Title Page: Thesis Report

Outcomes in patients with cirrhosis evaluated through routine healthcare data

Dr Jessica Elizabeth Shearer

Submitted in accordance with the requirements for the post graduate degree of Doctor of Medicine

The University of Leeds

Faculty of Medicine and Health

June 2023

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapters 2, 3 and 4 are based on work from jointly authored publications.

The following publications have been used:

1. Shearer JE, Gonzalez JJ, Min T, Parker R, Jones R, Su GL, Tapper EB, Rowe IA. Systematic review: development of a consensus code set to identify cirrhosis in electronic health records. Aliment Pharmacol Ther. 2022 Mar;55(6):645-657. doi: 10.1111/apt.16806. Epub 2022 Feb 15. PMID: 35166399; PMCID: PMC9302659.

Jessica E. Shearer and Ian A. Rowe were involved in study concept and design. Jessica E. Shearer, Juan J. Gonzalez, Thazin Min, Grace L. Su, and Elliot B. Tapper acquired, analysed, and interpreted data. Jessica E. Shearer drafted manuscripts. Ian A. Rowe, Richard Parker, and Rebecca Jones critically revised manuscript. All authors approved the final manuscript.

2. Shearer JE, Jones R, Parker R, Ferguson J, Rowe IA. The Natural History of Advanced Chronic Liver Disease Defined by Transient Elastography. Clin Gastroenterol Hepatol. 2023 Mar;21(3):694-703.e8. doi: 10.1016/j.cgh.2022.03.015. Epub 2022 Mar 23. PMID: 35337981.

Jessica E. Shearer: Conceptualization: Equal; Investigation: Lead; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Equal). Rebecca

Jones (Supervision: Equal; Writing – review & editing: Supporting). Richard Parker (Conceptualization: Supporting; Supervision: Equal; Writing – review & editing: Equal). James Ferguson (Data curation: Supporting; Writing – review & editing: Equal). Ian A. Rowe (Conceptualization: Lead; Formal analysis: Supporting; Methodology: Equal; Writing – review & editing: Equal

Ethics

The project has approval as a service evaluation/audit project from the Health Research Authority. IRAS Study ID: 224964. Letter of approval received 6th July 2017. Study compliant with relevant HRA standards.

Covid-19 impact statement

The Covid-19 pandemic has had no direct impact on the research project or thesis submission process. As such no re-design or mitigation has been necessary.

Acknowledgements page

Dr Ian A Rowe – *main supervisor*

Dr Richard Parker – *supervisor*

Dr Rebecca Jones - *supervisor*

Professor Eva Morris - *supervisor*

Dr James Ferguson – *provided data from Queen Elizabeth Hospital, Birmingham*

Dr Michelle Morris – *examiner for Transfer Viva*

Mr Raj Prasad – *examiner for Transfer Viva*

Mr David Chizhande – *IT analyst at Leeds Teaching Hospitals NHS Trust. Assisted with data acquisition.*

Mr Joel Kerry – *Librarian at Leeds Teaching Hospitals NHS Trust. Assisted with search strategy for systematic review.*

Ms Padma Dinesh – *Radiology IT systems support at Leeds Teaching Hospitals NHS Trust. Assisted with data acquisition.*

Ms Felicity Evison – *Information analyst at Queen Elizabeth Hospital, Birmingham. Assisted with data acquisition.*

Ms Libby Zhou - *Information analyst at Queen Elizabeth Hospital, Birmingham. Assisted with data acquisition.*

Professor Elliot B Tapper – *provided data and external validation from University of Michigan.*

Dr Juan J Gonzalez - *provided data and external validation from University of Michigan.*

Dr Grace L Su - *provided data and external validation from University of Michigan.*

Dr Thazin Min – *assisted with additional validation in UK cohort.*

Abstract

Background: Mortality from liver disease is rising. Recent efforts have been focussed on early detection and prevention of disease progression. Transient elastography (TE) is commonly used in clinical practice to diagnose fibrosis and is an accurate predictor of mortality, decompensation, and hepatocellular carcinoma (HCC). Electronic health records (EHR) have been used to observe 'real world' data in large cohorts of patients with liver disease.

Method: EHR data was used to observe outcomes in patients with advanced fibrosis. This included a systematic review followed by synthesis and validation of a code set to identify cirrhosis and complications in EHR data. Data extracted from EHR was used to assess survival and competing risk of liver and non-liver related events in a cohort of patients with advanced chronic liver disease defined by TE. Data was analysed to examine patterns of screening and surveillance for complications of cirrhosis in accordance with current practice guidelines.

Results: The developed consensus code set showed improved performance characteristics for identifying cirrhosis in comparison to previously used codes. In the analysis of over 3000 patients with advanced fibrosis, liver stiffness was associated with the development of varices, the transition from compensated cirrhosis to decompensated cirrhosis, and the development of hepatocellular carcinoma. Only a minority of patients had undergone the recommended surveillance interventions.

Conclusion: Electronic health databases can be used to evaluate screening and surveillance strategies, and to accurately define clinical progression and outcomes in large patient cohorts and estimates of disease progression in EHR cohorts are comparable to landmark studies of patients diagnosed using liver

biopsy. Transient elastography is strongly associated with outcomes in patients with advanced fibrosis. This study highlights the utility of EHR data in contemporary research practice in cirrhosis, highlighting the potential for a registry to impact on patient care and to improve outcomes for patients with cirrhosis.

Table of Contents

List of Figures

List of Tables

Glossary of abbreviations

ACLD – advanced chronic liver disease
AIH – autoimmune hepatitis
ArLD – alcohol related liver disease
BMI – body mass index
CAG – confidential advisory group
CCP – Canadian classification of diagnostic, therapeutic & surgical procedures
CI – confidence interval
CPRD – clinical practice research datalink
CPT – current procedural terminology
CSPH – clinically significant portal hypertension
CT – computer tomography
EHR – electronic health record
HCC – hepatocellular carcinoma
HBV – hepatitis B virus
HCV – hepatitis C virus
HE – hepatic encephalopathy
HES – hospital episode statistics
HH – hereditary haemochromatosis
HRS – hepatorenal syndrome
HSCIC – health and social care information centre
HVPG – hepatic venous pressure gradient
IBD – inflammatory bowel disease
ICD – international classification of diseases
IQR – interquartile range
kPa – kilopascals
LSM – liver stiffness measurement
LTHT – Leeds teaching hospitals NHS trust
MDS – minimum data set
MR – medical record
MRI – magnetic resonance imaging
NAFLD – non-alcoholic fatty liver disease
NCEPOD – national confidential enquiry into patient outcome and death
NHS – national health service
NICE – national institute for health and care excellence
NPV – negative predictive value

ONS – office for national statistics

OPCS – office of population and surveys censuses classification of interventions and procedures

PBC – primary biliary cholangitis

PSC – primary sclerosing cholangitis

PHE – public health England

PPV – positive predictive value

QEHB – Queen Elizabeth Hospital Birmingham

QUADAS – quality assessment of diagnostic accuracy studies

SBP – spontaneous bacterial peritonitis

TE – transient elastography

USS – ultrasound scan

UK – United Kingdom

Chapter 1

Introduction

Aims & Objectives

The main objective of this project is to demonstrate the effectiveness of electronic health record (EHR) data in facilitating the follow-up of patients with liver disease.

The main objectives of this study are:

1. Conduct a systematic review to evaluate the validity of diagnostic coding for identifying cirrhosis in electronic health record databases.
2. Develop a comprehensive set of ICD-10 codes that accurately define cirrhosis in electronic heath records
3. Validate the ICD-10 consensus code set and algorithms for determining aetiology and disease severity using a contemporary cohort of patients with chronic liver disease defined by transient elastography.
4. Analyse survival and competing risk of liver and non-liver related outcomes
5. Examine screening and surveillance patterns for complications of cirrhosis in accordance with practice guidelines

This chapter serves as an introduction to the central themes that will be discussed in further detail throughout the project. It will first consider the definition of liver disease, cirrhosis, and clinically significant portal hypertension. Studies which have described the natural history of liver disease will be explored, and the impact that non-invasive modalities have had on the diagnosis and risk stratification of liver disease Following this it will focus on the impact of liver disease in the United Kingdom, with a focus on the preventable causes of cirrhosis which are becoming increasingly prevalent. Finally, the role of routinely collected electronic health data in research in liver disease will be discussed.

1.1 Stages and causes of liver disease

Chronic liver disease refers to the process of gradual, progressive damage to the liver parenchyma occurring over an extended period. This chronic inflammatory process causes disruption to the liver architecture and scarring known as advanced fibrosis. The development of cirrhosis represents the end stage of chronic liver disease and is characterised histologically by the presence of regenerative nodules and distortion of hepatic vascular architecture on a background of advanced fibrosis (1). The main causes of cirrhosis in the UK are alcoholic related liver disease, non-alcoholic fatty liver disease (NAFLD) and chronic viral hepatitis. In addition to this there are rarer autoimmune and metabolic conditions including autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, and haemochromatosis.

Alcohol-related liver disease (ArLD) is hepatocyte damage occurring in the context of hazardous alcohol consumption, defined as greater than 14 units of

alcohol per week. Although reversible steatosis occurs in 90% of heavy drinkers (2), there is a risk of progressive fibrosis and irreversible cirrhosis in up to 37% of cases (3).

NAFLD refers to the development of hepatic steatosis in the absence of significant alcohol consumption, most often in conjunction with other metabolic risk factors such as diabetes mellitus, obesity and hypercholesterolaemia (4). It encompasses a spectrum of liver disease which are differentiated histologically depending upon the presence of hepatocellular inflammation known as non-alcoholic steatohepatitis (NASH) and fibrosis or cirrhosis.

The natural history of NAFLD is not fully understood, as most of our current understanding of the condition is based on estimates derived from studies of patients with risk factors for NAFLD who have undergone liver biopsy (5). In addition, the competing risk of non-liver mortality particularly from cardiovascular disease is substantial in this patient group, with relatively few patients with NAFLD progressing to cirrhosis (6). Despite these caveats and the reservations surrounding diagnostic testing, cost effectiveness and valid therapeutic options for NAFLD, European and National Institute for Health and Care Excellence (NICE) guidance supports screening for advanced liver fibrosis in ‘at-risk’ individuals (7, 8).

Chronic viral hepatitis refers to persisting viral infection which cause liver inflammation, fibrosis and eventually cirrhosis. There are two primary viruses which can cause both acute and chronic infection, hepatitis B virus (HBV) and hepatitis C virus (HCV). Hepatitis B is a virus is most often transmitted vertically from mother to child, but also through contact with infected blood and bodily fluids (9). If the infection persists beyond six months, it is chronic. Treatment strategies

are aimed at suppressing viral replication and thereby preventing disease progression and the development of primary liver cancer. 90% of hepatitis C is transmitted through blood borne contact by injecting drugs (10). Like chronic HBV infection, if left untreated HCV can lead to progressive liver fibrosis and ultimately cirrhosis. The introduction of curative direct acting anti-viral medication has led to a decline in the number of deaths relate HCV since 2016. During this time there has also been reduction in the number of patients requiring liver transplantation (11).

1.2 Complications of clinically significant portal hypertension

The chronic inflammatory process caused by any continued liver insult causes a cascade of cellular abnormalities resulting in parenchymal necrosis, raised intra-hepatic resistance and increased portal blood flow which ultimately leads to clinical significant portal hypertension (CSPH) (12). It is portal hypertension which is responsible for most complications associated with cirrhosis.

A formal diagnosis of CSPH relies upon hepatic venous pressure gradient (HVPG), which indirectly measures portal pressures. A HVPG of ≥ 6 mmHg defines portal hypertension and a threshold of >10mmHg is a strong predictor of the development of varices (13, 14), clinical decompensation (15) and hepatocellular carcinoma (HCC) (16).

Cirrhosis has historically been categorised into compensated and decompensated phases with distinct clinical courses and differing survival rates. Throughout the compensated phase the patient remains asymptomatic, and the duration may vary depending upon the underlying aetiology and the degree of

on-going liver injury. This is followed by a progressive decompensated phase characterised by complications of CSPH, specifically the development of varices, ascites, and hepatic encephalopathy.

Raised intra-hepatic resistance leads to splanchnic and systemic vasodilatation and portosystemic collaterals, which in turn leads to the formation of varices. A HVPG of >12mmHg correlates strongly with increased risk of bleeding and more advanced disease (14). Consequently, the incidence of decompensation and hepatocellular carcinoma (HCC) is higher amongst those patients with varices (17). The prevalence of varices in patients with compensated disease is 44% (18) with a yearly incidence of 7-8% (13, 19).

Variceal bleeding remains a major cause of mortality in cirrhotic patients (18), however advancements in the endoscopic and pharmacological management of bleeding have improved overall survival, with in-hospital mortality following an initial bleed estimated at 15% (20). Risk of re-bleeding is highest within the first six weeks with mortality occurring in 20% (21), although with increased access to early trans jugular intra-hepatic portosystemic shunt (TIPSS) in selected patients it is likely that this figure is now lower.

Splanchnic vasodilatation leads to hyperdynamic circulation, hypervolaemia and water retention which results in the development of ascites. This occurs at HVPG above 10 mmHg. Ascites is common in cirrhosis and it develops in half of cirrhotic patients over a 10-year period (22). It can be associated with several complications, including hepatorenal syndrome, dilutional hyponatraemia and refractory accumulation.

Although the management of ascites has improved in recent years, it remains a landmark in the progression of an individual’s disease and following its

development it has a five-year mortality rate of approximately 50%. Those patients who develop complications of ascites have a much higher mortality rate with refractory ascites carries a one-year survival probability of 30% (23).

The pathophysiology of hepatic encephalopathy is multifactorial and incompletely understood. The primary mechanism is considered to be due to impaired detoxification of ammonia in the context of portosystemic shunting leads to hyperammonaemia, which in turn causes neuronal dysfunction (24). Hepatic encephalopathy occurs in 30-45% of cirrhotic patients, with an incidence of 2-3% per year (22, 25, 26). It occurs in patients with more advanced disease and is rarely the first decompensating event to occur (27). Thus, the development of hepatic encephalopathy is associated with a poor prognosis with a transplant free survival probability of 42% at 1-year (28).

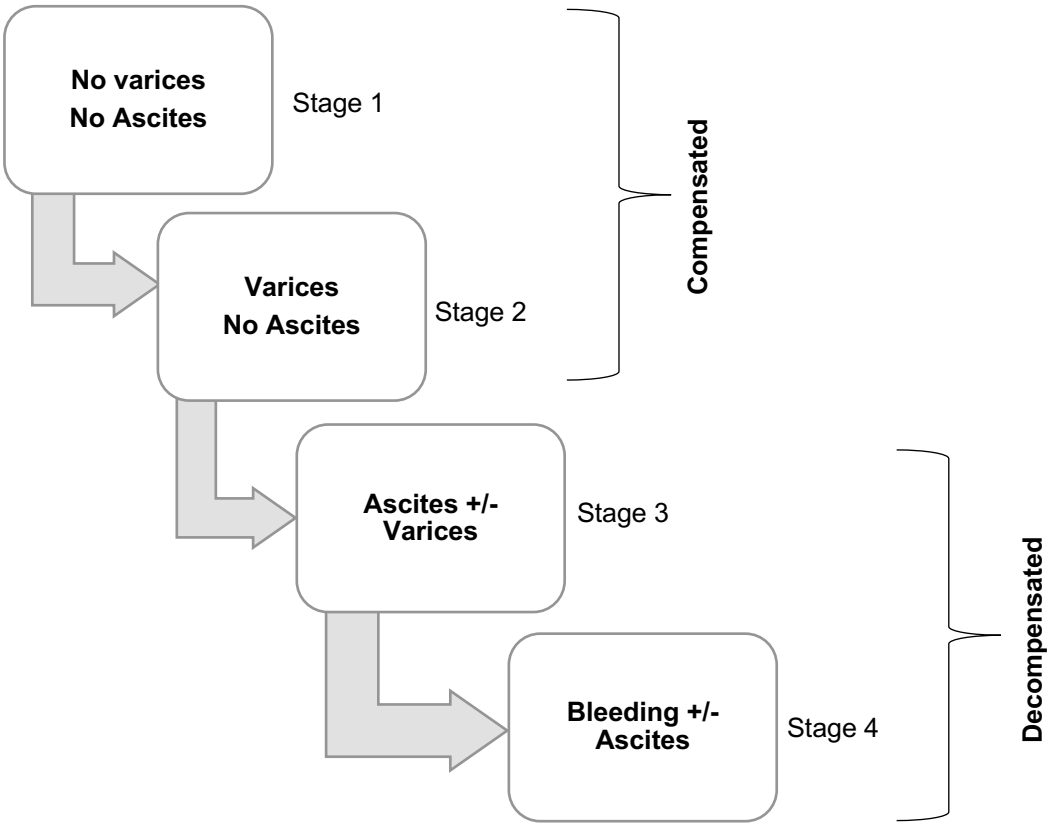
1.3 Natural history

The Baveno IV consensus sub-divides cirrhosis into stages based on the severity of CSPH, allowing more detailed stratification of those patients at increased risk in patients with compensated cirrhosis without varices is as low as 1% per year, in contrast to those with decompensated disease which carries a mortality rate of 57% (18). The Baveno IV classification can be applied to all patients with cirrhosis, irrespective of underlying aetiology.

Compensated cirrhosis encompasses two stages: *Stage 1* indicating the absence of varices and ascites and *stage 2* which is characterised by the presence of oesophageal varices without ascites. The remaining stages correspond to decompensated disease: *Stage 3* indicates the presence of ascites without

varices, whilst *stage 4* refers to those patients who have bled from varices with or without ascites. A schematic of this staging system is shown in **Figure 1.1**

Figure 1.1 Schematic representation of Baveno IV classification of cirrhosis severity. Adapted from D'Amico *et* al (18)



Whilst it provides valuable information, it is recognised that the four-stage system had limitations, in so far as patients do not move unidirectionally through each stage, and that some decompensating episodes carried a poorer prognosis. Additionally, it does not consider the risk of non-liver events, such as non-variceal gastrointestinal bleeding. In addition, the system relies heavily on endoscopic evaluation to determine the presence of varices. It is worth noting that the Baveno IV staging system was developed in 2005, and has since been refined by D'Amico *et* al, to reflect the poorer outcomes observed in decompensated patients with ascites than those without (29, 30). The most recent multistate model involves

six stages which differentiate between first and second non-bleeding decompensation events and end state decompensation (31). These newer systems aim to address some of the limitations of the original Baveno IV system and provide a more comprehensive risk assessment.

Progression through stages of cirrhosis remains unpredictable with numerous variables which influence both the rate and direction in which a patient may transition. More recently natural history studies of cirrhosis have incorporated multistate models of progression, which consider multiple outcomes and competing events which can influence each other over time (31, 32). This concept is particularly relevant in cirrhosis, as epidemiological studies are difficult due to the asymptomatic phase of the disease and the slow and variable rate at which patients may progress.

Competing risk refers to an event which precludes or impacts upon the occurrence of a second event within a patient's lifetime. There are many significant clinical events which can occur throughout the course of cirrhosis, which may not be captured when simply performing survival analysis. For example, a clinically relevant outcome such as the development of HCC will have the potentially relevant competing events of death and decompensation (31). Patients with varices are at risk not only from bleeding, but also from other decompensating events and death before or after further decompensation. These models should be considered when studying the natural history of cirrhosis.

1.4 Diagnosis and transient elastography

Establishing the presence and degree of fibrosis is important in the prognosis and management of liver disease. The diagnosis, grading and staging of cirrhosis has traditionally relied upon histology obtained by percutaneous liver biopsy. However this procedure is not without risk; up to 3% of patients will require admission for complications following liver biopsy, with pain and hypotension being amongst the most frequent complications (33). In addition, concerns remain regarding the accuracy of histological diagnosis due to sampling variability and intra and inter-observer reliability (34, 35).

Non-invasive techniques have gained popularity in recent years, to confirm and measure the degree of fibrosis present in the liver. The most widely used modality in the United Kingdom is transient elastography (TE), which is well validated, easily accessible and endorsed by National Institute for Health and Care Excellence (NICE) guidelines (36).

Transient elastography was initially developed 20 years ago by the food industry to assess the maturity of cheese (37). It describes the process of using an ultrasound impulse to measure the velocity of shear waves transmitted across a tissue, thereby giving a measurement of its' elasticity (38).

As a liver becomes more fibrotic it increases in stiffness, which correlates with fibrosis in patients with chronic liver disease (39). The result is based upon the median of ten valid measurements obtained by an experienced operator. There are a number of quality indices which must be satisfied in order to produce a valid measurement, including an interquartile range (IQR) of less than 30%, which indicates the variation between each measurement, and a success rate of greater

than 60%, reflecting the ratio of successful measurements to the total number of scans taken (40). A body mass index of greater than 28 is associated with higher risk of failure (41), although this has been mitigated by the introduction of an XL probe (42) and conditions which increase liver stiffness, such as cholestasis, congestion, inflammation and insufficient fasting period prior to scan may produce falsely elevated results.

Liver stiffness is measured in kilopascals (kPa) and ranges between 2.5kPa to 75kPa. Meta-analyses have been conducted to assess the overall performance of TE in the diagnosis of cirrhosis. Friedrich-Rust *et* al found that a threshold of 13kPa could accurately differentiate cirrhosis with a mean area under the receiver operating curve (AUROC) of 0.94 (43). Similarly Tsochatzis *et* al demonstrated that a reading of above 15.4kPa had a 90% probability of diagnosing cirrhosis across different aetiologies (44). Both studies confirm that TE performs better in the diagnosis of cirrhosis as opposed to fibrosis, for which the AUROC drops to 0.84.

Whilst it is accepted that a reading of >10kPa suggested advanced fibrosis, this cut-off value varies amongst studies and different diseases. It is perhaps more precise to consider elastography measurements as a continuum through which a patient may progress or indeed regress depending upon a variety of co-factors, such as underlying disease activity, the degree of ongoing inflammatory insult and the introduction of therapeutic interventions.

As liver stiffness reflects increasing portal pressures, TE is a surrogate marker for portal hypertension. Meta-analyses have found that TE had a AUROC of 0.93 for CSPH and 0.84 for oesophageal varices (45), whilst a cut-off value of 21kPa correlated well with HVPG measurements (46). TE has also been shown to

accurately predict mortality and liver-related events including decompensation and hepatocellular carcinoma (47, 48). Whilst the majority of studies using TE to determine prognosis have been conducted in patients with viral hepatitis (49, 50), more recently its' prognostic value for both liver and non-liver related outcomes has been assessed within the NAFLD population (51).

