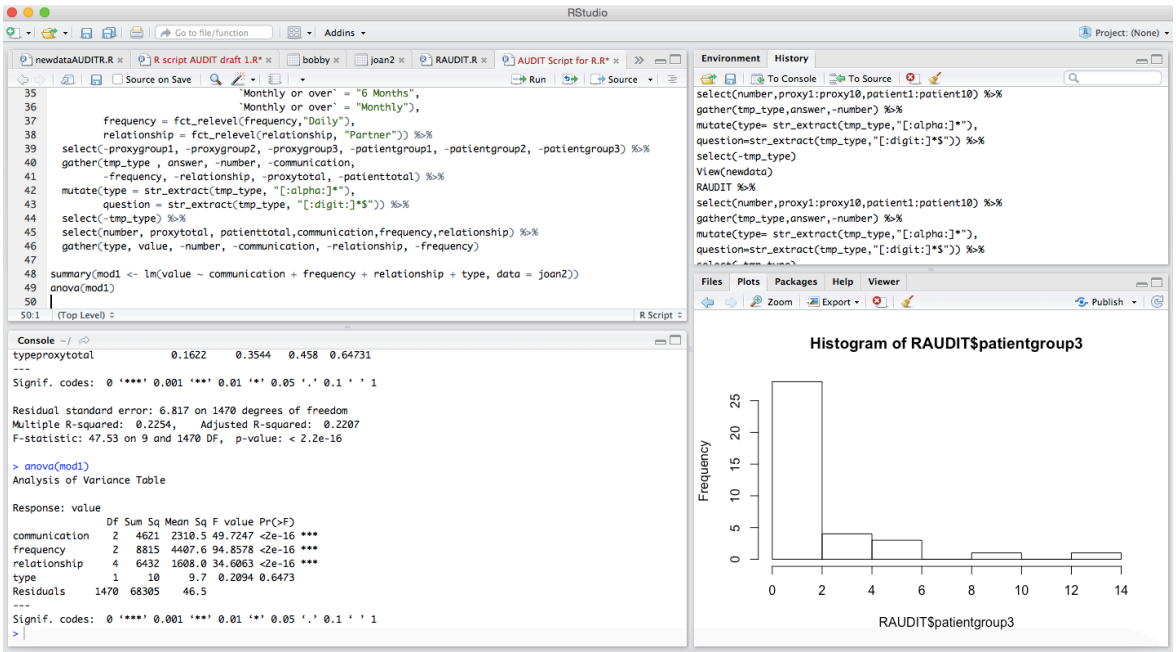
If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher in the first instance but the normal NHS complaint mechanism is also available to you.

Thank-you for your time

Appendix 11

Rstudio version 1.0.136: Screen shots





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