Various studies have evaluated the combination of TE with other measurements such as platelet count to determine if non-invasive methods can be used for risk stratification. The Baveno VI consensus suggests that patients with a liver stiffness measurement (LSM) of less than 20kPa with a platelet count of greater than $150x10^3/\mu l$ are unlikely to have varices and can therefore safely avoid screening endoscopy (52). This criterion has since been validated in several studies (53, 54) which show it can effectively 'rule out' CSPH with only a small number of patients being misclassified, but that the number of avoided endoscopies is relatively low. For this reason, the thresholds for avoidance of endoscopy have been adjusted to LSM less than 25kPa and platelet count greater than $110x10^3/\mu l$, which increases the number of endoscopies spared whilst maintaining a minimal number of missed high-risk varices (55).

It is likely that the widespread use of non-invasive techniques to diagnose advanced chronic liver disease (ACLD) will alter the recognised trajectory of liver disease and its' complications. The landmark natural history studies which have influenced our understanding and practice over the past two decades are largely based on small prospective cohorts of patients with biopsy proven cirrhosis (18). This highly selected group are likely to have more advanced disease than those patients considered to be 'high risk' who are diagnosed opportunistically through

non-invasive modalities. This is an important consideration when using TE data to predict and compare outcomes in liver disease.

1.5 The burden of liver disease

Liver disease is a public health crisis, the scale of which has been overlooked and under-prioritised for decades. There is an abundance of statistics which illustrate the concerning rise in liver disease in the United Kingdom (UK). Over the past fifty years liver-related deaths have increased by 400%, accounting for 2.5% of all deaths in England in 2018 (56, 57). The majority of these deaths occur in those aged between 18 and 65 years (58), with liver disease now accounting for 10% of deaths in 35 to 49 year olds, surpassing mortality relating to suicide and heart disease in this age group (59).

The impact of liver disease is not limited to loss of life; it also falls within the top five leading causes of years of working life lost for both men and women, accounting for 28,000 years lost amongst women, and 45,000 years in men in 2020 (57). The impact on the National Health Service (NHS) is substantial, with the number of cirrhosis-related hospital admissions doubling between 2005 and 2015 to over 65,000 admissions per year (58). This compares to unplanned admissions relating to respiratory medicine and cardiology 143,000 and 163,000 during the same period (60). The total number of unplanned admissions to NHS hospitals in 2015/2016 came to 5.7 million.

Preventing premature death secondary to liver disease has gained prominence in the media over recent years. In 2012, it was recognised as a key public health priority in the Chief Medical Officers Annual Report (61), followed by a 2014 All-

Party Parliamentary Hepatology Group report entitled ‘Liver Disease: Today’s Complacency, Tomorrow’s Catastrophe’ (62). This report gained extensive media coverage and prompted Public Health England (PHE) to develop a framework aimed at addressing preventable causes of liver disease. In 2017, PHE published the Atlas of Variation in Liver Disease, illustrating the widespread variation in premature mortality, hospital admissions and health inequality across England (63).

The Lancet Commission on Liver Disease was established in 2014 to address the growing burden of liver disease and to improve the quality of care for patients with this condition. The Commission has published five strategic documents that focus on lifestyle issues and risk factors for cirrhosis, with the goal of reducing the morbidity and mortality associated with liver disease (10, 64-67).

Despite the progress which has been made over the past decade, the final Lancet publication in 2019 stressed the on-going public health crisis posed by liver disease due to preventable causes and the lack of public awareness into the hazards of obesity and excess alcohol (68). The report also highlighted the unacceptably high levels of in-hospital mortality due to liver disease outside of specialist centres and the perceived short-comings in government policies aimed at tackles liver disease.

Cirrhosis is a disease of deprivation, which disproportionately affects the poorest and most marginalised members of society. Rising social inequality across the UK in comparison to other developed countries (69) has resulted in high levels of unemployment, substance misuse and poor access to healthcare services in this vulnerable patient population, all of which are risk factors for liver disease. On average those from the poorest socioeconomic group die from liver disease ten

years earlier than the most affluent economic group (63), highlighting the significant impact of socioeconomic status on health outcomes.

Stigma surrounding drug and alcohol abuse as well as obesity further compounds the problem for patients with cirrhosis, and is associated with poor quality of life, and reduced social support (70). This stigma also discourages patients from seeking medical help, leading to delays in diagnosis and treatment.

In addition to these challenges, public awareness of liver disease in general remains poor. A recent survey of over 2000 British adults demonstrated that only 1 in 10 people were able to correctly identify the three major causes of liver disease and only 16% of responders were aware of the guidance surrounding safe number of units of alcohol per week for low-risk drinking (68).

Overall, it is estimated that 20% of the population are at risk of developing liver disease, primarily due to preventable causes including alcohol consumption, NAFLD and chronic viral hepatitis (67). These risk factors highlight the importance of promoting healthy lifestyle choices and effective disease prevention strategies to reduce the incidence of liver disease in the general population.

In the UK, one in five adults are considered to drink excessively (71) and alcohol misuse is the leading cause of morbidity and mortality in those under 50 years of age (72). Hospital stays relating to alcohol have risen over the past decade, accounting for 338,000 admissions in 2017/18, whilst the number of admissions due to ArLD has increased by almost 60% during this time (71).

Age, gender and socioeconomic status are all risk factors for alcohol-related harm; socially deprived individuals are eight times more likely to be admitted to

hospital with alcohol related issues, and six times more likely to die from ArLD (63). The societal cost of alcohol misuse in the UK is estimated as high as £52 billion per year, due to a combination of alcohol-related admissions, working years lost and benefit allowance (73).

A quarter of adults in England are classed as obese (74), and NAFLD is the most common liver disease worldwide with an estimated prevalence of 20%, whilst the prevalence of NASH ranges between 3% to 5% (75). In England the rate of hospital admissions due to NAFLD lies at 4.5 per 100,000 with 7,425 people being admitted in 2019 (76). The economic burden is considerable, with a projected annual cost of €35 billion in European countries and more than $100 billion in the United States (77).

There are 180,000 people in the UK with chronic HBV and 240 million worldwide (78, 79). Prevalence in Europe is influenced by migration from high endemic areas and 95% of newly diagnosed cases of chronic HBV in the UK occur in migrant groups who have contracted the virus during childhood (80).

The five-year cumulative incidence rates of cirrhosis in chronic untreated HBV ranges from 8-17%, whilst the annual incidence rate of hepatocellular carcinoma in patients with established cirrhosis secondary to HBV ranges from 2-5% (81). Due to geographical limitations in the diagnosis and treatment of HBV in endemic areas, in 2016 only 10.5% of individuals were aware of their diagnosis, with 16.7% receiving treatment (9). As a result, routine childhood immunisation against HBV forms the cornerstone of the worldwide prevention strategy.

There are approximately 71 million individuals worldwide living with chronic HCV and 160,000 people in England (82, 83). 40-50% of individuals with HCV remain unaware of their diagnosis (11). This group form some of the poorest and most

vulnerable members of society with very limited access to healthcare, and the challenge remains in identifying and engaging these undiagnosed patients in treatment. The estimated financial cost of HCV in the UK through lost productivity is £367 million per year (9), although there is some evidence to suggest that the cost-effectiveness of anti-viral medication will mitigate this (84).

1.6 Data and electronic health records

NHS Digital was established in 2016, replacing the Health and Social Care Information Centre (HSCIC). It is the primary provider of data and IT systems in England and facilitates data sharing between different sectors of the NHS, as well as annual statistical publications. NHS Digital also collects data submitted to the national Hospital Episodes Statistics (HES) database, which contains details regarding all hospital attendances, admissions, and appointments to NHS hospitals in England.

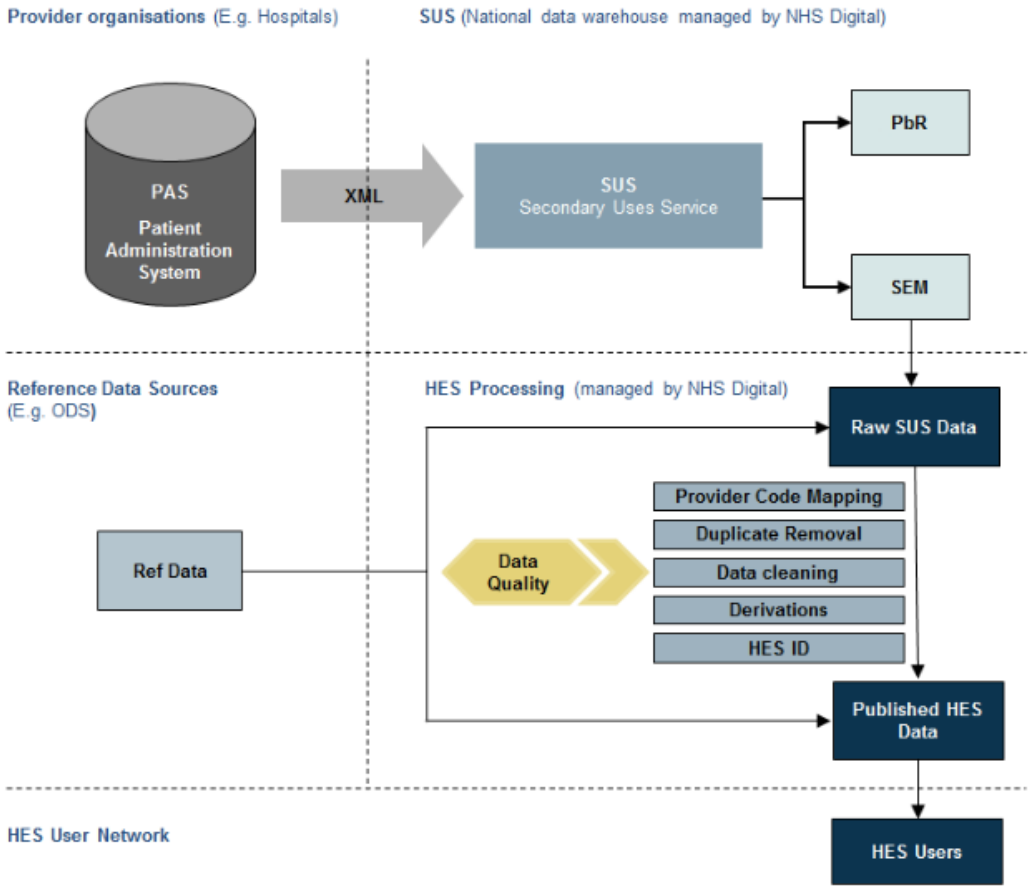
In the context of HES data, an ‘admission’ and an ‘episode’ refer to different aspects of an in-patient hospital encounter. An admission refers to a patient’s arrival into hospital and the beginning of an in-patient stay, whereas an episode can denote a specific period of care within an admission, for example a surgical procedure or a therapeutic intervention. In addition to this, a ‘finished consultant episode’ describes specific care provided by one consultant during a hospital stay. If care is transferred to another hospital or consultant, the finished consultant episode ends a new one begins. Thus, within an admission there may be multiple episodes with distinct start and end dates. A series of one or more of

these episodes each containing data regarding the patient journey combine to form a full admission, or in-patient spell.

In 2018-2019 this included 17.1 million admissions, an increase of 21% over the previous decade (85). On a local level each hospital has a Secondary Uses Service (SUS) system which extracts data monthly and submits this to NHS Digital. This data are then deposited in the HES data warehouse, which consolidates large amounts of anonymised data regarding dates and routes of in-patient admissions and discharge. It also contains patient demographic details such as age group, gender, ethnicity, and geographical data, as well as information regarding diagnoses and procedures. Out-patient activity is also recorded in the HES data warehouse, including records of appointment made and attendance and the specialty provider. It should be noted that payment by results only applies to HES Admitted Patient Care Data and as a result HES outpatient data coding is poor. A schematic of the HES data processing cycle is shown in **Figure 1.2.**

Figure 1.2. Schematic overview of the HES data extraction process[1].

Taken directly from 'The HES Processing Cycle and HES Data Quality' (86).



Electronic health records (EHR) collate longitudinal data generated throughout the course of routine clinical care. This data are easily accessible and there have been epidemiological studies relating to liver disease which use these databases to provide comprehensive information from a 'real-world' setting (87-89).

Both EHR and the HES database use coded patient data to allow uniformity and comparability. This is classified using the International Statistical Classification of Diseases and Related Health Problems (ICD). The World Health Organisation published the first ICD dictionary in 1948 and this has been updated and revised

[1] PbR; Payment by results, SEM; Standard extraction mart, SUS; Secondary uses service

periodically over time (90). The most recent version is ICD-11, which came into use in January 2022. ICD-10 has been used in the UK since 1995 and is updated every three years, whilst in the United States the ICD-9 system is still commonly used. The ICD dictionary contains codes for diseases, signs, symptoms, or injuries depending upon the reason for hospital attendance or admission. A list of the ICD-10 chapters and descriptions is shown in the **Appendix Pg 198(Table 1).** Each admission contains a primary diagnosis code and multiple secondary codes for each hospital admission or encounter (91).

An admission may also contain details regarding procedures and diagnostic investigations (92, 93), which are based on the Office of Population and Surveys Censuses Classification of Interventions and Procedures version 4 (OPCS-4) (94). This version has been in use since 1990 and has been updated periodically, most recently in 2007 (95). A list of OPCS-4 chapters and descriptions is shown in the **Appendix Pg 199 (Table 2).**

The primary use of the HES dataset is to allow reimbursement to hospitals from NHS England for services provided during a care episode. But one of the key additional uses of HES has been for research purposes, for which it is well validated (96). Between 2011 and 2016 there were 264 publications using the HES dataset (97). As a result, the same raw data stored on EHR which feed into secondary use service and subsequently HES can also be used. NHS Digital provide numerous different electronic datasets which have been utilised for healthcare planning, clinical audit, service development and research.

There are practical restrictions to using routinely collected EHR data for research. The process of data extraction can be time consuming and may require input from specialist data processors. This can lead to delays in receiving and quality

checking the data, which can then impact upon the available for analysis. Permissions are required for access to data, with stringent Information Governance procedures to ensure the data sharing and privacy laws are adhered to. This can be a challenging and lengthy process for researchers (98, 99).

The Department for Health and Social Care outlined the importance of health technology systems in their Policy paper in 2018. In this they describe how clinicians should have easy access to data and be able to apply algorithms to analyse this for research purposes (100). Indeed the use of EHR data for research has expanded in recent years, encouraged by funding through Health Data Research UK (101) and the development of research Hubs, including the 'Gut Reaction-Health Data Research Hub for Inflammatory Bowel Disease' (102), which is used for secure data processing. To date there is no Heath Data Research funded research focussed on liver disease.

Chapter 2

A systematic review of codes used to identify cirrhosis in electronic health records

2.1 Introduction

The ability to identify large cohorts of patients with chronic liver disease can improve understanding of the natural history of cirrhosis and liver-related complications. Data collated in EHR, and administrative databases are easily accessible and can provide comprehensive information regarding 'real-world' care patterns, costs, and outcomes (87-89).

The meaning and value of these data are directly related to both their validity and applicability to the population with cirrhosis. There have been several studies conducted which evaluate the validity of diagnostic codes in identifying patients with cirrhosis (103-106). As there are many codes relating to liver disease and its complications there is variation amongst studies in terms of the codes used to define the presence of cirrhosis. To date there is no consensus set of codes which is used internationally to define cirrhosis in EHR.

This chapter will provide evidence supporting the utility of EHR data in the follow-up of patients with liver disease. This chapter aims to synthesize a comprehensive code set which can be used for future studies using EHR to study patients with cirrhosis by comparing definitions of cirrhosis based upon sets of existing diagnostic and procedural codes across studies and countries.

2.2 Method

2.2.1 Data sources and search strategy

A systematic review was conducted. The aim of this was to analyse and compare studies utilising EHR data to define cirrhosis. A systematic search strategy was developed. This was adapted from previous studies validating ICD codes within databases (107, 108). The search terms used were as follows:

1. Health Services Research/
2. administrative data.mp.
3. hospital discharge data.mp
4. icd9.mp.
5. icd10.mp
6. icd-9.mp
7. icd-10.mp
8. icd-9-CM.mp
9. icd-10-CM.mp
10. “International Classification of Diseases”/
11. medical record*.mp
12. health information.mp
13. surveillance.mp
14. physician claims.mp
15. claims.mp
16. hospital discharge.mp
17. coding.mp
18. codes.mp
19. clinical coding.mp
20. medical coding.m
21. diagnostic coding.mp
22. (validity or validation or case definition or algorithm or agreement or accuracy or sensitivity or specificity or positive predictive value or negative preditive value or validity of results or reliability or reference values or reference range).af
23. cirrhosis.mp
24. hepatic cirrhosis.mp

25. exp Liver Cirrhosis/
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
27. 22 and 26
28. 23 or 24 or 25
29. 27 and 28
30. Limit 29 to English language
31. Limit 30 to humans
32. Remove duplicates from 31

A search was completed using the OVID platforms of MEDLINE and EMBASE electronic bibliographic databases from inception (1946 and 1947 respectively) to March 2020 including 'In-Process' citations of all peer reviewed literature and conference abstracts. The search was limited to articles published in English and human studies, and the studies were de-duplicated prior to evaluation. To identify additional studies, the author hand-searched bibliography lists. Following this, the identified studies were reviewed in full text and assessed for eligibility against the inclusion and exclusion criteria.

The systematic review protocol was prospectively registered with PROSPERO (International prospective register of systematic reviews) registration ID: CRD 42019118848. The systematic review protocol is included in the **Appendix Pg 200-202.**

It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and checklist (109). This is show in **Table 2.1**.

Table 2.1. PRISMA Checklist[2]

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	24
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	23
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	24-25
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	25
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	29
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	24-25

[2] PICO; population, intervention, comparison, outcome

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	29
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	30
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	30
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	31
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	30-31
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	31
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	34
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	40
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	35-36
Synthesis of	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

results			
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	40
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	51-57
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	58-59
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	60
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.	N/A

2.2.2 Study selection

Studies were evaluated for inclusion in two stages. In the first stage all identified titles and abstracts were screened. In the second stage relevant studies were retrieved and a full text review was done on all studies which met the pre-defined inclusion criteria. All observational cohort studies assessing the validity of diagnostic and procedural codes (ICD-9 and ICD-10) to identify cirrhosis in adult patients either as their primary aim or as part of a larger epidemiological paper were included. Studies had to report the code set or algorithm employed to search the electronic database.

2.2.3 Inclusion and exclusion criteria

A study was included in the systematic review if it met the following predefined criteria: age >18 years, information regarding hospital admissions stored in electronic records as part of routine care, ICD-9 or ICD-10 codes explicitly defined and validated in medical record review. Studies using laboratory data to identify and define those patients with cirrhosis were excluded, as this data are not routinely available through EHR data alone. Where conference abstracts and full manuscripts of the same study are identified, data were extracted from the full manuscript.

2.2.4 Data extraction and quality assessment

The full text of each article was reviewed. Data was extracted, tabulated, and summarised onto a standardised template. The information gathered included study author, year of publication and site, start date and duration of data collection, electronic data source, sample size, ICD codes or algorithm employed. If statistical estimates were not reported in the original paper, estimates were calculated from the available data. This included sensitivity, specificity, positive predictive value, negative predictive value, and kappa value (a measure of agreement beyond that expected by chance).

In this context, sensitivity refers to the ability of a code or algorithm to correctly identify individuals who have liver disease (true positives), whilst specificity measures the ability to correctly identify individuals who do not have liver disease (true negatives). A highly specific test rarely produces false positive results, therefore when the test yields a positive result, it strongly suggests the presence of the condition being tested for. Similarly, a highly sensitive test rarely produces false negative results, meaning that when a test is negative it effectively rules out a disease. A test with both high sensitivity and high specificity is ideal, as it accurately detects the presence or absence of a disease.

Positive predictive value refers to the probability of a patient having liver disease when a code or algorithm is present. Conversely, negative predictive value is the probability of patient not having liver disease when a code or algorithm yields a negative result. These measures are influenced by the prevalence of liver disease within a specific population, thus as prevalence increase so too does the positive predictive value. In summary, positive predictive value and negative predictive value are measures that assess the accuracy of a code or algorithm in

determining the presence or absence of a disease. **Table 2.2** shows a 2x2 table describing the performance metrics of interest recorded in the analysis.

Table 2.2. 2x2 table to describe performance characteristics included in systematic review

	Confirmation of presence of liver disease in medical record	Confirmation of absence of liver disease in medical record	Performance characteristic
ICD-10 Code Algorithm positive (suggesting liver disease present)	True positive (A)	False positive (B)	A/A+B Positive predictive value
ICD-10 Code Algorithm negative (suggesting liver disease absent)	False negative (C)	True negative (D)	D/C+D Negative predictive value
Performance characteristic	Sensitivity A/A+C	Specificity D/B+D	

As there is no validated quality assessment tool for non-comparator retrospective studies (studies which examine the outcome or characteristics based on data from existing records of a group of individuals without comparing them to a separate control group). an adaptation of the QUADAS tool (Quality Assessment of Diagnostic Accuracy Studies) was used to evaluate the quality of the included studies (110). This is included in the **Appendix Pg 204 (Figure 2).**

2.2.5 Data synthesis and citation analysis

Data was synthesised qualitatively, with the authors reviewing the data extraction table and then re-reviewing the relevant articles. Citation analysis was conducted using the web resource Scopus to assess the impact, geographical reach, and applicability of the studies. This analysis was conducted in September 2020. Abstracts were excluded and only those studies in which the primary objective

was validation of codes within liver disease were included, as it was felt that this would be a more accurate reflection of the impact and use of these validated code sets. Only those studies published at least five years ago were included, and citations were analysed per publication year.

2.3 Results

2.3.1 Study characteristics

A flow chart of studies identified is shown in **Figure 2.1.** Results from the search strategy are shown in the **Appendix Pg 203 (Figure** 1**).** A total of 1975 abstracts were identified. After de-duplication 1626 abstracts remained. 138 studies were reviewed in full text. A further twenty-nine papers were identified and reviewed through hand-searching of reference lists. Overall, eighteen studies met the inclusion criteria and were included in the final qualitative analysis. The studies and a description of their characteristics and source populations are shown below in **Table 2.3**.

The sample size ranged between 84 to 6714 people, with a total of 18,704 patients included. Twelve studies were conducted in the United States (103-106, 111-118), two in Denmark (119, 120), two in Canada (121, 122) and two in the United Kingdom (123, 124). Of those studies from the United States, five used cohorts from the Veterans Administration (VA) population (103, 104, 112, 114, 125). In two studies the evaluation was carried out in a single hospital setting (105, 117).

Seventeen of the studies used medical record review to validate the diagnosis of cirrhosis (103-106, 111-117, 119-122, 124, 125). In these studies, the full medical

record was retrieved and compared with the diagnostic codes of interest. Amongst the seventeen studies, thirteen outlined an explicit definition of their primary outcome measure (103-106, 111, 113, 114, 116, 117, 119, 121, 123, 124). All these included histological and/or radiological evidence of liver disease and five also included specific laboratory parameters (103, 104, 113, 116, 119). One study searched primary and secondary care records and death registry data for codes or free-text terms relating to cirrhosis as their validation standard (123). A detailed description of validation standards used is shown in **Table 2.4**.

Ten studies evaluated codes using electronic health records (104, 105, 111, 113-115, 117, 123-125) and seven used administrative databases (103, 106, 112, 116, 119, 121, 122), the majority of which reported on in-patient and out-patient data. One study used a national registry database (120). Validation was the primary outcome measure in fourteen studies (103-106, 111-115, 117, 120-122, 124). Two of these studies focussed on validation of the comorbidity variables which constitute the Charlson index, of which liver disease was extracted separately (120, 122). Seven of the validation studies analysed disease severity i.e., codes representing decompensation events in addition to cirrhosis codes (104-106, 113, 114, 121, 124). One study validated an algorithm using ICD codes with and without the addition of a natural language processing algorithm (111).

Figure 2.1. Study flow chart

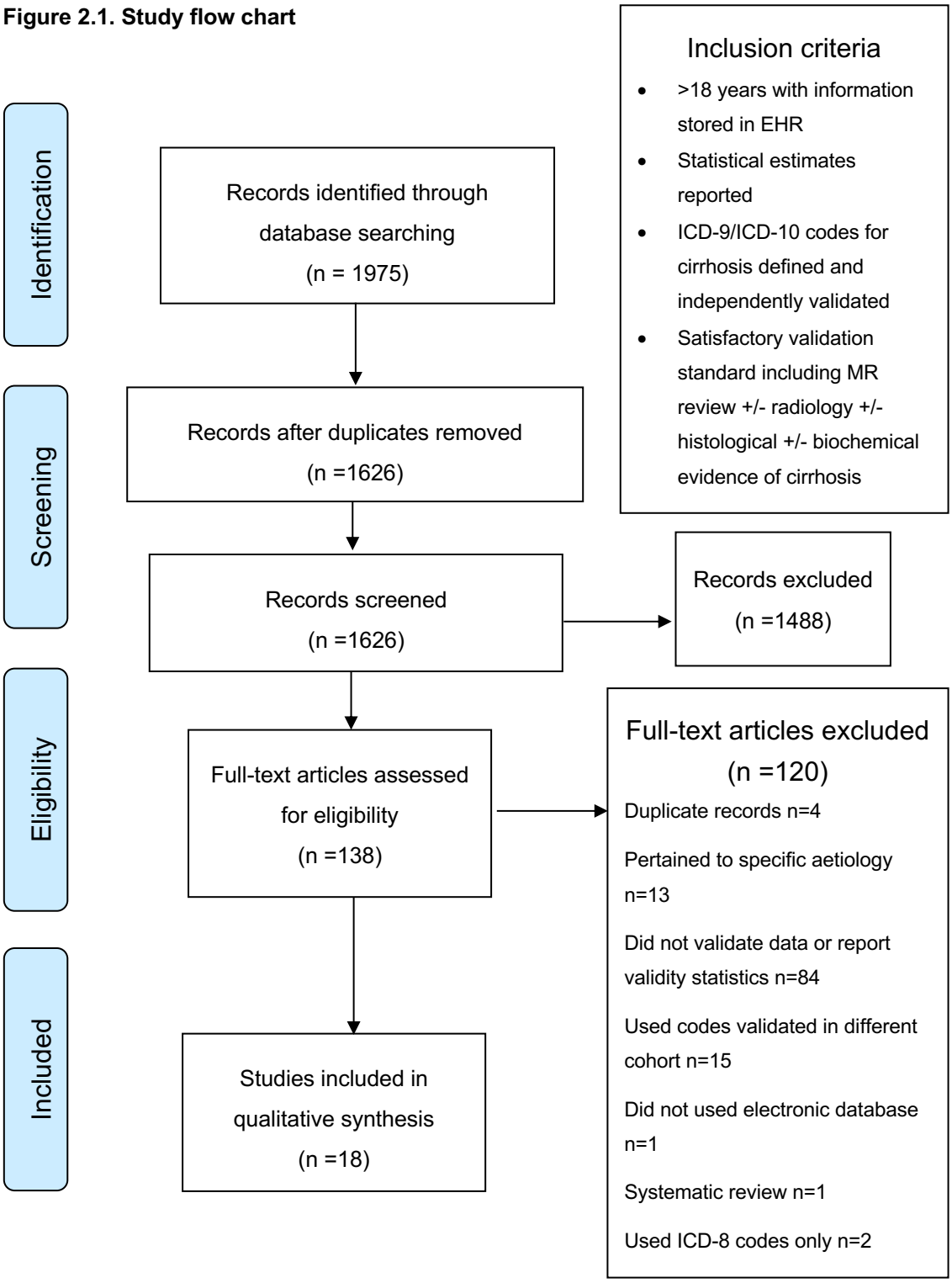


Table 2.3. Study characteristics of studies validating diagnostic codes in liver disease in order of publication year[3].

Author (year)	Country	Study years	Source population	Type of database	Sample size	Records validated
Quan et al (122) (2002)	Canada	1996-1997	Patients admitted to one of three hospitals within the Calgary Regional Health Authority	AD	1200	1200
Hachem et al (112) (2008)	US	1995-2005	Veterans registered at VA medical clinics in Houston, Texas	AD	84	84
Kramer et al (103) (2008)	US	1998-2004	Veterans registered at VA medical clinics in Houston, Texas	AD	331	331
Re et al (104) (2011)	US	2005	Patients enrolled in the Veterans Aging Cohort Study	EHR	137	137
Thygesen et al (120) (2011)	Denmark	1998-2007	Patients registered in the Danish National Registry in the North Jutland Region, Denmark	NR	950	50
Singal et al (117) (2011)	US	2008-2009	Patients admitted to one hospital in Dallas County	EHR	1589	1589
Goldberg et al (106) (2012)	US	1997-2011	Patients receiving IP or OP care at two tertiary care hospitals in Pennsylvania	AD	266	244
Kanwal et al (125) (2012)	US	2000-2007	Patients receiving IP or OP care at 3 VA medical centres and 15 clinics in the Midwest	EHR	774	300
Rakoski et al (116) (2012)	US	2008	Patients enrolled in the national Health and Retirement Study & receiving care at University of Michigan	AD	317	100
Fialla et al (119) (2012)	Denmark	1996-2006	Patients enrolled in the Funen Patient	AD	1369	1369

[3] AD; administrative database, MR; medical record, IP; inpatient, OP; outpatient, EHR; electronic health record, VA; veterans affairs, NR; national registry, US; United States, UK; United Kingdom

			Administrative System registry in Denmark			
Rabin et al (115) (2013)	US	2013	Patients enrolled in the Chronic Hepatitis Cohort Study in Detroit, Michigan*	EHR	283	283
Nehra et al (105) (2013)	US	2008-2011	Patients receiving IP or OP care at one hospital in Dallas County	EHR	2893	2893
Ratib et al (123) (2014)	England	1998-2009	Patients enrolled in primary and secondary registries in England	EHR	5118	2282
Chang et al (111) (2016)	US	2013-2015	Patients receiving IP or OP care at 4 hospitals in Los Angeles	EHR	5343	168
Lu et al (113)(2017)	US	2015-2016	Patients enrolled in the Chronic Hepatitis Cohort Study in Detroit, Michigan	EHR	296	296
Mapakshi et al (114) (2018)	US	2015-2016	Patients with data stored within the VA Corporate Data Warehouse	EHR	325	325
Lapointe-Shaw et al (121) (2018)	Canada	2006-2013	Patients receiving IP or OP care at two tertiary care hospitals in Ontario, Canada	AD	6714	6714
Driver et al (124)(2019)	UK	2007-2016	Patients diagnosed with hepatocellular carcinoma in two NHS cancer centres in England	EHR	339	339

Table 2.4. Details of validation standard used to identify cirrhosis and complications[4].

Author (year)	Gold standard	Definition of validation	Validator
Quan et al (122) (2002)	MR	Details not given in paper	1 clinician
Hachem et al (112) (2008)	MR	Pathology +/- radiology +/- evidence in medical records	1 clinician
Kramer et al (103)(2008)	MR	Stage 4 cirrhosis on liver biopsy or ≥2 of ascites, cirrhosis, HCC, or portal hypertension on imaging or ≥2 of cirrhosis, ascites/peritonitis, varices, HCC, HRS, HE on imaging (CT/MRI/USS) or in notes or ≥2 albumin <30g/L, bilirubin>2.0mg/dL, INR >1.2 (or 1 of laboratory parameters with one of above)	1 clinician, 20% by 2nd clinician, 10% by 3rd clinician
Re et al (104) (2011)	MR	Radiological evidence of ascites (CT/MRI/USS) or evidence of peritoneal fluid analysis +/- polymorphonuclear leukocyte count ≥250 cells/mL or bacterascites or bleeding varices on endoscopy report or documentation of mental confusion in absence of non-hepatic causes or diagnosis of HCC on biopsy or radiology (CT/MRI)	1 non-clinician, results reviewed by 2 clinicians
Thygesen et al (120)(2011)	MR	Discharge summary/medical record describing exact diagnosis	1 clinician, 1 arbitrator
Singal et al (117) (2011)	MR	Consistent histology +/- cirrhotic-appearing liver on imaging with evidence portal hypertension (ascites, HE, varices, or splenomegaly with thrombocytopenia) *	1 clinician
Goldberg et al (106) (2012)	MR	Liver biopsy demonstrating cirrhosis or radiological evidence of cirrhosis (CT/MRI/USS), or documentation of cirrhosis based on biopsy/radiology	1 clinician
Kanwal et al (125) (2012)	MR	Documentation, laboratory, or radiological evidence of ascites, HE, in-patient GI bleeding, paracentesis or SBP	1 clinician, 10% by 2nd clinician
Rakoski et al (116) (2012)	MR	Liver biopsy demonstrating cirrhosis or radiological evidence of cirrhotic liver with splenomegaly + platelet count of <120,000mm/3 or evidence of decompensated cirrhosis with HE, HRS, ascites, or variceal bleeding	1 clinician

[4] HCC; hepatocellular carcinoma, HRS; hepatorenal syndrome, HE; hepatic encephalopathy, CT; computerised tomography, MRI; magnetic resonance imaging, USS; ultrasound scan, SBP; spontaneous bacterial peritonitis, FTD; primary care free text data, TE; transient elastography, INR; International Normalised Ratio; GI; gastrointestinal, MR; medical record, N/A; not available, MDT; multidisciplinary team

Fialla et al (119) (2012)	MR	Consistent histology cirrhosis or evidence of portal hypertension with hepatic wedge pressure of >8mmHg or INR >1.5 or cirrhotic liver on USS or perioperatively or evidence of complications such as varices, ascites +/- HE	N/A
Rabin et al (115) (2013)	MR	Radiology, laboratory parameters, biopsy, and clinical events	2 clinicians, 1 arbitrator
Nehra et al (105) (2013)	MR	Stage 4 cirrhosis on liver biopsy or radiological evidence of cirrhosis + evidence of portal hypertension on imaging or clinical evidence of portal hypertension/complications (ascites, varices, HE, HCC)	1 clinician
Ratib et al (123) (2014)	EHR + FTD	Search of primary and secondary care records and ONS death registry data for codes related to liver disease + examination of FTD for any of the following terms: “cirrhosis”, “ascites”, “varices”, “liver”, “portal hypertension”, “hepatic”, “jaundice” or “paracentesis”	N/A
Chang et al (111) (2016)	MR	Stage 4 cirrhosis on liver biopsy, radiological evidence of cirrhosis (CT/MRI/USS) or documented clinical diagnosis	1 clinician, 1 non-clinician
Lu et al (113)(2017)	MR	Documented evidence of HE or GI bleeding due to portal hypertension or jaundice with bilirubin >2.5mg/dL or ascites/hydrothorax due to portal hypertension/HCC	2 clinicians, 1 arbitrator
Mapakshi et al (114) (2018)	MR	Stage 4 cirrhosis on liver biopsy or documentation of cirrhosis or complications in medical record, radiological or endoscopic evidence of cirrhosis	1 clinician
Lapointe-Shaw et al (121) (2018)	MR	Stage 4 cirrhosis on liver biopsy or cirrhotic appearance on USS, non-invasive test result consistent with Stage 4 fibrosis or evidence in clinical record of ascites, bleeding varices, encephalopathy, use of spironolactone or nadolol without alternative indication or explicit mention of cirrhosis/decompensation/non-bleeding varices	2 clinicians,1 arbitrator, 5% by 2nd clinician
Driver et al (124) (2019)	MR	Documentation of cirrhosis in MR or MDT minutes, radiological/endoscopic evidence of portal hypertension, cirrhosis on liver biopsy, consistent TE result	3 clinicians

2.3.2 Study quality

Study quality was assessed using an adapted QUADAS tool (110). A detailed copy of the tool and a breakdown of individual scores for each study is shown in **Table 2.5.** The QUADAS scores ranged from 7 to 11 with a maximum of 14 (median 10).

Three studies used a selected population of patients; patients enrolled in the chronic hepatitis cohort study (113, 115) and patients with an ICD-10 code for hepatocellular carcinoma (124). Two studies did not adequately describe their selection criteria in detail (120, 122). Three studies used a random selection from their total sample to verify as a gold standard comparison (111, 116, 118). Seven studies stated that the individual abstracting data from the medical record was blinded to the database coding (103, 112, 114, 117, 118, 121, 122), whilst the rest did not specify. Seven studies used a single clinician to conduct chart review (105, 106, 112, 114, 116, 117, 122) the remaining ten studies used more than one clinician often in addition to an arbitrator.

Table 2.5. QUADAS assessment for papers included in systematic review

	Studies included in systematic review																	
Item	Quan	Hachem	Kramer	Re	Thygesen	Singal	Goldberg	Kanwal	Rakoski	Fialla	Rabin	Nehra	Ratib	Chang	Lu	Mapakshi	Lapointe-Shaw	Driver
1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
7	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
8	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
9	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
10	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
11	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
12	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
13	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
14	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Score (max 14)	**8**	**10**	**11**	**10**	**8**	**10**	**10**	**10**	**10**	**10**	**7**	**10**	**10**	**10**	**9**	**11**	**11**	**11**

● YES; ● NO; ● UNKNOWN

2.3.3 Quality of coding sets

Details of the type and number of codes used are shown in **Table 2.6.** Fifteen studies reported specific ICD codes used to define liver disease in their cohort (103-106, 111-114, 116, 119-121, 123-125). The remaining three studies (115, 117, 122) did not specify the codes however it was possible to obtain the information from other related studies (126-128). Seven papers adopted ICD code sets which had previously been used and validated by other authors (112, 113, 115, 120, 122-124), whilst eleven studies developed their own selection of codes (103-106, 111, 114, 116, 117, 119, 121, 125).

Quan *et* al used a coding algorithm developed previously by Deyo *et* al (126), which included fourteen ICD-9 codes in total. The 'mild' liver disease category of the Charlson criteria included 3 codes for cirrhosis, and this was therefore combined with the codes for 'moderate or severe' liver disease. Thygesen *et* al used a larger number of codes to define 'mild' liver disease which included codes considered to be less specific for cirrhosis (K71; K74; K76.0) (120). For this reason, only the coding algorithm which was employed for 'moderate or severe liver disease' were included.

There was significant variation in the number and type of codes used. These are shown in the **Appendix Pg 206-212 (Tables 4-7).** Overall, there were a total of sixty-three ICD-9 codes and fifty-four ICD-10 codes as well as seventy-seven procedural codes used to identify cirrhosis. Of those papers using the ICD-10 classification, this included codes from five disease manifestation categories (B15.0-94.2; C22; E80-E84.5; I81-I98.3; K22-K92.2) and two symptom-related and external causation categories (R16-R18.8; T86). Three ICD-9 and four ICD-

10 codes appeared as clustered codes denoting that all the sub-codes were used in that paper. Five papers incorporated procedural codes into their code sets. In one paper the specific procedural codes were unavailable (115). In the remaining four papers the number of procedural codes used ranged between 7 and 60 (113, 121, 123, 124). Whilst there were similarities between some of the code sets used, none of the papers used the same codes from the same ICD dictionary.

2.3.4 Assessment of validation in the literature

The validation statistics are shown in **Table 2.7.** PPV was available in all but one study (121) and was >90% in ten studies with a range of 71-100% (103, 104, 106, 111, 114, 117, 120, 123-125). Negative predictive value (NPV) was reported in seven studies (103-105, 111, 115, 122, 124) with a range of 72-99%. Nine studies reported sensitivity and/or specificity values (104, 105, 111, 113, 115, 116, 121, 122, 124), the range for which were 20-98% and 43-99% respectively. Kappa values were reported in only four studies and the values ranged from 0.48-0.71 (103-105, 122). Of the ten papers which reported a PPV of >90%, six of these included codes taken from both the in-patient and outpatient setting.

The median number of codes used was thirteen. There was no increase in the PPV in those papers that used more codes within their definition (≤13 codes PPV range 71-100%; >13 codes PPV range 71-91%). However, four studies which validated diagnostic codes found that combinations of codes improved sensitivity in comparison to a single code (104-106, 121).

There was no difference in the range of PPV between studies using ICD-9 codes (71-95%) and those using ICD-10 codes (71-100%). There was also no discernible difference in PPV depending upon the type of database from which coded information was extracted (administrative database 71-94%; EHR 71-99%). The study which used the Danish national registry reported PPV of 100%, although only 50 patient records were reviewed. There was an increase in the minimal value of the PPV range in the five studies conducted in the Veterans Affairs population (89-93%) in comparison to the remaining studies (71-100%).

The eighteen studies included were published over a 17-year period (2002-2019). The range of time for data collection varied widely from 1 to 14 years with a median length of 4 years and four of the studies collected data from over ten years (106, 112, 119, 123). None of the studies commented upon any longitudinal changes in statistical estimates during the study collection period. It was noted that here was no difference in the trend in PPV in later years compared to earlier years; in the six earliest studies published between 2002-2012 (103, 104, 106, 112, 116, 118-120, 122, 128), the PPV ranged between 71-100% whilst in the most recent studies published between 2013-2018 the PPV ranged between 71-99%.

Table 2.6. Details of code dictionary and number of codes used in each study [5]

Author (year)	Codes used	Case definition	Number of codes
Quan et al (122) (2002)	ICD-9	≥ 1 code (IP only)	14
Hachem et al (112) (2008)	ICD-9	≥ 1 code (IP or OP)	2**
Kramer et al (103)(2008)	ICD-9	≥ 1 code (IP or OP)	3
Re et al (104) (2011)	ICD-9	1 IP+2 OP codes	22**
Thygesen et al (120)(2011)	ICD-10	1st listed code (IP or OP)	11
Singal et al (117) (2011)	ICD-9	≥ 3 codes	11*
Goldberg et al (106) (2012)	ICD-9	≥ 2 codes (IP or OP)	58**
Kanwal et al (125) (2012)	ICD-9	≥ 2 codes (IP or OP)	12
Rakoski et al (116) (2012)	ICD-9	≥ 1 code (IP or OP)	12**
Fialla et al (119) (2012)	ICD-10	≥ 1 code (IP or OP)	4
Rabin et al (115) (2013)	ICD-9 +CPT	≥ 1 code	41
Nehra et al (105) (2013)	ICD-9	≥ 1 code (IP or OP)	11
Ratib et al (123) (2014)	ICD-10 + OPCS4	≥ 1 code	21
Chang et al (111) (2016)	ICD-9	≥ 1 code (IP or OP)	16
Lu et al (113)(2017)	ICD-9/10 + CPT	≥ 1 code (IP or OP)	43
Mapakshi et al (114) (2018)	ICD-10	≥ 1 code (IP or OP)	7
Lapointe-Shaw et al (121) (2018)	ICD-9/10+ CCP	≥ 1 code (IP or OP)	40
Driver et al (124) (2019)	ICD-10- +OPCS4	≥ 1 code (IP only)	33

[5] ICD; international classification of diseases, CPT; current procedural terminology, ONS; office for national statistics, CCP; Canadian classification of diagnostic, therapeutic and surgical procedures, IP; in-patient, OP; out-patient; OPCS office of population and surveys censuses classification of interventions and procedures

* Information not in original abstract-deduced from subsequent paper (30)

** Paper uses ICD-9-CM (clinical modification) classification

Table 2.7. Performance characteristics of each study. [6]

Author (year)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Kappa (κ)
Quan et al (122) (2002)	72	99	80	99	0.75
Hachem et al (112) (2008)	-	-	89	-	-
Kramer et al (103)(2008)	-	-	90	87	0.70
Re et al (104) (2011)	20*	99*	91	99*	0.48*
Thygesen et al (120)(2011)	-	-	100	-	-
Singal et al (117) (2011)	-	-	95	-	-
Goldberg et al (106) (2012)	-	-	94	-	-
Kanwal et al (125) (2012)	-	-	91	-	-
Rakoski et al (116) (2012)	67	-	88	-	-
Fialla et al (119) (2012)	-	-	71	-	-
Rabin et al (115) (2013)	91	72	71	91	-
Nehra et al (105) (2013) ‡	98**	43**	78	91**	0.71**
Ratib et al (123) (2014)	-	-	90	-	-
Chang et al (111) (2016)	47	97	92	72	-
Lu et al (113)(2017) ‡	83	89	85	-	-
Mapakshi et al (114) (2018)	-	-	93	-	-
Lapointe-Shaw et al (121) (2018) §	67-82	77-90	-	-	-
Driver et al (124) (2019)	86	98	99	79	-

[6] Se; Sensitivity, Sp; Specificity, PPV; positive predictive value, NPV; negative predictive value

*Estimated performance statistics using random sample of 100 patients without codes/hepatic decompensation

**Authors validated sensitivity using cohort of patients prospectively determined to have cirrhosis

‡ Paper uses a specific combination of codes to achieve these performance characteristics

§ Range given as results separated into 3 separate cohorts

2.3.5 Citation Analysis

Citation analysis is a research method used to examine the pattern, impact, and quality of citations within academic publications. In this case, this method was used to evaluate the research impact of articles by assessing the number of times it has been cited by other authors.

Citation analysis was conducted focussing on those manuscripts cited most frequently over the last 3 years, specifically those authored by Kramer *et* al, Nehra *et* al, Re *et* al and Goldberg *et* al. The total number of citations per study, mean number of citations per year over that period and the field-weighted citation impact (FWCI), which compare how a frequently a document is cited in comparison to similar documents (values greater than 1.00 indicate that a publication is cited more than expected according to the average) (129), are displayed in **Table 2.8.**

Table 2.8. Details of citation analysis.[7]

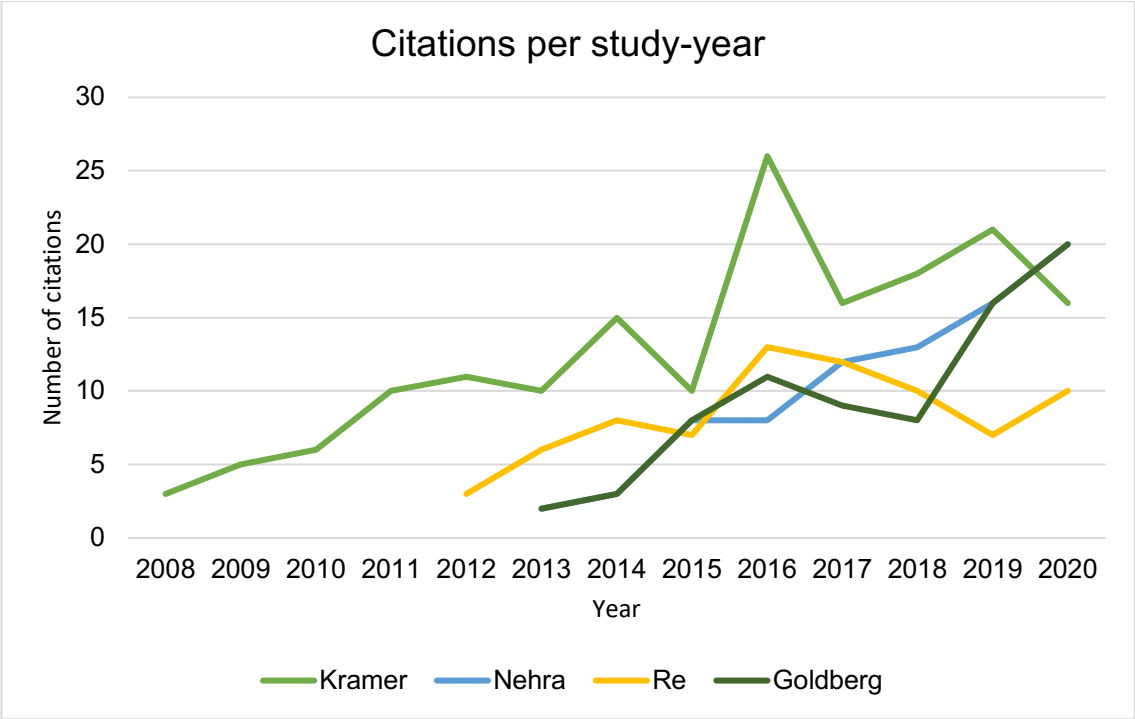
Author (year)	Total number of citations	Number of citations within last 3 years	FWCI	Mean number of citations per year
Kramer et al (103)(2008)	166	56 (18, 21, 17)	2.67	12.8
Re et al (104) (2011)	76	29 (10, 7 12)	1.87	8.4
Goldberg et al (106) (2012)	77	46 (8, 15 23)	1.45	9.6
Nehra et al (105) (2013)	86	46 (8, 20 18)	2.97	10.3

Over that period, the code set most frequently cited was from Kramer *et al*, but those from Nehra *et al*, and Goldberg *et al* were also often reported (103, 105, 106). This use of different code sets between studies highlights the need for a

[7] Total number of citations since publication is shown alongside the number of citations within the most recent three years (2018, 2019, 2020). FWCI; field-weighted citation impact

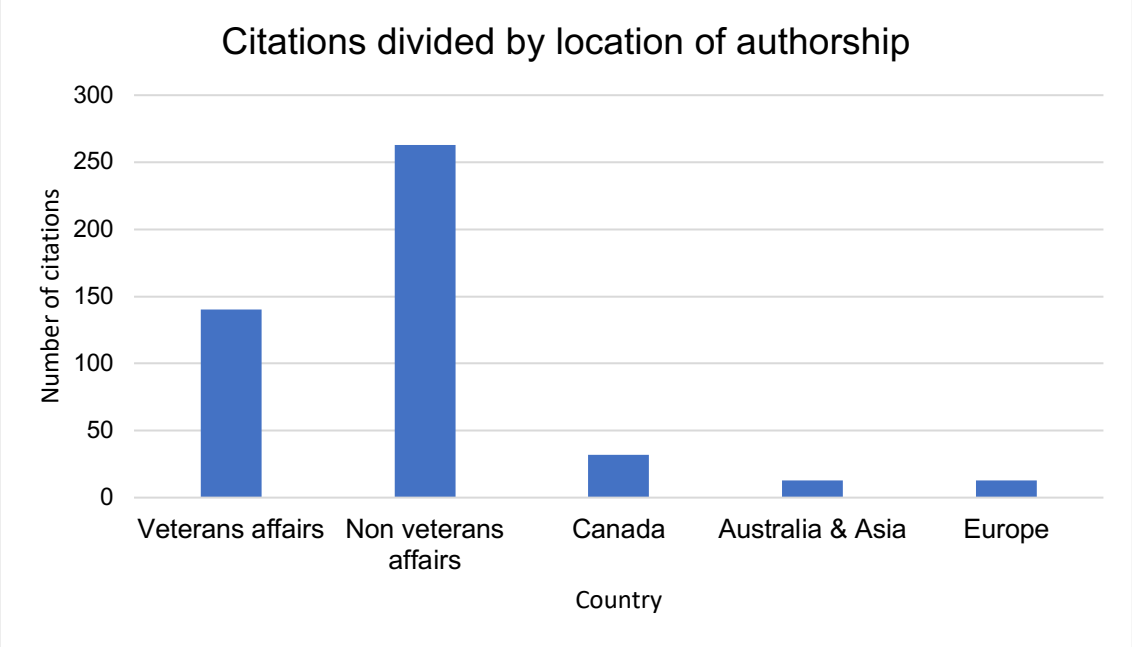
consensus approach to EHR research in the identification of patients with cirrhosis. **Figure 2.2** shows the citations per study-year since publication.

Figure 2.2. Comparison of citations per study year since publication



Analysis showed that the studies had been cited on 401 occasions. 342 of these studies were conducted within the United States and 140 of these were affiliated with Veterans Affairs institutions. **Figure 2.3** shows the total number of citations sub-divided by the country of authorship.

Figure 2.3. Citation analysis subdivided by country of author.[8]



The most cited paper within this subset was by Kramer *et* al (103), which was referenced by 166 articles over an eleven-year period. As the Kramer paper also validated codes for viral hepatitis each citing paper was reviewed individually to determine how many used the cirrhosis code set. Seventy-nine of the 166 studies used the cirrhosis code set, whilst forty-two papers referenced Kramer *et* al after using the code set to identify viral hepatitis. The remaining twenty-one articles did not use either code set.

[8] Publications from US divided into Veterans Affairs and non- Veterans Affairs affiliated. Papers conducted in Asia included Israel, Japan, South Korea, and Taiwan. Papers conducted in Europe included Denmark, Germany, Italy, Portugal, Spain, and UK

2.3.6 Consensus code set synthesis

ICD-9 codes were converted to the closest possible ICD-10 equivalent. This was done using General Equivalence Mapping, a technique developed by the Centers for Medicare & Medicaid Services and the Centers for Disease Control and Prevention (130). This process is used in medical coding to map codes from one system to another, ensuring continuity and accuracy in coding when transitioning to new systems. Mapping has been used extensively in the United States during the transition of coding systems from ICD-9 to ICD-10.

Here, the 2018 General Equivalence Mapping conversion table was used (131), and all converted codes were manually reviewed for accuracy and appropriateness prior to inclusion in the consensus code set. In most cases, a direct one to one translation was observed. However, there was one exception in which the ICD-9 code 571.6, which represents ‘biliary cirrhosis’, was mapped to two distinct ICD-10 codes: K74.4 for ‘secondary biliary cirrhosis’ and K74.5 for ‘biliary cirrhosis, unspecified’. It is noteworthy that a third code, K74.3, which corresponds to the ICD-9 code 571.6, denoting ‘primary biliary cirrhosis’, was not considered for inclusion. This omission was made because K74.3 is commonly used to specifically indicate the condition primary biliary cirrhosis rather than merely underlying cirrhosis.

The most common codes and definitions used across all studies were identified and considered for inclusion in the consensus code set **(Table 2.9).** The most frequently used codes were (when mapped to ICD-10) K70.3 – alcoholic cirrhosis, and K74.6 – other / unspecified cirrhosis. Other commonly used codes related to complications of cirrhosis and portal hypertension, including the presence of oesophageal varices and ascites.

Table 2.9. Most common codes used to identify cirrhosis [9]

ICD-9 code	ICD-10 code	Description (ICD-10 version)	Number of authors using code
571.5	K74.6	Other and unspecified cirrhosis of the liver	16
571.2	K70.3	Alcoholic cirrhosis of the liver	16
456 *-456.0* *-456.1* -456.2 *-456.21* *-456.20*	I85 *-I85.0* *-I85.9* I98 *-I98.2* *-I98.3*	Oesophageal varices *-with bleeding* *-without bleeding* Oesophageal varices in diseases classified elsewhere *-without bleeding* *-with bleeding*	14
572.3	K76.6	Portal hypertension	13
572.2	K72.9	Hepatic failure, unspecified	12
572.4	K76.7	Hepatorenal syndrome	9
571.6	K74.4 K74.5	Secondary biliary cirrhosis Biliary cirrhosis, unspecified	9
572.8	K72.1	Chronic hepatic failure	8
789.5	R18.0	Ascites	8

Since ascites can occur in conditions unrelated to liver disease (e.g., cardiac, or renal failure, or intra-abdominal malignancy) this code was of low specificity, and it was excluded from the proposed consensus code set to evaluate for future use **(Table 2.10).**

This is supported in previous studies (105, 132), which have found that using the code for ascites alone rather than in combination with other codes for chronic liver disease yields a PPV between 43-63%.

[9] Conversions using General Quivalence Mapping from ICD-9 to ICD-10 dictionary have been applied to determine the most appropriate code(s). The number of authors using the code includes those papers which used the code in either ICD-9 or ICD-10 format. ICD; international classification of diseases

Table 2.10. Consensus code set [10]

ICD-10 code	Description
K74.6	Other and unspecified cirrhosis of the liver
K70.3	Alcoholic cirrhosis of the liver
I85 *-I85.0* *-I85.9* I98 *-I98.2* *-I98.3*	Oesophageal varices *-with bleeding* *-without bleeding* Oesophageal varices in diseases classified elsewhere *-without bleeding* *-with bleeding*
K76.6	Portal hypertension
K72.9	Hepatic failure, unspecified
K76.7	Hepatorenal syndrome

2.4 Discussion

Accurate assessments of the population burden and the impact of cirrhosis in EHR research depend on the performance and validity of the coding algorithms used to identify cases. The aim of the systematic review was to review the available literature and to synthesise a comprehensive set of codes which can be used to facilitate future research internationally. There was substantial variation in the codes used to define cirrhosis. The nine most frequently used and relevant codes were extracted and combined into a consensus code set (**Table 2.10).**

[10] Final code set used to define cirrhosis in electronic health records. ICD; international classification of disease

2.4.1 The purpose and context of diagnostic coding

The increasing importance of EHR based research and the role of real-world evidence in clinical decision making demands a critical appraisal of the tools used to identify cirrhosis in such studies. When reviewing the literature to determine the validity of diagnostic coding one must consider the study purpose, location, and the data source from which the codes were extracted.

The provision of healthcare and the databases in use vary considerably worldwide, and in developed countries the most important factor to consider is the role of medical billing. In the UK and most Scandinavian countries healthcare is financed through tax payments. European countries such as Germany and France use insurance systems and Canada employs a government-led publicly funded model, with the option of privately paid insurance as a supplement. In the United States there are numerous systems in place, the majority of which rely upon medical billing and coding. Administrative and physicians claims databases were developed primarily for the purpose of billing and financial re-payment. Whilst the accuracy of these databases in identifying diseases has been widely reported upon (133-135) how precisely these findings translate to those countries where databases and healthcare systems differ remains unclear.

In addition to different EHR databases, coding practices within EHRs vary both between different countries and across the UK. These variations can be attributed to several factors, including healthcare structures, ICD revisions and adaptations and regional differences. The 10th revision of ICD is the most widely used version worldwide, however countries often adopt modified versions of the ICD to suit their specific needs. For example, the United States uses a national variation

known as ICD-10 CM (clinical modification), whilst Canada uses the ICD-10-CA. These adaptations are designed to align the coding system with the countries healthcare requirements and practices. Furthermore, the transition to new revisions of the ICD published by WHO can be a gradual process, leading to further variation and making comparisons between different healthcare systems challenging.

Regional variations also exist within the UK and the transition to newer coding standards, such as SNOMED CT (136), contributes to variations in coding practices across different regions and organisations. Devolved regions have separate policies and preferences, leading to differences in how data is coded and recorded. Moreover, local coding practices may vary between hospitals, as NHS trusts have the autonomy to set their coding standards based on local policies and priorities. These variations in coding practices can present difficulties in data exchange and interoperability.

The HES database contains coded information regarding admissions and procedures carried out in NHS hospitals in England. Whilst it reports upon outpatient activity, including demographic data and whether or not an appointment was attended, it rarely assigns diagnostic codes to outpatient visits (137). This is a key difference when considering EHR-based studies which are conducted in England compared to those done in the US, where outpatient information is coded similarly and with much greater frequency to in-patient data.

In addition, the HES database does not link with primary care data. Whilst the Clinical Practice Research Datalink (CPRD) provides linked data between registered GP practices and secondary care (138), it is not routinely available and

require annual funding for access. As a result, a study using secondary care data, particularly those limited to tertiary care centres, will inevitably capture those patients with more advanced decompensated disease and overlook patients who are more ambulatory and require primary care input only. This may lead to an underestimation of the prevalence of liver disease within a population.

2.4.2 The need for a consensus code set

Information in databases has been used widely in epidemiological studies of liver disease, yet many of these use code sets which have been developed by previous authors. Of those papers which were excluded after full text review, the majority of these were because they did not validate codes within their own data or did not report validity statistics.

The most widely used coding algorithm within the literature to date is adopted from Kramer *et al* (103). The Veterans Affairs system differs from the rest of healthcare provided in the US, both in terms of structure and funding and demographically. Most Veterans Affairs patients with cirrhosis are middle-aged males with a higher prevalence of HCV and comorbidities than the general population (139, 140). Despite this, more than half of studies citing the Kramer code set were from outside the Veterans Affairs system suggesting wide adoption of these codes for EHR research particularly in the US. However, to facilitate international collaboration and comparison a consensus code set that is better able to identify cirrhosis has several advantages and indeed these have gained traction in other disease areas (107, 108, 141).

2.4.3 Assessing code set performance

There was variation in the measures of performance of the various code sets reported. Most frequently the positive predictive value was reported, and this was often related to the study design, in which the medical record reviewed were already selected to enrich for the presence of cirrhosis. As a result, to avoid verification bias only the PPV could be reported.

Several factors can be identified that improve the performance of code sets recognising that there is a balance to be found between the sensitivity and the PPV of these. Increasing numbers of codes used, codes from both the inpatient and outpatient setting, and codes that encompass the whole range of cirrhosis complications all yield improvements in the sensitivity of the described code sets. This increase in sensitivity however must be considered in the light of any reductions in the PPV. For example, Nehra and colleagues reported that the inclusion of multiple codes relating to liver decompensation, except for ascites, maximised detection of cirrhosis. Additionally, they found that almost 5% of cirrhotic patients had a code for a complication of cirrhosis without a specific cirrhosis code, supporting their inclusion within a code set (105).

Only three of the studies from the United States examined ICD-10 codes, despite the transition from the ICD-9 dictionary in 2015. In comparison, all of the studies conducted in Europe and Canada use ICD-10 codes aside from the earliest study by Quan *et* al which pre-dated the introduction of the ICD-10 dictionary in Canada (122). Over two-thirds of the included studies came from the United States and only a small minority were from Europe. Whilst there was no difference in

performance statistics based on location, this lack of geographical variation is likely to impact on the reproducibility of their findings worldwide.

The impact of using poorly specific algorithms is that patients with mild liver conditions will be mislabelled and cases of cirrhosis will be over-predicted. This is of relevance when considering those studies using more generalised codes to identify cirrhosis. Two studies used broad definitions that included aetiology and codes such as jaundice, coagulopathy and melaena (106, 113). Goldberg *et* al developed three separate algorithms to identify cirrhosis, decompensation, and end stage liver disease. Whilst the PPV for cirrhosis remained high without using chronic liver disease codes, very few patients with cirrhosis were identified overall (35 patients; PPV 94.3%), suggesting that these codes reduce the sensitivity of the algorithm considerably. Unsurprisingly, this study also found that when these non-specific codes were used alone, they were able to identify only 8.8% of patients with end stage liver disease (106).

Very few studies incorporated procedural codes into their code sets to identify cirrhosis. This approach has been adopted by Public Health England in the most recent Atlas of Variation in liver disease, in which they combine procedural codes with cirrhosis codes (OPCS T461/T462 and ICD-10 K70-K77) to determine the number of emergency admissions for paracentesis (142). None of the studies commented upon whether the addition of procedural codes improved the performance measures.

2.4.4 Inclusion of consensus code set in HDRUK Phenotype Library

To enhance the reach and applicability of the consensus code set the HDRUK Phenotype Library was reviewed (143), to determine if any code sets for liver disease were already included.

The HDRUK Library is a comprehensive collection of terms and descriptions used to describe clinical conditions. It provides a standardised vocabulary and classification system which facilitates the analysis and interpretation of a broad spectrum of clinical data in research. None of the included studies have published lists to the HDRUK Library.

The library contains a set of ICD-10 codes to define liver fibrosis, sclerosis and cirrhosis (144). This code set was developed and published as part of a broader study which defined and published 308 disease phenotypes (145). While this code set offers valuable insights, it is important to note that it does not incorporate any ICD-10 codes specifically addressing decompensation, which is an important aspect of liver disease progression. In addition, the recommended set of codes includes specific codes for alcoholic hepatitis, the presence of which does not always indicate the existence of underlying cirrhosis. While alcoholic hepatitis can be a manifestation of advanced liver disease, cirrhosis encompasses a broader spectrum of liver damage and functional impairment.

A request to publish the consensus code list via the HDRUK Phenotype library has been submitted and is pending approval at the time of thesis publication (submission: June 2023).

2.4.5 Limitations

There are several limitations to consider regarding this systematic review. First, many of the included studies relied on small validation sets from single institutions, which may introduce bias in assessing the presence of cirrhosis through medical chart review. The lack of external validation further limits the generalisability of the findings. In addition, whilst many of the studies combined in-patient and out-patient codes, these are often limited to tertiary care centres with access to specialist input. An inherent bias which results from using electronic health databases is that they rely upon the patient receiving hospital care, either as an in-patient or out-patient. As a result, it will inevitably capture those patients with more advanced decompensated disease and overlook patients who are ambulatory.

Second, the weight of importance of the individual codes analysed in the primary reports was seldom reported, meaning that a quantitative analysis was not possible to define the codes carrying the most information in the EHR and how this varied between studies.

Third, developing a consensus code set that can be used across all healthcare systems is a challenge and it is recognised that no two electronic systems are the same with differing structures, coding practices, and terminologies. Achieving standardisation and comparability between different systems can be difficult due to these inherent variations.

Finally, the QUADAS tool was used to assess the methodological quality and risk of bias between the included studies. Whilst this tool provides a standardised framework for evaluating study design, it does not capture other aspects of study

reporting such as generalisability and clinical utility in the real-world setting. In addition, the QUADAS tool requires subjective judgement in rating of each item, which can lead to potential variability in scoring, and the interpretation of the overall score is not clearly outlined. There is no universally agreed-upon score which unequivocally reflects a good quality study. Some authors suggest a score greater than 10 denotes a good quality paper, whilst others propose a score of 7. Such discrepancies make it challenging to interpret the results objectively.

Whilst the QUADAS tool may provide a structured and quantitative measure with which to compare studies, evaluating each individual item response offers a more comprehensive understanding of the strengths of each study and helps identify potential biases. It is important to emphasise that this tool does not replace the need for critical appraisal and interpretation of the study findings within the broader context of the research question and available evidence.

2.5 Conclusions

Many diagnostic codes have been proposed to define cirrhosis in EHR research. To promote international collaboration and comparisons, a consensus code has been established to standardize the use of these codes in EHR studies on cirrhosis. This will help ensure consistent and comparable data across different research initiatives and ultimately contribute to a better understanding of this condition.

Chapter 3

Validation of a consensus code set to identify cirrhosis, aetiology and disease severity using electronic health records

3.1 Introduction

Validation is a necessary process in medical research, particularly in studies which use electronic health data. It is important to verify the accuracy of diagnostic coding and algorithms which employ these codes to identify patients and clinical events, to product useful, generalisable results.

This chapter aims to validates the ICD-10 consensus code set developed and outlined previously in **Chapter 2**. Following this it will describe algorithms which will determine aetiology and disease severity in a contemporary cohort of patients with chronic liver disease defined by transient elastography.

3.2 Methods

3.2.1 Cohorts used to validate the consensus code set

To comprehensively assess the relevant performance characteristics of the consensus code set , validation was conducted using four distinct independent cohorts.

The first validation cohort consisted of 300 patients (referred to as the UK cohort [sensitivity]) with cirrhosis as determined by transient elastography. Patients who attended the outpatient hepatology department at Leeds Teaching Hospitals NHS Trust (LTHT) between 2012 and 2017 were included. LTHT provides comprehensive hepatology and liver transplantation services across Yorkshire, the Humber, Lincolnshire and the North West of England (146). Those patients who underwent TE with a LSM of ≥15 kPa were included. This threshold was chosen as studies have shown that irrespective of underlying aetiology, a liver stiffness of 13kPa or above accurately differentiates cirrhosis (43).

This cohort was utilised to evaluate the sensitivity of the consensus code set (**Table 2.10),** which refers to its ability to accurately identify individuals with cirrhosis. The sensitivity was calculated by dividing the number of true positives (correctly identified cirrhosis cases) by the sum of true positives and false negatives. Here, the sensitivity refers to the ability of the consensus code set to correctly identify individuals who have cirrhosis (true positives/true positives + false negatives).

The second aspect assessed was the PPV of the consensus code set. As the initial cohort mentioned above only included patients with cirrhosis, an additional

patient cohort was necessary for this evaluation. A cohort of 335 patients admitted to LTHT (referred to as the UK cohort [PPV]) in 2019, who had one or more codes from the consensus code set, was employed for this purpose. The PPV indicates the probability of a patient having cirrhosis when a code from the consensus code set is present. It was calculated by dividing the number of true positives by the sum of true positives and false positives.

External validation was conducted to verify whether the consensus code set was generalisable and reliable. The validation process began by applying the consensus code set to a cohort of 113 patients from the University of Michigan Hepatology Clinic (referred to as the US cohort [sensitivity]). These patients were enrolled prospectively in a chronic disease monitoring system between 2010-2015 and were followed for a minimum of 3 years. By validating the consensus code set in this independent cohort, its performance could be evaluated in a different healthcare setting and patient population.

Finally, the PPV was evaluated in 241 patients identified by any one or more of the codes in the consensus code set with an outpatient encounter in May or June 2021 at the University of Michigan (US cohort [PPV]). To determine the PPV, the full medical records of these patients were thoroughly reviewed, to confirm if each patient had a verified diagnosis of cirrhosis. This comprehensive assessment allowed for accurate determination of the true positives (patients with confirmed cirrhosis) as well as the false positives (patients incorrectly identified as having cirrhosis).

Process of validation used in UK cohort [sensitivity]

TE measurements were taken in an outpatient setting using FibroScan© equipment. Examinations were done by trained practitioners using the conventional approach (decubitus position with right arm in abduction), with access to both the medium and XL probes. Those patients with inadequate or low quality TE readings were excluded (success rate <60%; IQR >30%) (40), as well as patients under 18 years at the time of TE. When multiple scans were performed on the same patient, the first scan indicating the presence of fibrosis was included.

Each patient was assigned an incident diagnosis of chronic liver disease as the date of TE. Those patients who had undergone liver transplantation prior to TE were discounted, as well as those who had a prior decompensation event (variceal bleeding, ascites, and hepatic encephalopathy) to identify newly diagnosed cases of advanced fibrosis. Demographic data including gender, ethnicity, and age at baseline (continuous variable) were collected. Ethnicity was grouped together into the five broad ethic groups as recommended by the UK government and Public Health England (147): White, mixed/multiple ethnic groups, Asian, Black/African/Caribbean, other ethnic group/not known.

The MR was reviewed and all events following identification of fibrosis were recorded. Diagnosis was taken from documentation by a specialist clinician in the medical notes and relied upon either histological and/or biochemical and/or radiological evidence of cirrhosis, Details including out-patient visits in the hepatology clinic and admissions to hospital with decompensation were recorded. Patients were followed up to either death, transplantation, or the end

of the data collection period (Censor date: 1st July 2019). Cause of death was taken directly from documentation on death certificate or bereavement summary where available on the clinical record.

Data was extracted from the hospital EHR, which contains coded data submitted to the HES database as described previously. Coded information (ICD-10 and OPCS-4) relating to hospital admissions, investigations, procedures, and mortality was collected. During the validation process, all diagnostic and procedural codes associated with each admission were considered, rather than solely relying on the primary diagnosis code. The patient had to have at least one of the codes outlined in the consensus code set (**Section 2.3.6**) associated with an in-patient admission to be identified. Out-patient codes were not available to analyse in this cohort.

The performance of the consensus code set was compared to the most frequently used code set by Kramer *et* al identified through citation analysis (103). The codes included in the Kramer code set are shown in the **Appendix Pg 213 (Table 8).**

Process of validation used in UK cohort [PPV]

Two experienced clinicians[11] independently reviewed the medical record to confirm if the diagnosis of cirrhosis was correct. A positive diagnosis of cirrhosis was made following review on one or more of the following criteria:

[11] The candidate (Jessica Shearer) and Thazin Min (credited in the acknowledgements section)

1. Histological confirmation of cirrhosis, portal hypertension on imaging (varices/ascites)
2. Documentation in medical record by a Specialist Gastroenterologist or Hepatologist of an episode of decompensation (ascites, variceal bleeding, hepatic encephalopathy)
3. Synthetic dysfunction consistent with cirrhosis (Albumin ≤30, Bilirubin ≥20, INR ≥1.2).

This criterion was considered the gold standard and was based upon the criteria used by Kramer *et* al (103), described previously in **Table 2.4**. The gold standard was agreed upon in advance by the clinicians reviewing the medical record and members of the research supervisor team.

Process of validation used in US cohort [sensitivity & PPV]

As described elsewhere (148), in the sensitivity cohort all patients had a CT scan within 365 days of enrolment and received their diagnosis of cirrhosis based on imaging, laboratory and/or histological parameters from a board-certified transplant hepatologist and were followed clinically thereafter. All diagnosis codes were entered in or mapped to ICD-10 in the electronic medical record, using the process described in the previous chapter (**Section 2.3.6).** In both cohorts the patients had compensated cirrhosis at baseline (without ascites, encephalopathy, variceal haemorrhage, or liver cancer). A proportion of patients (24%) experienced one or more decompensation events during the follow-up period. Further details regarding these events are described later in this chapter.

The full medical record was reviewed. Basic demographic information was extracted, including age at time of TE, gender, aetiology of liver disease (Viral, autoimmune, metabolic, ArLD, NAFLD) and ethnicity (Asian, Black, Hispanic, White, other, unknown). All events following the identification of fibrosis were recorded. This included out-patient visits in the hepatology clinic and admissions to hospital with decompensation (variceal bleeding, ascites, and hepatic encephalopathy). ICD-10 codes from the consensus code set which were attached to in-patient admissions were extracted from the EHR. Only those codes occurring after transient elastography were included and out-patient codes were not used for consistency with the UK cohort data.

In the PPV cohort, the medical record of patients with an out-patient encounter was reviewed to confirm if each patient had a verified diagnosis of cirrhosis.

Data analysis

All analysis was carried out using Stata/SE 15.1 Package (Single User License; Serial Number 401506311102).

The '*strpos'* command was used to determine the location of specific codes in the consensus code set. It works by identifying the position of the desired code within a string, returning zero if the substring is not found and one if it is. The syntax for '*strpos'* is as follows:

Strpos(varname, substring)

The ‘varname’ is the string variable which is being searched. In this case this refers to the codes attached to each in-patient admission. ‘Substring’ is the string that is to be located within ‘varname’, which refers to the code of interest from the consensus code set. A full description of the Stata code used to validate the consensus code set is included in the **Appendix (Page 214-215).**

3.2.2 Validation of coding algorithm for aetiology

The cohort of 300 patients used to validate sensitivity of the consensus code set (UK cohort [sensitivity]) were used to validate coding algorithms to determine aetiology.

Aetiology was assigned in the following hierarchical order: viral hepatitis, autoimmune, metabolic disease, ArLD, NAFLD. This method has been described and validated previously in the literature (123). The algorithm was adjusted to include codes for fatty liver disease and diabetes if no other aetiology codes were identified. If no relevant codes were recorded the patient was recorded as having unknown aetiology. The ‘*strpos’* command was used to identify codes of interest for each disease group from the EHR. Following this the ‘*regexm*’ command was used to create the hierarchical diagnosis system. This command applies regular expressions to string variables to search for a specific pattern. The basic syntax is as follows:

Regexm(string_variable, regular_expression)

As such, each string is checked for a particular sequence and the result is stored as a new variable. The codes included and the algorithm used to determine aetiology are shown in full the **Appendix (Table 7).**

The true aetiology was determined through review of the medical record and documentation of a positive diagnosis by a Specialist Gastroenterologist or Hepatologist.

3.2.3 Validation of coding algorithm for cirrhosis staging

The cohort of 300 patients used to validate sensitivity of the consensus code set (UK cohort [sensitivity]) were used to validate the coding algorithms for cirrhosis staging. Coding algorithms to determine decompensation and underlying cirrhosis severity were developed, using the validated Baveno IV classification (149), which sub-divides cirrhosis into four stages based on the presence and severity of CSPH (**Figure 1.1)** (150).

The medical records were reviewed to determine changes in Baveno IV stage at yearly intervals throughout follow-up. Patients were classified as Baveno IV stage one if they had had an endoscopy which showed that they did *not* have varices. Only those patients who remained either Baveno IV stage one or were 'low risk' according to the Baveno VI criteria at the end of 12 months follow-up were included in the analysis (LSM <20kPa; platelet count >150x10^3/μl (52)).

The Baveno IV determined by the coding algorithms was compared to the true Baveno stage identified through the clinical records. This was reassessed at yearly intervals during follow-up. The *'strmatch''* command was used to determine

if an exact string variable matched a specified set of values. The basic syntax is as follows:

Strmatch string_variable, match_values

The ‘string variable’ refers to the variable which is matched against and the ‘match values’ is a list of values which are checked for a match. A worked example using ICD-10 codes from EHR data is shown:

```
replace bav = 1 if (strmatch(epicode,"*I85.9*") | ///
                    strmatch(epicode,"*G10.4*")| strmatch(epicode,"*G10.8*")| ///
                    strmatch(epicode,"*G10.9*")| strmatch(epicode,"*G14.4*")| ///
                    strmatch(epicode,"*I85.9*")| strmatch(epicode,"*I86.4*")| ///
                    strmatch(epicode,"*I98.2*")| ///
                    strmatch(epicode,"*J06.1*")| strmatch(epicode,"*J06.2*")| ///
                    strmatch(epicode,"*G17.4*")| strmatch(epicode,"*G43.4*")| ///
                    strmatch(epicode,"*G43.7*"))
```

In this, *‘epicode’* refers to the string variable and the ICD-10 code is the match value. The codes and detailed algorithms used to define Baveno stages are shown in the **Appendix (Table 8).**

3.2.4 Data management

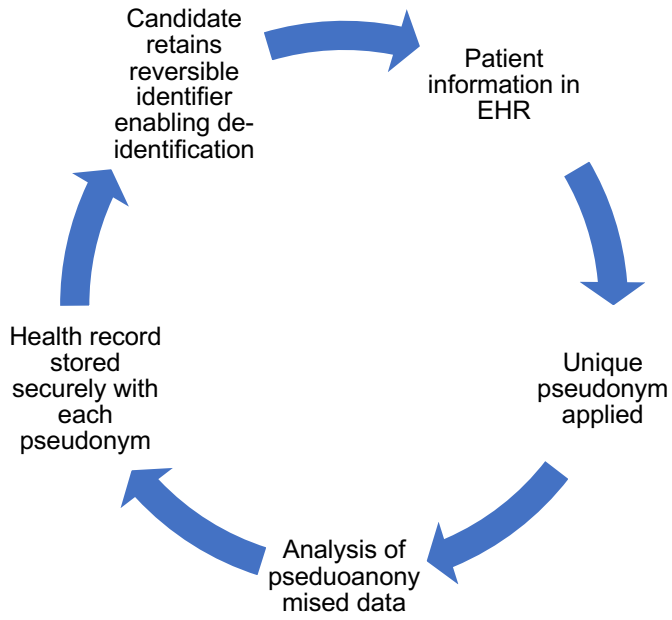
The source data for patients included in the validation were obtained from local hospital EHR systems with the assistance of information technology analysts located at participating sites. Source data comprised the following demographic variables: gender, ethnicity, and age at baseline (time of TE). Diagnostic and procedural codes attached to hospital admissions occurring after the date of TE were obtained.

The candidate (Dr Jessica Shearer) applied and obtained data and is accountable for data management. Permission to access data was strictly granted to those individuals directly involved in the study, namely the candidate (Dr Jessica Shearer) and members of the research supervisor team.

To ensure data security, the data were stored on an encrypted Leeds Teaching Hospitals NHS Trust Laptop (Standard specification; IT equipment number: 1590849). The laptop was kept in a physically secured room on site in the Clinical Sciences Building at the St James' University Hospital site. The building requires access via swipe card and the room is kept locked with access only to authorised specific members of research team.

Data undergo anonymisation prior to analysis in adherence with the NHS Code of Confidentiality (151). The anonymisation process was carried out by the candidate utilising the method of pseudonymisation. Each individual within the data set was assigned a unique pseudonym following the pseudonymisation process outlined in the General Data Protection Regulation privacy rules (152). The candidate retained the identification key, thereby maintaining privacy and ensuring secure data analysis. **Figure 3.1** shows the pseudonymisation process used.

Figure 3.1. Flow chart illustrating the data pseudonymisation process



Raw data spreadsheets containing identifiable information were stored on a password-encrypted Excel spreadsheet stored on the NHS Trust Laptop. Data obtained from external sites were also anonymised prior to transfer. Any transmission of sensitive data electronically was done through encrypted channels using secure NHS email. Importantly, no patient data were storied on personal laptops or private computers.

For long-term storage and sharing purposes beyond the project's duration, the data were stored on secure LTHT disk space. This ensured that the data could be shared, reused, and cited while maintaining proper security measures.

Ethical approval was gained prior to data acquisition (IRAS Study ID: 224964), and throughout the process, data collection and storage adhered to the privacy rules set forth in the General Data Protection Regulation.

3.3 Results

3.3.1 Demographics

Table 3.1. Demographic details of UK and US cohort (sensitivity)[12]

Variables	**UK cohort (sensitivity) (n=300) (%)**	**US cohort (sensitivity) (n= 113) (%)**
Age (years)	55 (47, 69)	64 (57, 72)
Male, n (%)	188 (62.6)	67 (59.2)
Ethnicity, n (%)		
White	266 (88.6)	100 (88.5)
Black/Hispanic/Asian	25 (8.3)	10 (8.8)
Other/Unknown	9 (3)	3 (2.7)
Disease, n (%)		
NAFLD	131 (43.7)	21 (18.6)
Alcohol	82 (27.3)	11 (9.7)
Viral hepatitis	56 (18.7)	52 (46)
Autoimmune/cholestatic	19 (6.3)	15 (13.3)
Metabolic/Other/Unknown	12 (4)	14 (12.4)
Transient elastography (kPa)		
15-25	144	-
>25	156	-

[12] Continuous variables shown as median and interquartile range. Categorical variables shown as numbers and percentages. NAFLD; non-alcoholic fatty liver disease, UK; United Kingdom, US; United States

Table 3.2 Details of validation cohorts used to determine positive predictive value of consensus code set.[13]

Variables	UK cohort (PPV) (n=335) (%)	US cohort (PPV) (n=241) (%)
NAFLD	40 (11.9)	69 (29)
Alcohol	181 (54)	98 (41)
Viral hepatitis	23 (6.9)	57 (24)
Autoimmune/cholestatic	13 (3.9)	9 (3.7)
Metabolic	10 (3)	0
Other/unknown	68 (20.3)	8 (3.3)

Four independent samples were used to validate the sensitivity and PPV of the consensus code set, with a total of 989 patients included in the cohort. The demographic details of these patients are shown in **Table 3.1** and **Table 3.2.**

300 patients were included in the UK cohort (sensitivity). The mean age at time of diagnosis was 55 years. The median length of follow-up was 45 months. 43% of the cohort had NAFLD, followed by 27% with alcohol related liver disease and 19% with viral hepatitis. Most patients in the cohort were white British (89%). The median transient elastography measurement was 25.4 kPa. 113 patients were included in the US cohort (sensitivity). The mean age was 64 years, 59% were male, and the commonest liver disease aetiology was HCV infection. In both the UK and US (PPV) cohorts, the most common liver disease aetiology was alcohol (54% and 41% respectively).

[13] NAFLD; Non-alcoholic fatty liver disease, UK; United Kingdom, PPV; Positive predictive value, US; United States

3.3.2 Consensus code set

The sensitivity for individual codes within the consensus code set was low **(Table 3.3).** There were three codes (K74.4, K74.5 and K72.1) which did not appear within either the UK or US validation cohorts (sensitivity). Given the additional benefit gained from including these codes was likely to be negligible, these were subsequently excluded from the proposed consensus code set.

The final consensus code set improved the sensitivity in the UK cohort from 44% using the Kramer *et al* code set to 61% using the consensus code set ($p < 0.0001$, McNamar's test). Sensitivity in the US cohort was also improved from 89% to 100% ($p = 0.0015$, McNamar's test) highlighting the utility of the consensus code set in diverse patient populations.

The consensus code set was further evaluated in the subset of the UK validation cohort using different liver stiffness measurements (LSM) to define cirrhosis. When using a threshold of >20kPa rather than >15kPa, the sensitivity for the detection of cirrhosis was improved from 61% to 68% in 227 patients. If the threshold was raised to >25kPa LSM the sensitivity improved to 74% in 156 individuals. In comparison to the Kramer *et al* codes the sensitivity was 51% and 58% for patients with a liver stiffness measurement of >20kPa and >25kPa respectively.

To understand whether relevant information was lost by excluding the term for ascites, the analyses were repeated including this code. In these analyses the sensitivity was not significantly changed; in the UK cohort the sensitivity was 60%, whilst in the Michigan dataset sensitivity was maintained at 100%. Utilising only

the two most widely used codes (K74.6/K70.3) the sensitivity for detecting cirrhosis was reduced to 52% in the UK cohort and 84% in the Michigan dataset.

To determine if the inclusion of patients with evidence of prior decompensation altered the performance characteristics, the medical record of an additional 33 patients with decompensation events prior to index transient elastography was reviewed. Twenty-three of these patients would have been subsequently identified by the consensus code set as being cirrhotic. When combined with the UK cohort the overall sensitivity was unchanged at 61% (204 out of 333 patients correctly identified).

Of the 335 patients in the UK cohort, 278 patients had cirrhosis confirmed in the medical records, giving a PPV of 83%. In the US cohort 214 out of 241 patients had a confirmed diagnosis of cirrhosis, equating to a PPV of 89%.

Table 3.3. Table to show most common codes used to identify cirrhosis with sensitivity for the prediction of cirrhosis in combined validation cohort (UK and US cohorts).[14]

ICD-10 code	Description (ICD-10 version)	Sensitivity of individual codes in validation group (total 413 patients), n (%)
K74.6	Other and unspecified cirrhosis of the liver	177 (43)
K70.3	Alcoholic cirrhosis of the liver	74 (18)
I85 *-I85.0* *-I85.9* I98 *-I98.2* *-I98.3*	Oesophageal varices *-with bleeding* *-without bleeding* Oesophageal varices in diseases classified elsewhere *-without bleeding* *-with bleeding*	99 (24)
K76.6	Portal hypertension	153 (37)
K72.9	Hepatic failure, unspecified	29 (7)
K76.7	Hepatorenal syndrome	4 (1)
K74.4 K74.5	Secondary biliary cirrhosis Biliary cirrhosis, unspecified	0
K72.1	Chronic hepatic failure	0
R18.0	Ascites	58 (14)

[14] Approximate conversions from ICD-9 to ICD-10 dictionary have been used to determine the most appropriate code(s). The number of authors using the code includes those papers which used the code in either ICD-9 or ICD-10 format. In the sensitivity calculation a patient can have multiple codes contributing to the identification of cirrhosis. ICD-10; International classification of diseases 10th Edition

3.3.3 Aetiology

Out of the 300 patients studied, 67% (200 patients) had codes which could be used to determine underlying aetiology. When compared to the MR, the hierarchical coding algorithm had an overall PPV of 63%. A breakdown to show accuracy of the coding algorithm for underlying aetiology is shown in **Table 3.4.** The performance characteristics for individual diseases are shown in **Table 3.5.** The specificity remains above 90% across aetiologies, whilst sensitivity ranges from 55% in viral hepatitis to 100% in metabolic liver disease. PPV ranged from 73% to 94%, and NPV ranged from 91% to 100%.

All six of the patients with metabolic liver disease (haemochromatosis) were correctly identified. Patients with ArLD had a PPV of 73%, with patients most commonly mis-identified as having NAFLD. NAFLD had a PPV of 84% and were most misidentified as ArLD. The PPV for autoimmune liver disease was 79% and for viral hepatitis was 94%.

Table 3.4. Coding algorithm to determine underlying aetiology[15]

	Aetiology in medical records					
Aetiology in ICD-10 codes	Viral	Autoimmune	Metabolic	Alcohol	NAFLD	Unknown
Viral	31	0	0	2	0	0
Autoimmune	0	11	0	1	3	0
Metabolic	0	0	6	2	2	0
Alcohol	7	1	0	57	11	2
NAFLD	1	2	0	10	83	3
Unknown	17	5	0	10	32	1

Table 3.5. Performance characteristics for algorithms used to determine aetiology[16]

	Se (CI)	**Sp (CI)**	**PPV (CI)**	**NPV (CI)**
Viral	0.55 (0.41-0.69)	0.99 (0.97-0.99)	0.94 (0.80-0.99)	0.91 (0.86-0.94)
Autoimmune	0.58 (0.34-0.80)	0.99 (0.94-0.99)	0.73 (0.45-0.92)	0.96 (0.92-0.98)
Metabolic	1.00 (0.54-1.00)	0.98 (0.95-0.99)	0.60 (0.26-0.88)	1.00 (0.98-1.00)
Alcohol	0.70 (0.58-0.79)	0.91 (0.86-0.94)	0.73 (0.62-0.83)	0.89 (0.84-0.93)
NAFLD	0.63 (0.55-0.72)	0.91 (0.85-0.94)	0.84 (0.75-0.90	0.76 (0.70-0.83)

[15] ICD-10; International classification of diseases 10th Edition, NAFLD; non-alcoholic fatty liver disease

[16] Se; Sensitivity, Sp; Specificity, PPV; Positive predictive value, NPV; negative predictive value, NAFLD; non-alcoholic fatty liver disease, CI; confidence intervals

3.3.4 Decompensation

Within the validation cohort, 22% of patients (66 out of 300) experienced 90 decompensating events during the follow-up period, with ascites being the most prevalent event, affecting 32 of the 66 patients. Further details regarding clinical events are shown in **Table 3.6**.

Using coding algorithms to detect decompensation correctly identified 46 out of 66 patients with a sensitivity of 70%. A comparison of the occurrence of decompensation in medical records and the results obtained from coding algorithms is displayed in **Table 3.7** using a 2x2 table format**.**

Table 3.6. Number of patients with decompensation, including those who had more than one decompensating event[17]

Decompensation event	**Number in cohort**
Ascites	32
Hepatic encephalopathy (HE)	7
Variceal bleeding	5
Ascites + HE	9
Ascites + bleeding	7
Bleeding + HE	3
Ascites + HE + bleeding	3
Total	**66**

Table 3.7. Comparison of coding algorithms to identify decompensation with medical records

Table 3.7. Comparison of coding algorithms to identify decompensation with medical records[18]

[17] HE; Hepatic encephalopathy
[18] ICD-10; International Classification of Diseases 10th Edition

Individual patients	Decompensation in medical records	No decompensation in medical records
ICD-10 code for decompensation	46	1
No ICD-10 code for decompensation	20	233
Total	66	234

Table 3.8. Details of decompensation events not captured by coding algorithm[19]

Patient No:	Event	Reason event not captured
8	Ascites	Ascites on same admission as death
54	HE	HE on same admission as death
69	Ascites	Not coded on discharge summary
86	HE	HE on same admission as death
224	Ascites	Admission after retrieval of data from HES
224	HE	Admission after retrieval of data from HES
263	HE	Treated as OP
272	Ascites	Admission after retrieval of data from HES
297	Ascites	Ascites on same admission as death
357	HE	Not coded on d/c summary
357	Variceal bleeding	Coded for gastric varices only (non-bleeding)
378	HE	HE on same admission as death
399	HE	Treated as OP
829	Ascites	Admission in different hospital
829	HE	Treated as OP
903	Ascites	Treated as OP

When observing decompensation events rather than individual patients, the code algorithms identified 82% (74 out of 90) events. The remaining 16 events that were not identified by the algorithms included 8 admissions for hepatic

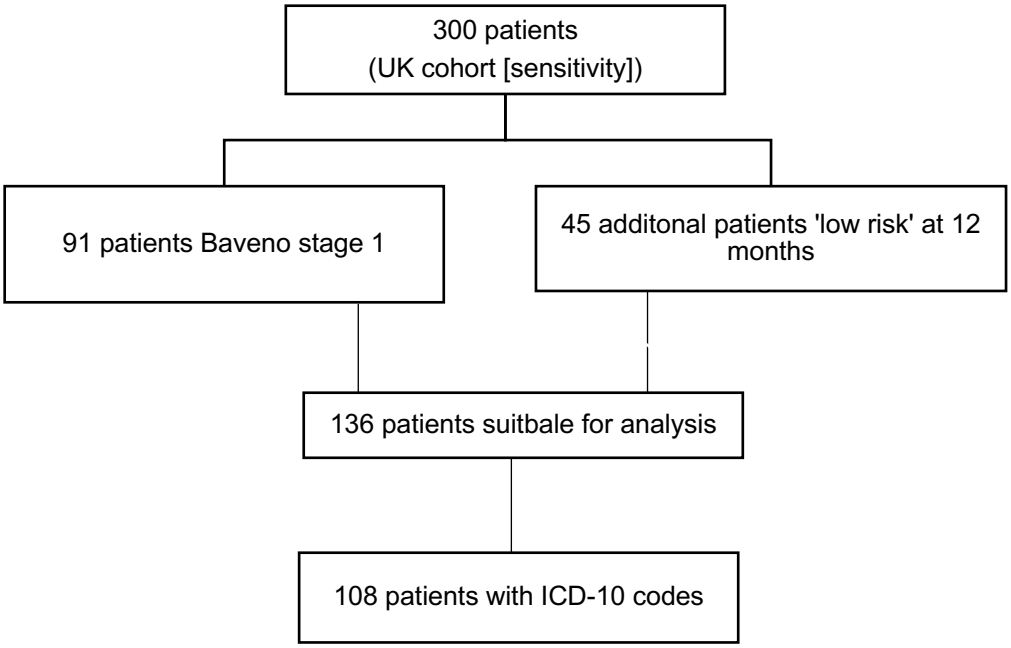
[19] HE: Hepatic encephalopathy, OP; out-patient, HES; Hospital Episode Statistics

encephalopathy, 7 cases of ascites, and 1 instance of variceal haemorrhage. Further details from these sixteen missed events are shown in **Table 3.8.**

Four events were treated as an outpatient and did not require in-patient admission; five decompensating events occurred during the same admission as the patients' death; three admissions occurred after the EHR data was retrieved; one patient was admitted to a different hospital. Three admissions had not been coded correctly on discharge. If the above discrepancies are accounted for and only those in whom the coding appeared incorrect are included, this improves the PPV of codes for decompensation events to 96% (71 out of 74).

3.3.5 Baveno staging

Figure 3.2. Patient identification for validation of cirrhosis staging



A flow chart to illustrate patient identification is showed in **Figure 3.2.** Patients within the validation cohort were then sub-divided according to the Baveno IV criteria.

Out of 300 patients, 136 were identified to be either Baveno Stage 1 or 'low risk' by Baveno risk stratifying criteria (LSM <20kPa; platelet count >150x10^3/μl) at the end of the 12 month follow up period. Among these 136 patients, 58 were specifically deemed 'low risk'. Out of these 58 patients, 13 were already identified as having a Baveno stage at the end of the first year based on clinical events. The use of the Baveno low risk criteria thus identified an additional 45 patients. The confirmed Baveno stages for the patients at the yearly transitions, as recorded in medical records, are presented in **Table 3.9.**

Table 3.9. Baveno stage transition during follow-up confirmed in medical records.

Follow-up (months)	12	24	36	48	60
Baveno 1	136	132	123	113	112
Baveno 2	-	-	1	5	6
Baveno 3	-	2	2	5	5
Baveno 4	-	-	2	2	2
Death	-	2	8	11	11

Out of the 136 patients classified as either Baveno Stage 1 or 'low risk', 79% (108 patients) had ICD-10 codes in their medical records that allowed determination of their Baveno stage. Of the remaining 28 patients who did not have any codes, 26 patients continued as Baveno stage 1 throughout the follow-up period. As previously stated, a patient was only classified as Stage 1 if they underwent an endoscopy that confirmed the absence of varices. Out of the 28 patients without codes, 18 were classified as Baveno Stage 1 based on their LSM and platelet count, and therefore, did not have endoscopy codes in their records. Upon further review of the medical records, it was discovered that the remaining 8 patients out of the 28 without codes had undergone endoscopies at private medical facilities and, therefore, did not generate any OPCS-4 codes. 2 of the 28 patients passed

away during the third year of follow-up, one of whom was admitted and died during the same admission, and therefore did not acquire any codes. The remaining 108 patients were utilised to validate the ICD-10 coding algorithms. A comparison of the coding algorithms to the medical records is presented in **Table 3.10.** where the top table displays the 'true' interval Baveno stage as confirmed by the medical records and the bottom table shows the interval Baveno stage determined by the ICD-10 codes.

Table 3.10. Comparison of cumulative Baveno stage transition during follow up between medical record and ICD-10 coding algorithm. [20]

	Follow-up (months)				
Baveno stage	12	24	36	48	60
Medical record					
1	108	104	97	87	86
2	-	-	1	5	6
3	-	2	2	5	5
4	-	-	2	2	2
Death	-	2	6	9	9
ICD-10 algorithm					
1	108	104	98	91	90
2	-	-	3	5	6
3	-	2	1	3	3
4	-	-	-	-	-
Death	-	2	6	9	9

The medical records and ICD-10 coding algorithms showed agreement in the interval Baveno staging for 101 out of 108 patients, or 94%, over the course of five years of follow-up.

[20] International classification of diseases 10th Edition

In the seven cases which the Baveno staging was incorrect, two patients were incorrectly classified as Baveno stage 1 by the algorithm, when they transitioned to Baveno stage 2 during follow-up. One of these patients had an endoscopy in the private sector, and thus no procedural code was generated in their NHS EHR record. The second patient had an endoscopy showing grade 1 varices which was not coded. Two patients were incorrectly classified as Baveno stage 2 when they were Baveno stage 4. Both patients had bleeding varices (one parastomal) which were incorrectly coded as non-bleeding varices. Two patients were incorrectly classified as Baveno stage 1 when they had transitioned to Baveno stage 3 during follow-up. One of these patients had developed ascites requiring admission to a different hospital, as a result no code was generated in the local EHR record. The remaining patient had moderate ascites controlled with diuretics which did not requiring admission for paracentesis. Finally, for one patient the transition time from Baveno stage 1 to 2 was incorrectly identified as occurring in the fifth year of follow-up when it occurred in the fourth year.

Taking these discrepancies into account and disregarding those in which the coding algorithm was not at fault, a correct identification was made in 101 out of 106 cases.

3.4 Discussion

3.4.1 Consensus code set

Important differences in the sensitivity between the validation cohorts were identified. This highlights the challenges in translating coding approaches derived from one dataset to another and the importance of reporting validation from different settings when these approaches are being developed and used. The lack of out-patient codes in the UK validation cohort likely impacted on the comparatively low sensitivity. Whilst diagnosis and procedural codes are included in the HES out-patient dictionary they are not frequently included alongside out-patient attendances (96), and this has been highlighted as an important area of improvement for studies using HES-derived datasets (153). Where available, both in-patient and out-patient codes should be used.

The Kramer code set performed poorly in the UK cohort, in comparison to the US database and previous validations within the Veterans Affairs database. This may be attributable to the different demographics observed between the UK and Veterans Affairs cohorts; Veterans Affairs databases are predominantly comprised of males with viral hepatitis (154), whilst the UK validation cohort is primarily comprised of patients with NAFLD. Treatment and monitoring practices differs between these two conditions, and this will impact upon the coded data.

Whilst the use of HES derived databases for research is becoming increasingly common (155), concerns remain regarding the quality and completeness of coding within HES-derived databases, which will impact upon its secondary use within research (137). Issues surrounding lack of clinician engagement and validity of clinical coding have been recognised as areas for improvement by the

Royal College of Physicians. Training, collaborative frameworks and financial incentives have been developed over the past decade in order to improve data quality (156). Conversely, the Veterans Affairs database was established in 1982, and was one of the first healthcare systems to embrace the notion of 'big data' and its' role within health research (157). As a result, it has a well-established and standardised infrastructure which has been developed to minimise variation in coding practice and has been utilised extensively for large scale research for the past three decades. Discrepancies between HES derived databases and Veterans Affairs systems, in addition to differences due to alterations in ICD coding revisions (158) must be considered when comparing the efficacy of coding algorithms between different cohorts.

It is notable that the PPV of the consensus code set ranged between 61-100% between the UK and US cohorts, which is lower than the PPV found through the systematic review (71-100%). This is most likely attributable to the lack of outpatient diagnostic codes, which was available for the majority validation studies conducted in the US (**Table 2.6)** and the lack of linked primary care data. Whilst diagnosis and procedural codes are included in the HES out-patient dictionary they are often not included alongside out-patient attendances (159). In a validation study of HES out-patient data in England it was found that only 0.9% of 12,154 appointments included any diagnosis code and 6.7% had an operation code (96). This lack of diagnosis record in out-patient datasets has been highlighted as an important area for improvement for studies using HES-derived datasets (153).

HES data are now linked to the Clinical Practice Research Datalink (CPRD) (160), which allows access to primary care records and inevitably provides a

more detailed picture of a patients clinical encounters. Access to CPRD has a data cost and was not available for this study however it has been interrogated successfully in other studies of liver disease (161). One might assume that most patients with established cirrhosis will be under secondary care follow-up, however it is possible that ambulatory patients without decompensation would be managed in a primary care setting and would be overlooked in the current validation. To maximise the efficacy of the code set access to linked primary care and out-patient data are preferrable.

There are several limitations to consider with this validation. Validation using chart review has inherent limitations with the potential for misclassification, though extraction was done blind to the code set evaluation. The approaches taken in the qualitative synthesis recognise these limitations and validation in four diverse patient populations addresses, to some extent, issues regarding the validity of the consensus code set across healthcare systems. It is recognised that the sensitivity in the UK cohort was comparatively low (61%). This was in part owing to the population, which comprised of patients who had undergone transient elastography in the out-patient setting, and due to the lack of out-patient coded data meaning a proportion of patients did not have any coded information that could be used. Furthermore, as the patients in the assessment of PPV were identified using the consensus code set it was not possible to assess its specificity or negative predictive value since no code set negative cases were identified to enter the cohort. This is also a limitation to the description of existing code sets where these measures are infrequently reported. The potential impact of the uncertainty regarding the specificity of the consensus code set should be considered in the design of EHR-based studies. Finally, as the validation was

conducted in two tertiary care systems, further evaluation of the performance of the consensus code set in other healthcare systems would be appropriate.

3.4.2 Aetiology

The natural history and treatment of liver diseases varies depending upon the underlying aetiology. It is therefore essential to accurately differentiate between different diseases when using electronic databases to examine clinical outcomes in this patient group. There have been several studies which have examined the validity of codes for liver disease aetiology, which are shown in **Table 3.11.** The PPV in these studies varies considerably from 40 to 93%.

In this study, the performance of the coding algorithms in determining aetiology was found to have an overall PPV of 63%. However, this accuracy varied between diseases. Part of this is likely due to overlapping aetiology in those patients with viral hepatitis with alcohol as a co-factor, which is not accounted for using the hierarchical algorithm. There was a similar overlap between those with ArLD and metabolic co-factors; ten patients with ArLD were coded as NAFLD, whilst 11 patients with NAFLD were coded incorrectly as ArLD.

A recent validation study of a hierarchical algorithm to identify liver disease aetiology in Canadian administrative databases combined ICD code algorithms with viral serology (162). This showed excellent PPV for both HCV and HBV (PPV; 100% and 86% respectively). A further study using Veterans Affairs databases to identify NAFLD employed a predictive algorithm based on ICD codes, laboratory data, viral serology, and AUDIT-C (Alcohol Use Disorder Identification Test: a validated three item screening test used to identify

hazardous alcohol consumption), achieving a PPV of 81% (163). These studies suggest that a combination of ICD codes alongside laboratory data in a hierarchical algorithm is superior to codes alone and is a worthwhile consideration when using EHR data to define patient populations in liver disease.

Ultimately performance of the algorithm was limited largely due to the lack of available coded data from hospital admissions in a proportion of the cohort. This is an inherent limitation of this analysis and should be taken into consideration in future studies.

Table 3.11. Studies evaluating the validity of codes to define aetiology in liver disease.[21]

Author (Year)	Disease	ICD-9/ICD-10 Codes	PPV
Kramer et al (103) (2008)	HCV	070.41, 070.44, 070.51, 070.54	0.93
Kramer et al (103) (2008)	ArLD	571.0x, 571.1x, 571.3x, 571.2	0.83
Kramer et al (103) (2008)	HBV	070.2, 070.3, V02.61	0.67
Myers et al (164) (2010)	PBC	K74.3	0.73
Molodecky et al (165) (2011)	PSC	K83.0	0.59
Niu et al (166) (2014)	HCV	070.41, 070.44, 070.51, 070.54, 070.7, 070.1	0.88
Niu et al (166) (2014)	HBV	070.2, 070.02, 070.21, 070.22, 070.23, 070.31, 070.32, 070.33	0.81
Philip et al (162) (2020)	ArLD	F10.0-F10.9, X45, Y15, X65 K70.0-K70.4, K70.9, K29.2, G31.2, G62.1, G72.1, I42.6, K85.2, K86.0, E24.4, T51.0, T51.9, R78.0, O35.4, Q86.0, P0.43	0.40
Philip et al (162) (2020)	HH	E83.10	0.90
Philip et al (162) (2020)	AIH/PBC/PSC	K74.3, K83.0, K75.4	0.90
Corey et al (167) (2015)	NAFLD	571.8, 571.9	0.89

[21] PBC; Primary biliary cholangitis, PSC; Primary sclerosing cholangitis; AIH; autoimmune hepatitis, HH; hereditary haemochromatosis, ICD; International classification of diseases, PPV; positive predictive value, HCV; hepatitis C, HBV; hepatitis B, ArLD; alcohol related liver disease, NAFLD; non-alcoholic fatty liver disease

3.4.3 Decompensations & Baveno staging

Algorithms to determine decompensation and disease staging according to Baveno status showed excellent PPV, at 96% and 95% respectively. This has important implications for studies using electronic databases to study liver disease, as it allows accurate identification of incident decompensation events. Following this, patients can be risk stratified according to underlying disease and biochemistry which in turn can be used to target those patients who are at the highest risk of disease progression.

It is important to note that the use of inpatient-only data may lead to an underrepresentation of patients who experienced decompensation that was managed as an outpatient. Thus, the performance of the algorithm could have been improved with the inclusion of data from outpatient care. Nonetheless, the results of this study are still comparable to those found in other studies that have utilised ICD codes to identify decompensation, which demonstrates the potential usefulness of such algorithms (104).

There was a relatively low incidence of decompensation events in the cohort, which contributes to the high PPV observed in the Baveno staging analysis. Decompensation events were infrequently missed overall, but it is important to note that some individuals who decompensate and die during the same admission may be overlooked. In this validation study, only one patient fell into this category, which suggests that the number of such events is likely to be small. However, it is an important factor to keep in mind when differentiating between liver and non-liver related deaths.

The use of the four-stage system is acknowledged as having limitations, as it has since been advanced into more sophisticated bidirectional multistate models. The coded data used in this study could not accurately capture certain critical clinical details, such as the need for organ support and the presence of renal dysfunction, which could affect the observation of outcomes in cirrhosis. Although the four-stage system remains prognostically relevant, it is crucial to consider the missing clinical information when using EHR data for this purpose.

3.5 Conclusions

This chapter demonstrated the reliability of the consensus code set in identifying cirrhosis, aetiology, and decompensation. The results show that the coding algorithms used provide a robust foundation for evaluating the burden of cirrhosis in a population. The algorithms described in this chapter will be utilised in the next chapter to analyse a larger data set, providing deeper insights into the impact of cirrhosis in a population.

Chapter 4

The natural history of advanced chronic liver disease defined by transient elastography

4.1 Introduction

Progression of cirrhosis is unpredictable, with numerous variables which influence both the rate and direction in which a patient may transition. As a result, the concept of competing risk in cirrhosis has been explored recently in natural history studies using multistate models of disease progression (31).

Over the past decade, non-invasive techniques for the detection of liver fibrosis have become widely available. TE provides a liver stiffness measurement, which correlates with fibrosis in patients with compensated ACLD (39), a term which has been adopted by the Baveno VI consensus to reflect the spectrum of disease in asymptomatic patients, ranging from severe fibrosis to cirrhosis (52). A TE reading of greater than 12kPa is highly predictive of ACLD irrespective of the underlying aetiology (168). Moreover, TE is a surrogate marker of portal hypertension which can be used as a prognostic tool to predict mortality and liver-related events including decompensation and hepatocellular carcinoma (47, 48).

Indirect fibrosis tests are used to estimate the degree of liver fibrosis and predict the risk of liver-related complications. These tests incorporate clinical and laboratory data to estimate the degree of liver fibrosis and categorise patients into low, medium, or high risk of advanced fibrosis or cirrhosis. Indirect fibrosis tests such as Fibrosis-4 (FIB-4) and ALBI score are convenient, low risk and circumvent the need for liver biopsy and are widely used in clinical practice.

Traditionally natural history studies of liver disease have been limited to cohorts of patients with biopsy proven cirrhosis. The introduction of TE, together with the use of routinely collected EHR data, represents an opportunity to study larger and more heterogenous groups of patients with chronic liver disease (169).

This chapter describes the natural history of ACLD defined by TE in terms of the first evidence clinical events and the overall progression of disease.

4.2 Survival and competing risk

4.2.1 Patients and methods

Study population

Data was collected from consecutive patients undergoing TE at St James's University Hospital in Leeds and the Queen Elizabeth Hospital in Birmingham (QEHB) between 2008 and 2019. St James's University hospital is managed by LTHT, which provide specialist services for a region of 5.4 million people (170). QEHB is within the University Birmingham NHS Foundation Trust, which covers a catchment population of 5.2 million people (171). Both NHS Teaching Hospitals are large tertiary referral centres with access to liver transplantation. Patients with liver disease were managed in these centres according to established national and international guidelines.

All LSM were taken routinely in the outpatient setting by practitioners trained in its use. Whilst Baveno VI consensus states that values between 10-15kPa are suggestive of ACLD, and that further tests may be required for confirmation (52), more recent studies have suggested a lower threshold of 13.6kPa maintains a high sensitivity and that with a reading of >10kPa suggested probable ACLD (39). Thus, patients with a median LSM of >10kPa were included. Those patients with inadequate or low-quality TE readings were excluded. This was defined as a success rate <60% and interquartile range >30%, in keeping with established

reliability criteria (172). Patients who had undergone more than one measurement were excluded, as well as patients under 18 years at the time of TE.

Data collection

Each patient was assigned the incident diagnosis of chronic liver disease as the date of TE plus three months to exclude those with TE done at the time of incident decompensation or HCC diagnosis. To account for ascertainment bias, those patients who had undergone liver transplantation prior to TE, and those who had a prior decompensation event (hepatic encephalopathy, variceal bleeding, ascites, spontaneous bacterial peritonitis) were discounted. This enabled identification of newly diagnosed cases of compensated ACLD. In addition, patients with events occurring within three months of TE were excluded from the analyses.

Demographic data including gender, ethnicity and age at baseline were collected. Specific age in years was considered identifiable patient data by Information Governance in accordance with the Data Protection Act. To avoid breaches in sharing of patient confidential information, age was grouped into 5 yearly groups and later, for the purposes of analysis, 10-yearly. Ethnicity was grouped together into the five broad ethnic groups as recommended by the UK government and Public Health England (147): White, mixed/multiple ethnic groups, Asian, Black/African/Caribbean and other ethnic group/unknown.

When biochemical data was available at baseline or within six months of TE, this was analysed using the ALBI score [(log_{10} bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.0852): ALBI score ≤ − 2.60 (ALBI grade 1), > −2.60 to ≤ −1.39 (ALBI grade 2), and > −1.39 (ALBI grade 3)] (173). The ALBI score is validated in chronic liver disease for the prediction of patients at risk of decompensation both with and without hepatocellular carcinoma (173-176). In addition the FIB-4 index (Age* x AST)/Platelets x √(ALT)) (177) was calculated, which has been validated in viral hepatitis and non-alcoholic fatty liver disease (NAFLD) cohorts (178, 179).

EHR data description

Local EHR data containing coded longitudinal information regarding admissions and attendances to the NHS hospitals in England were used to identify clinical events. Validated coding algorithms described in the previous chapter were used to interrogate the HER to determine underlying aetiology.

EHR data was used to identify relevant clinical events occurring after TE. This included liver specific events comprising of bleeding and non-bleeding varices, ascites, hepatic encephalopathy, hepatocellular carcinoma, and liver-related death. In addition, algorithms were developed to identify relevant non-liver events such as cardiovascular events, non-hepatic malignancy, and non-liver deaths. The codes and algorithms used to define diagnoses and clinical events are shown in the **Appendix Pg 213 (Table 7).**

Code exploration by disease group

Prior to analysis of outcome data, the specific codes, frequency of admissions and number of admissions per patient were examined. The codes were grouped according to Charlson comorbidity index (CCI) (180). This index was first developed in 1987 and has been used to predict mortality within 1-year of hospitalisation for patient with varying degrees of comorbidity. The index is weighted depending upon the number, type, and severity of comorbid condition. Coding algorithms have been developed using ICD-10 codes for use of the index in electronic health databases, and the CCI is now recognised as a well-validated prognostic indicator of mortality (181). Coding algorithms used to define Charlson are shown in the **Appendix Pg 222 (Table 10).**

Following this the number and type of codes were divided by disease group to observe for differences. The total and mean number of codes per admission was analysed, followed by the ten most frequently used codes per disease group was determined.

Survival analysis

All analysis was carried out using Stata/SE 15.1 Package (Single User License; Serial Number 401506311102).

Survival time was calculated from the date of TE either to the end of the data collection period, death, or liver transplantation. Cause of death in the full cohort was deemed to be liver-related if it occurred after decompensation or the development of HCC. Otherwise, death was deemed to be non-liver. Variation in survival according to TE measurement, ALBI grade and disease group was assessed visually using Kaplan-Meier plots. Log-rank tests of equality were used for categorical variables to compare survival distributions, testing the null hypothesis that there was no difference in the probability of death between the groups.

To identify prognostic factors associated with overall survival, univariable Cox proportional hazard regression modelling was done. This method of analysis measures the effect of variables upon time to an event occurring. This included age group, sex, liver stiffness, ALBI score and aetiology. Following this, multivariable Cox regression analyses was conducted using these variables. A p value of <0.05 was considered significant. The *stcox* command was used to fit the proportional hazard model via maximum likelihood.

Cumulative incidence analysis

The cumulative incidence of liver events, transplant and death was calculated at one, three and five years of follow-up. This was displayed per 100 person years

and categorised according to the severity of liver fibrosis as assessed by baseline liver stiffness, ALBI grade and FIB-4 score. The command *stptime* was used to calculate person-time (estimate of time at risk of all participants) and incidence rates at specific intervals.

Competing risk analysis

The Stata command *stcrreg* was used to fit a competing risk regression model, according to the method of Fine and Gray (182). This approach allows for the modelling of the subhazard function for a specific event of interest, considering the presence of multiple competing events. By utilizing this command, incidence curves can be generated to visualize the observed data. The syntax is as follows (183):

stcrreg x1 x2, compete(fvar==2)

Here, the competing-risks regression model uses covariates x1 and x2 and the competing event is defined by fvar = 2. Data is structured using the *stset* command beforehand, which creates a survival-time structure for survival analysis.

The Fine and Gray method provides a framework for estimating the subhazard function. This method was chosen to account for the occurrence of an event which occurs in a patient with cirrhosis, that may prevent the occurrence of other events. The benefit of this analysis is that it provides a more accurate and comprehensive understanding of event probabilities and the impact these have upon the overall survival of the patient. This is of relevance in patients with liver

disease who are at risk of multiple different events during their lifetime. This method provides insight into risk factors associated with each event, which in turn can guide management.

In this analysis the following outcomes were modelled:

1. Death
2. Development of varices
3. Bleeding varices
4. Non-bleeding decompensation (hepatic encephalopathy, ascites)
5. Hepatocellular carcinoma
6. Cardiovascular event
7. Non-hepatic malignancy

The following syntax was used:

stset time, failure(status== 1) id(id)

stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status==2 3 4 5 6 7

Firstly, the *stset* command is used to specify the survival-time data and identify the event of interest, which is denoted by *status==1* (in this case, death). This step ensures that the data is recognized and prepared for survival analysis.

Next, the *stcrreg* command is employed to perform a competing risk regression. The covariates (independent variables) included in the model are age, gender, TE score, aetiology, ALBI score, and FIB-4. These covariates are used to assess their association with the cumulative incidence of the event of interest (death), while considering other events as competing risks.

The competing events in this analysis are specified as *status* values 2, 3, 4, 5, 6, and 7, which represent varices, bleeding varices, non-bleeding decompensation, hepatocellular carcinoma (HCC), cardiovascular events, and non-hepatic malignancy, respectively.

Complete case analysis was used to handle missing data in the dataset, which analysed only the cases with complete information for all variables of interest whilst excluding cases with missing values.

In summary, the Fine and Gray model is employed to perform a competing risk regression analysis, evaluating the cumulative incidence of death while accounting for the aforementioned covariates. Meanwhile, varices, bleeding varices, non-bleeding decompensation, HCC, cardiovascular events, and non-hepatic malignancy are treated as competing events in the analysis.

4.2.2 Results

Table 4.1.Demographic details for full cohort[22]

Patient demographics	Full cohort (n-3028)	LTHT (n=941)	QEHB (n=2087)	Missing Data
Age (years), n (%)				-
18-27	173 (5.7)	26 (2.8)	147 (7)	
28-37	289 (9.5)	97 (10.3)	192 (9.2)	
38-47	533 (17.6)	169 (18)	364 (17.4)	
48-57	794 (26.2)	271 (28.8)	523 (25.1)	
58-67	759 (25.1)	247 (26.3)	511 (24.5)	
68-77	397 (13.1)	111 (11.8)	286 (13.1)	
78+	84 (2.8)	20 (2.1)	64 (3.1)	
Sex, n (%)				-
Male	1766 (58.3)	583 (62)	1183 (56.7)	
Female	1263 (41.7)	358 (38)	904 (43.3)	
Aetiology, n (%)				1287 (42.5)
NAFLD	835 (27.6)	305 (32.4)	530 (25.4)	
Alcohol	333 (11)	142 (15.1)	191 (9.2)	
Viral hepatitis	292 (9.6)	112 (11.9)	180 (8.6)	
Autoimmune/cholestatic	210 (6.9)	44 (4.7)	166 (8)	
Metabolic	71 (2.3)	26 (2.8)	45 (2.2)	
Ethnicity, n (%)				-
White	1918 (63.3)	746 (79.3)	1172 (56.2)	
Mixed/Multiple ethnic groups	27 (0.9)	11 (1.2)	16 (0.8)	
Asian	335 (11.1)	93 (9.9)	242 (11.6)	
Black/African/Caribbean	76 (2.5)	35 (3.7)	41 (2)	
Other ethnic group/not known	672 (22.2)	56 (6)	616 (29.5)	
Biochemistry				
Albumin (g/l, missing = 296)	44 (41, 47)	42 (39, 44)	45 (42, 48)	296
Bilirubin (μmol/L, missing = 296)	10 (7, 16)	10 (8, 15)	10 (7, 16)	296
Platelets ($x10^3/\mu l$, missing = 319)	192 (141, 243)	206 (157, 258)	185 (134, 237)	319
INR	1 (1, 1.1)	1 (0.9, 1.1)	1.1 (1, 1.2)	
AST (iu/L)	48 (32, 76)	48 (35, 70)	48 (31, 78)	
ALT (iu/L)	51 (32, 83)	55 (35, 84)	49 (30, 82)	
ALBI grade at baseline, n (%)				292 (9.6)
1	2242 (74)	708 (75.2)	1534 (73.5)	
2	474 (15.7)	221 (23.5)	253 (12.1)	
3	20 (0.7)	7 (0.7)	13 (0.6)	
FIB-4 Index at baseline, n (%)				877 (29)

[22] Continuous variables: median with interquartile range; categorical variables; number and percentage. LTHT; Leeds teaching hospitals NHS Trust, QEHB; Queen Elizabeth Hospital Birmingham, NAFLD; non-alcoholic fatty liver disease, INR; international normalised ratio, AST; Aspartate transaminase, ALT; Alanine transaminase

<1.45	768 (25.4)	250 (26.6)	518 (24.8)	
1.45-3.25	850 (28.1)	227 (24.1)	623 (29.9)	
>3.25	534 (17.6)	105 (11.2)	429 (20.6)	
Transient elastography (kPa), n (%)				**-**
10-15	1480 (48.9)	460 (48.9)	1020 (48.9)	
15-25	811 (26.8)	243 (25.8)	568 (27.2)	
>25	738 (24.4)	238 (25.3)	499 (23.9)	

Baseline characteristics

Demographic details are shown in **Table 4.1.** In total 3459 patients underwent TE during the study period, of which 3028 were eligible for inclusion. The total follow-up was 10,909 patient years with median length per patient follow-up of 3.3 years. Age at baseline was grouped into 10-year categories, with the most frequently occurring age group being between 48-57 years. 58% of the cohort were male. Aetiology was determined in 58% of individuals: 28% had NAFLD, 11% alcohol and 10% viral hepatitis. 63% of the cohort were white British.

Biochemistry data to calculate ALBI grade at baseline was available for 90% of the cohort. The majority of these were ALBI grade 1 (74%) and the median ALBI score was -3.08. Sufficient data were available to calculate FIB-4 grade for 71% of the overall cohort and the median FIB-4 score was 1.86. The median transient elastography measurement was 15.1kPa. 49% of patients had a baseline TE measurement of between 10-15kPa, 27% between 15-25kPa and 24% >25kPa.

Admissions and codes

The study analysed medical records of the 1967 patients (65%) who had experienced at least one hospital admission after index TE. A total of 6689 admissions were recorded, with the average number of admissions being summarised for each disease group in **Table 4.2.** During these admissions, 17,632 codes were utilised, with most patients having between one and three codes assigned per admission, as depicted in the graphical representation of the data in **Figure 4.1.** The range of codes assigned per admission was between 1 to 12.

Figures 4.2 to 4.7 illustrate the 10 most frequent codes used in each disease group. Full definitions for these codes provided in the ICD-10 dictionary (90) which can be found in the **Appendix (Table 9).** Out of these codes 19 appeared in the top ten.

Table 4.2 Number of admissions divided by aetiology[23]

Aetiology	Number of patients	Number of admissions	Average number of admissions per patient
Viral	273	1274	4.7
Autoimmune	188	645	3.4
Metabolic	72	518	7.2
Alcohol	330	1538	4.7
NAFLD	790	2714	3.4
Unknown	842	314	2.7

[23] NAFLD; Non-alcoholic fatty liver disease

Figure 4.1. Number of codes per admission sub-divided by aetiology

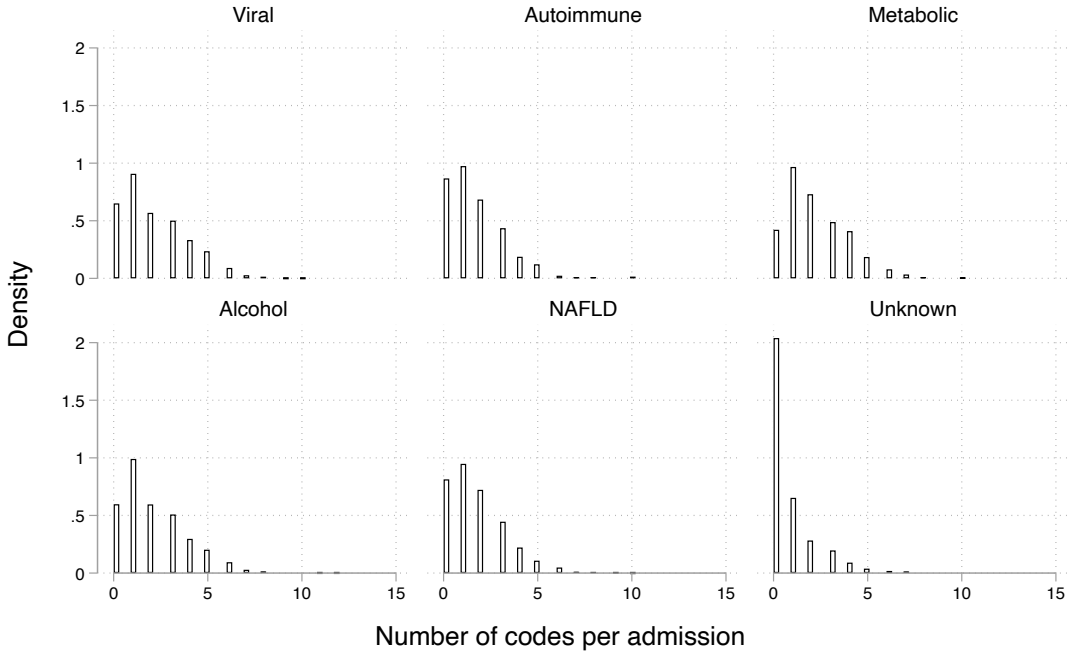


Figure 4.2. Top ten most frequently occurring in patients with viral hepatitis[24]

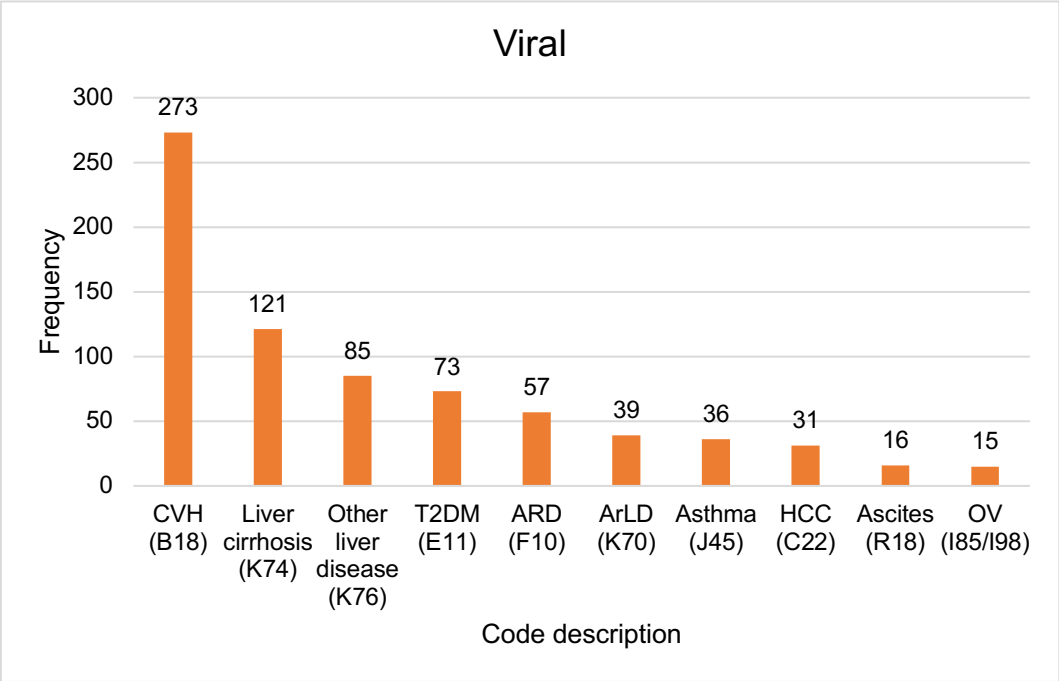
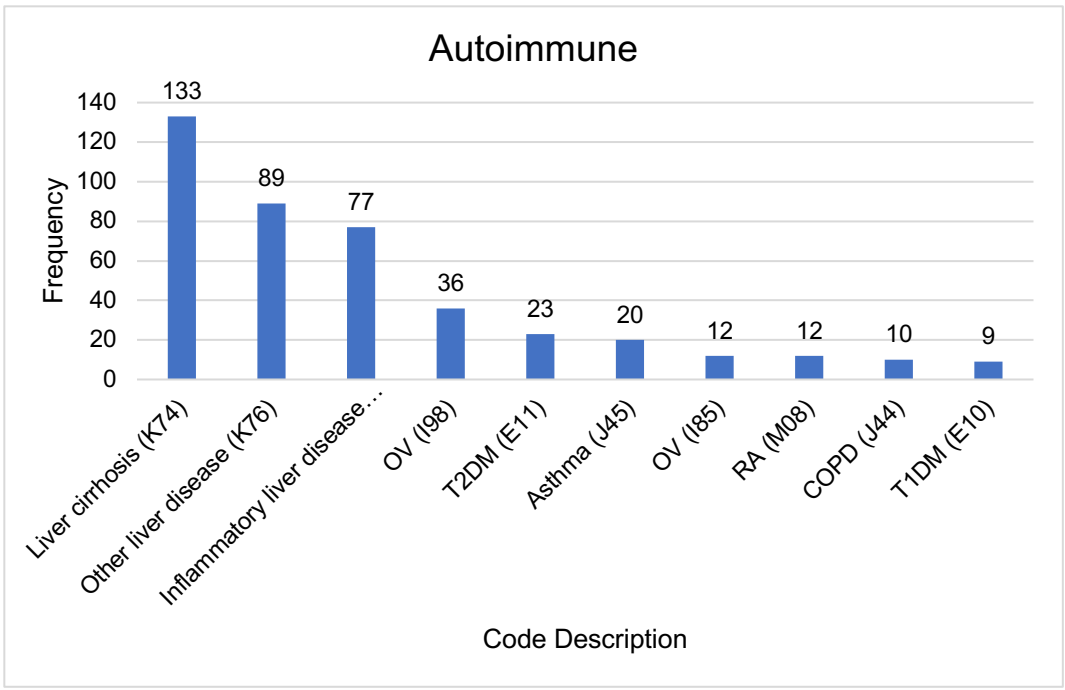


Figure 4.3. Top ten most frequently occurring in patients with autoimmune liver disease



[24] CVH; chronic viral hepatitis, T2DM; Type 2 diabetes mellitus, ARD; Alcohol related disorders, ArLD; alcohol related liver disease, HCC; hepatocellular carcinoma, OV; oesophageal varices, RA; rheumatoid arthritis, COPD; chronic obstructive pulmonary disorder, T1DM; Type 1 diabetes,

Figure 4.4. Top ten most frequently occurring in patients with metabolic liver disease[25]

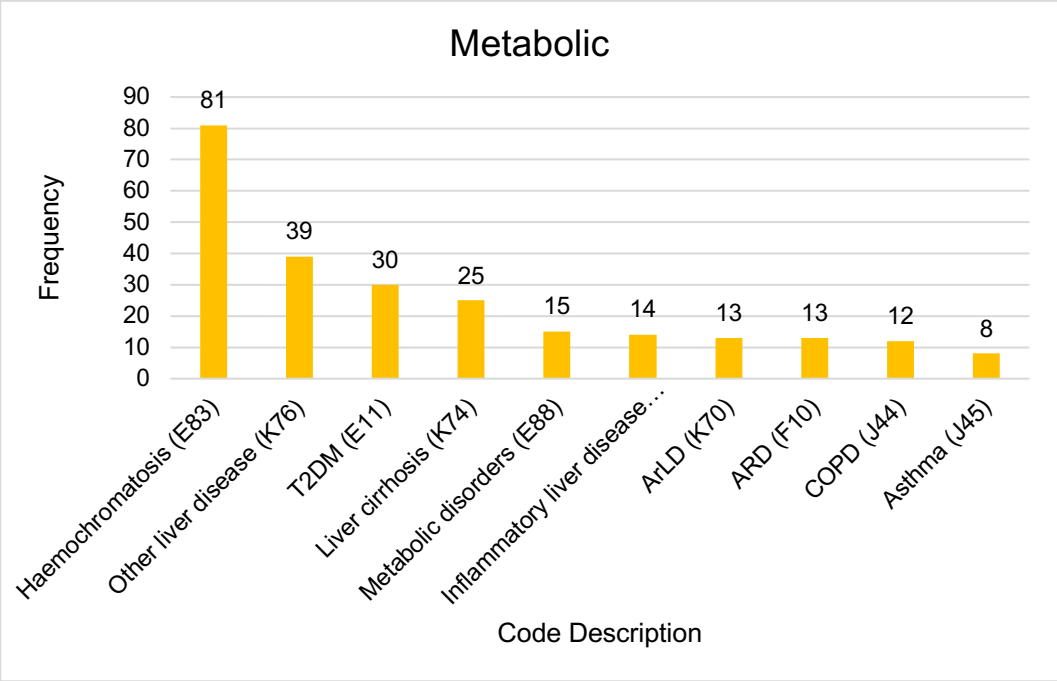
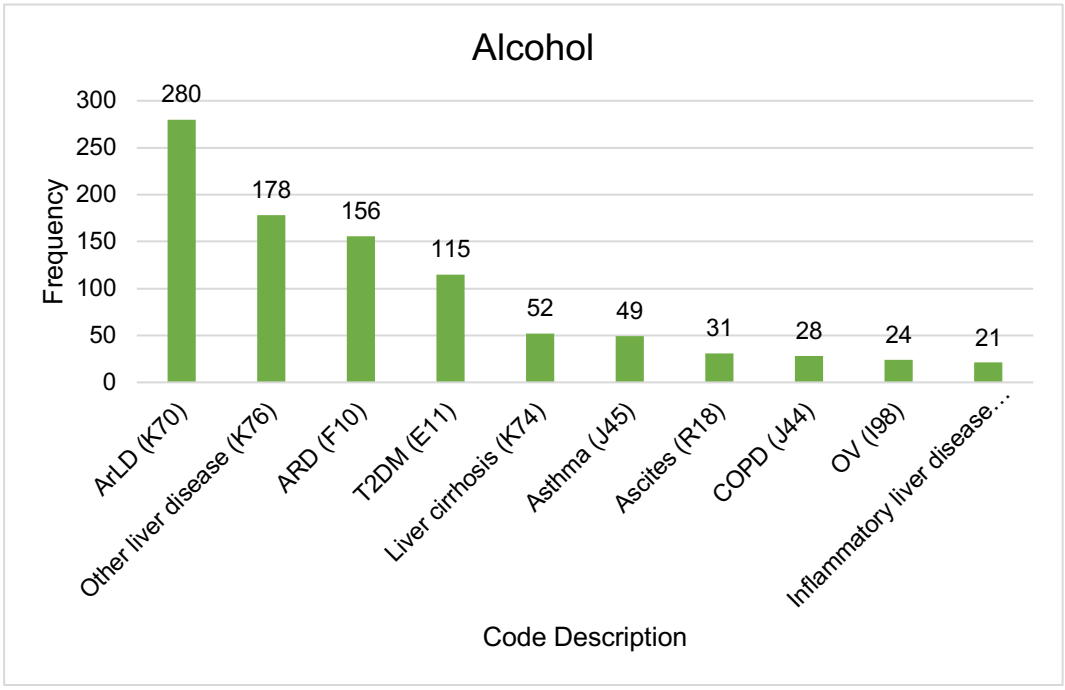


Figure 4.5. Top ten most frequently occurring in patients with alcohol related liver disease



[25] T2DM; Type 2 diabetes mellitus, ArLD; Alcohol related liver disease, ARD; alcohol related disorders, COPD' chronic obstructive pulmonary disorder, OV; oesophageal varices

Figure 4.6. Top ten most frequently occurring in patients with NAFLD[26]

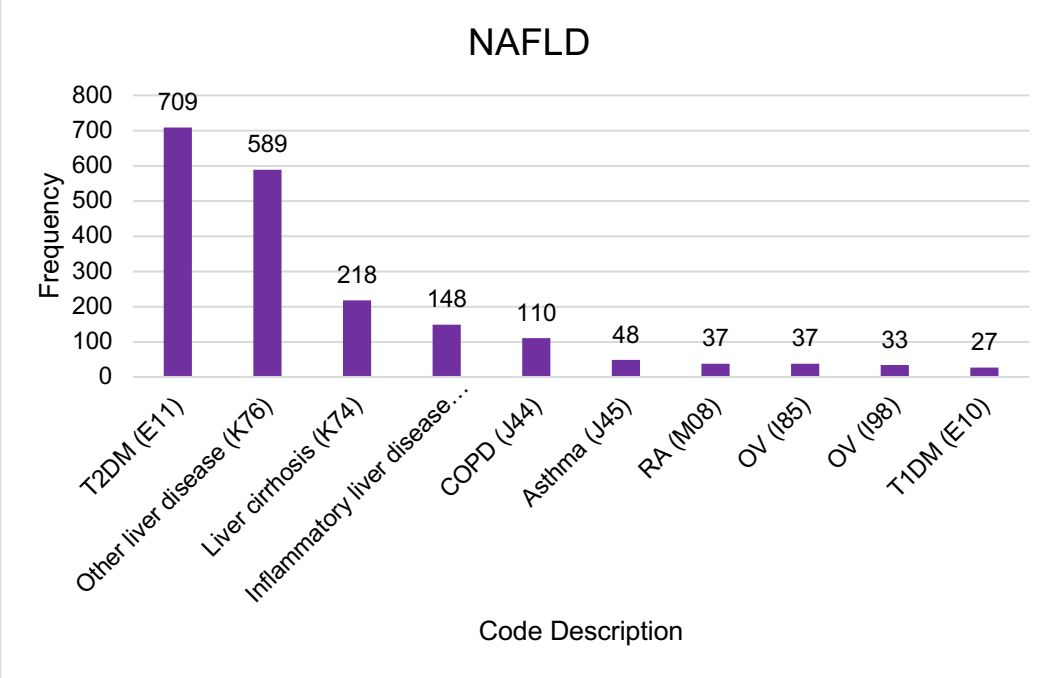
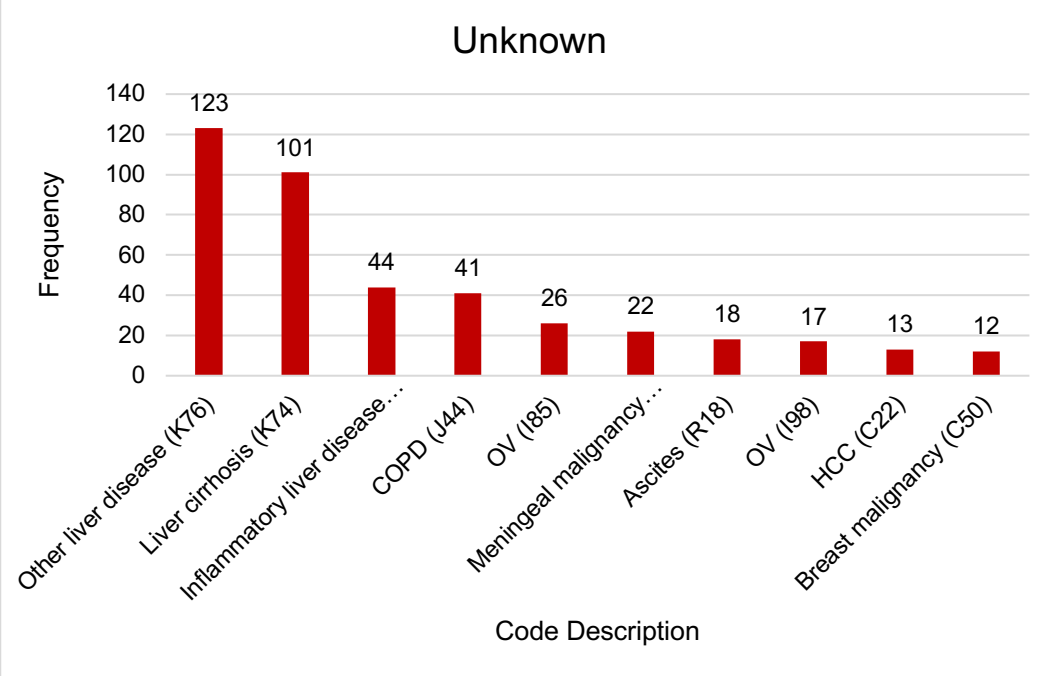


Figure 4.7. Top ten most frequently occurring in patients with unknown aetiology



[26] T2DM; Type 2 diabetes mellitus, COPD' chronic obstructive pulmonary disorder, OV; oesophageal varices, T1DM; Type 1 diabetes mellitus, HCC; hepatocellular carcinoma

Major clinical outcomes

During the follow-up period 9.8% of patients died and 2.9% received a liver transplant**.** 6% of deaths were non-liver deaths, as the patient had no evidence of decompensation or hepatocellular carcinoma prior to death. The frequency of liver transplantation and both liver and non-liver death was greatest in those patients with LSM >25kPa. Death after decompensation and transplantation occurred in 9.1% and 5.8% of patients with a LSM >25kPa compared with 1.0% and 1.5% of patients with LSM 10-15kPa. 7.6% of patients were diagnosed with varices, and a further 2.1% had admissions with bleeding varices. 5.5% of patients had a non-bleeding decompensation event and 2.4% were diagnosed with hepatocellular carcinoma.

Information regarding clinical events, death and transplantation are shown in **Table 4.3.**

Table 4.3 First clinical events during follow-up sub-divided by baseline liver stiffness measurement

Clinical outcome	**Overall n=3028 (%)**	**10-15kPa n=1480 (%)**	**15-25kPa n=811 (%)**	**>25kPa n=738 (%)**
Death or transplantation				
Liver-related death	105 (3.5)	15 (1)	23 (2.8)	67 (9.1)
Non-liver related death	192 (6.3)	62 (4.1)	44 (5.4)	86 (11.7)
Liver transplantation	87 (2.9)	22 (1.5)	22 (2.7)	43 (5.8)
Clinical events				
Varices (non-bleeding)	230 (7.6)	41 (2.8)	64 (7.9)	125 (16.9)
Varices (bleeding)	65 (2.1)	17 (1.1)	17 (2.1)	31 (4.2)
Non-bleeding decompensation	167 (5.5)	28 (1.9)	36 (4.4)	103 (14)
Hepatocellular carcinoma	73 (2.4)	18 (1.2)	19 (2.3)	36 (4.9)

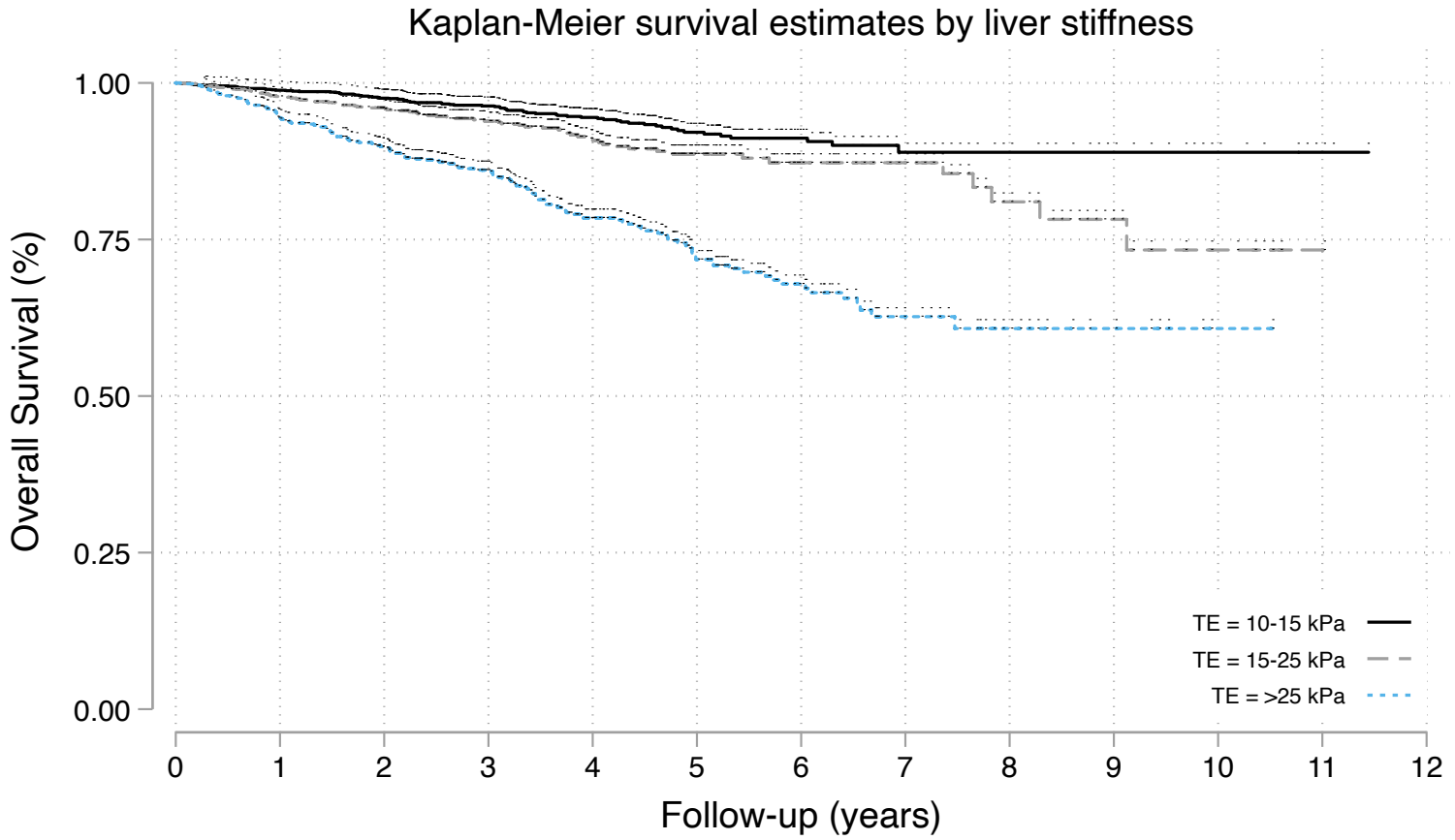
Survival outcomes

The relationship between overall survival and various baseline parameters was analysed and visualized in **Figures 4.8** to **4.14**. **Figure 4.8** displays the survival estimates divided by the baseline LSM, offering a clear understanding of the impact of liver stiffness on overall survival. The pattern is consistent when survival is divided by the ALBI grade **(Figure 4.9)** and FIB-4 score **(Figure 4.10).**

Further analysis was performed on the relationship between survival and non-invasive parameters. **Figure 4.10** presents survival estimates divided by the TE score and ALBI score, while **Figure 4.11** demonstrates the division of survival by the FIB-4 score. As each of these measures increase, the prognosis and long-term survival of the patient is notably impacted.

The incorporation of a non-invasive risk score alongside liver stiffness measurement (LSM) brings valuable prognostic information that surpasses the individual predictive capabilities of either measure alone. This integration offers a more comprehensive understanding of the relationship between fibrosis severity and patient survival, emphasising the importance of considering both factors when risk stratifying patients with liver disease. This combined approach provides a more accurate assessment of the disease severity and enables better risk stratification, aiding in the identification of patients who may require closer monitoring, intervention, or targeted therapies. The impact of underlying disease on survival is depicted in **Figure 4.13** including cases where the cause could not be determined. Lastly, **Figure 4.14** illustrates the division of these results by liver stiffness.

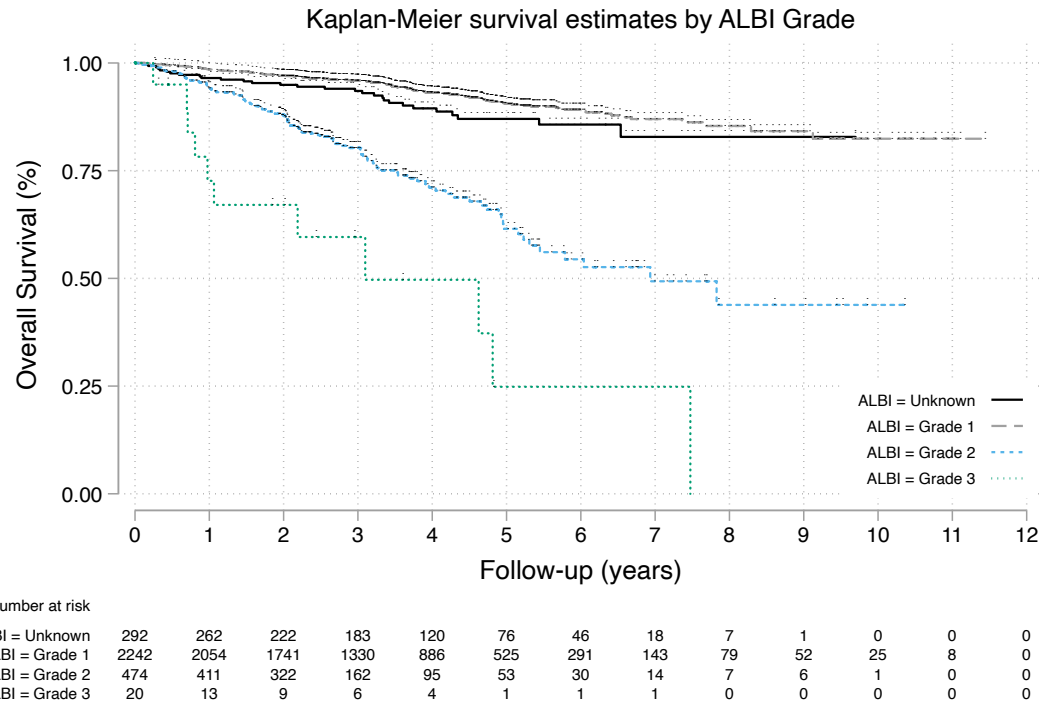
Figure 4.8. Survival estimates divided by baseline liver stiffness



Number at risk

TE = 10-15 kPa	1480	1357	1152	841	548	321	173	75	40	29	16	6	0
TE = 15-25 kPa	811	731	615	450	299	172	97	58	32	18	9	2	0
TE = >25 kPa	737	652	527	390	258	162	98	43	21	12	1	0	0

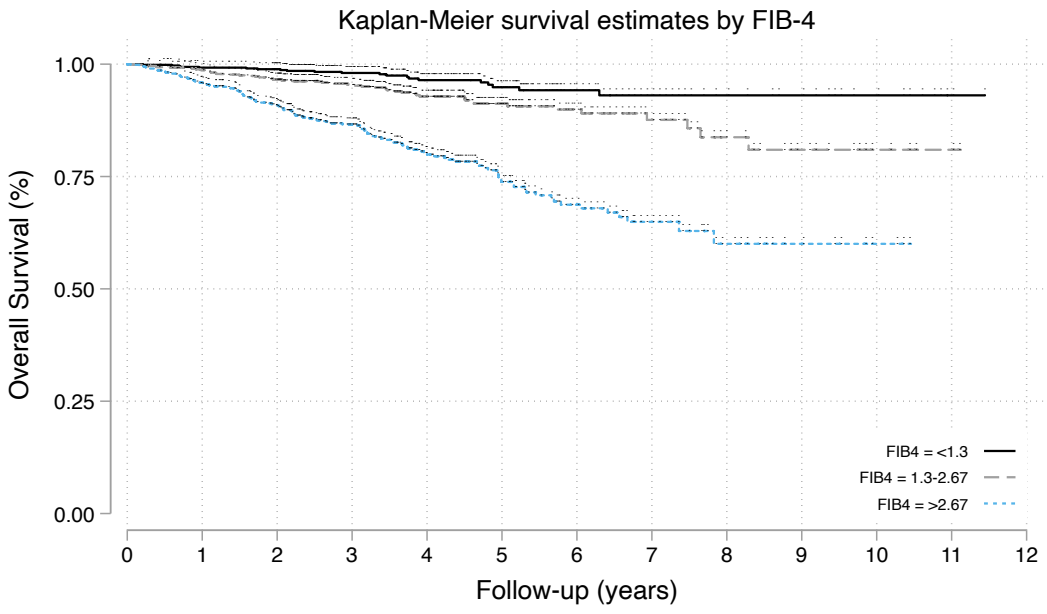
Figure 4.9. Survival estimates divided by baseline ALBI grade



Number at risk

ALBI = Unknown	292	262	222	183	120	76	46	18	7	1	0	0	0
ALBI = Grade 1	2242	2054	1741	1330	886	525	291	143	79	52	25	8	0
ALBI = Grade 2	474	411	322	162	95	53	30	14	7	6	1	0	0
ALBI = Grade 3	20	13	9	6	4	1	1	1	0	0	0	0	0

Figure 4.10. Survival estimates divided by baseline FIB-4



Number at risk

FIB4 = <1.3	662	615	532	393	256	158	89	43	27	22	13	4	0
FIB4 = 1.3-2.67	775	701	589	431	287	175	107	58	32	19	9	4	0
FIB4 = >2.67	715	638	486	343	222	140	86	42	18	11	3	0	0

Figure 4.11. Survival estimates divided by ALBI grade and liver stiffness at baseline

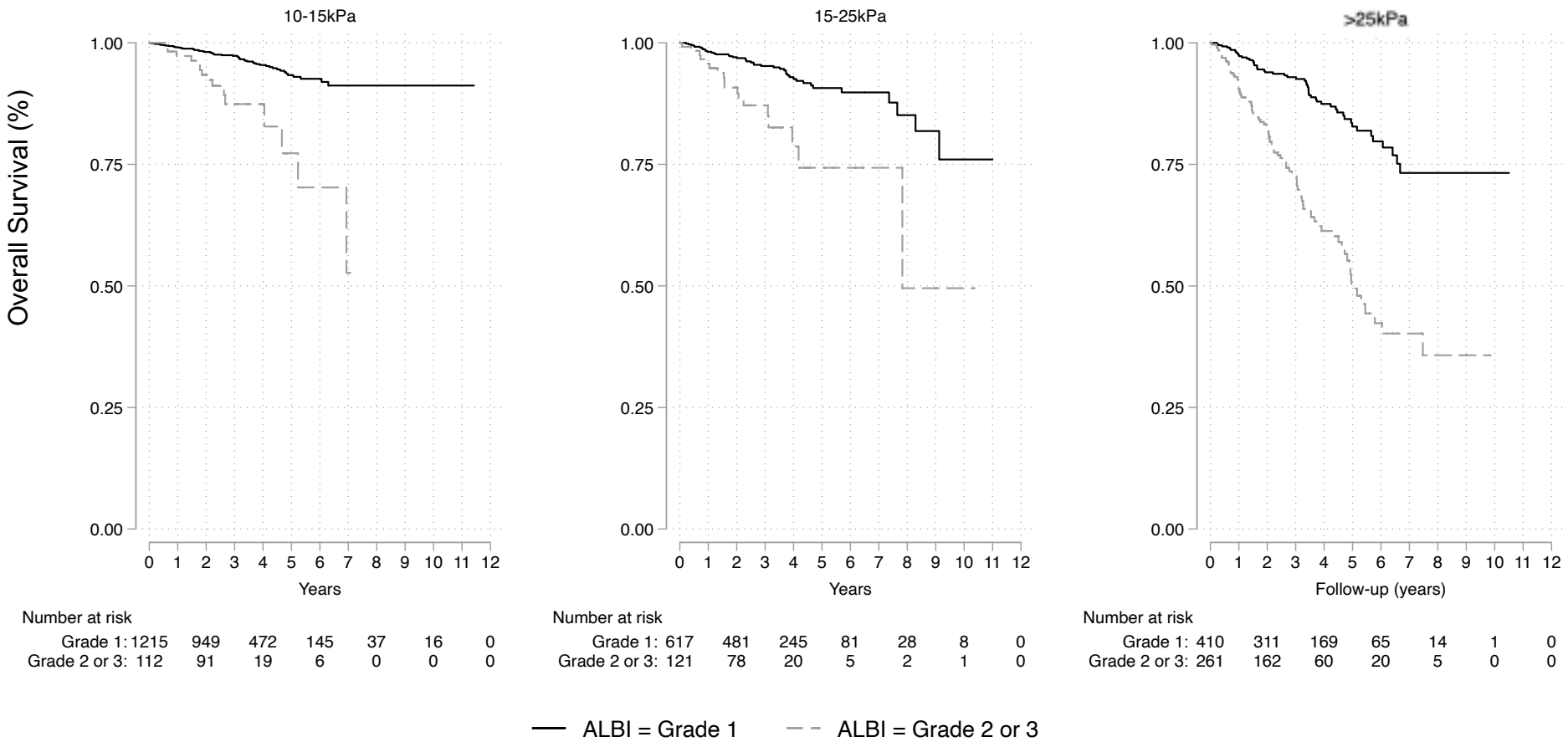


Figure 4.12. Survival estimates divided by FIB-4 score and liver stiffness at baseline

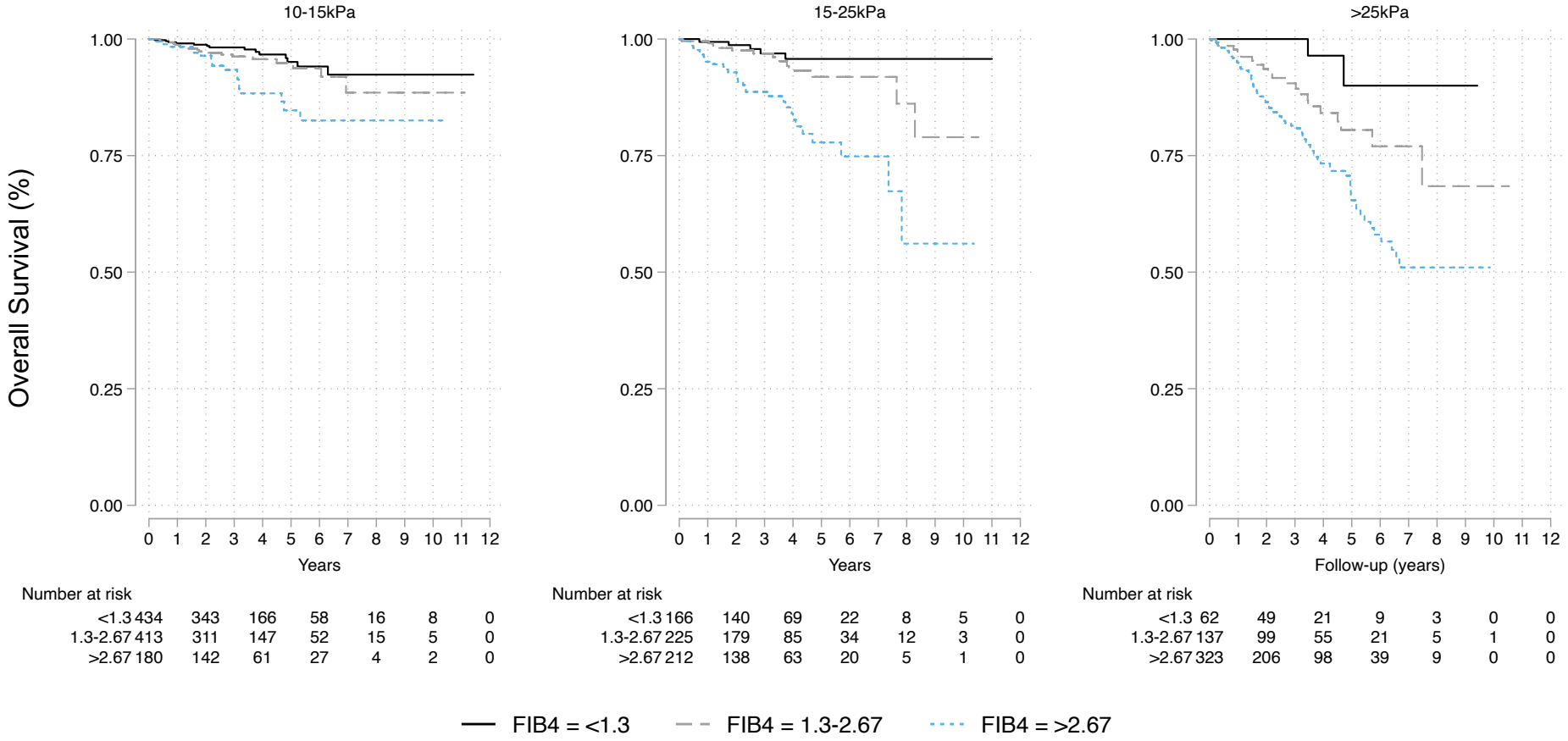
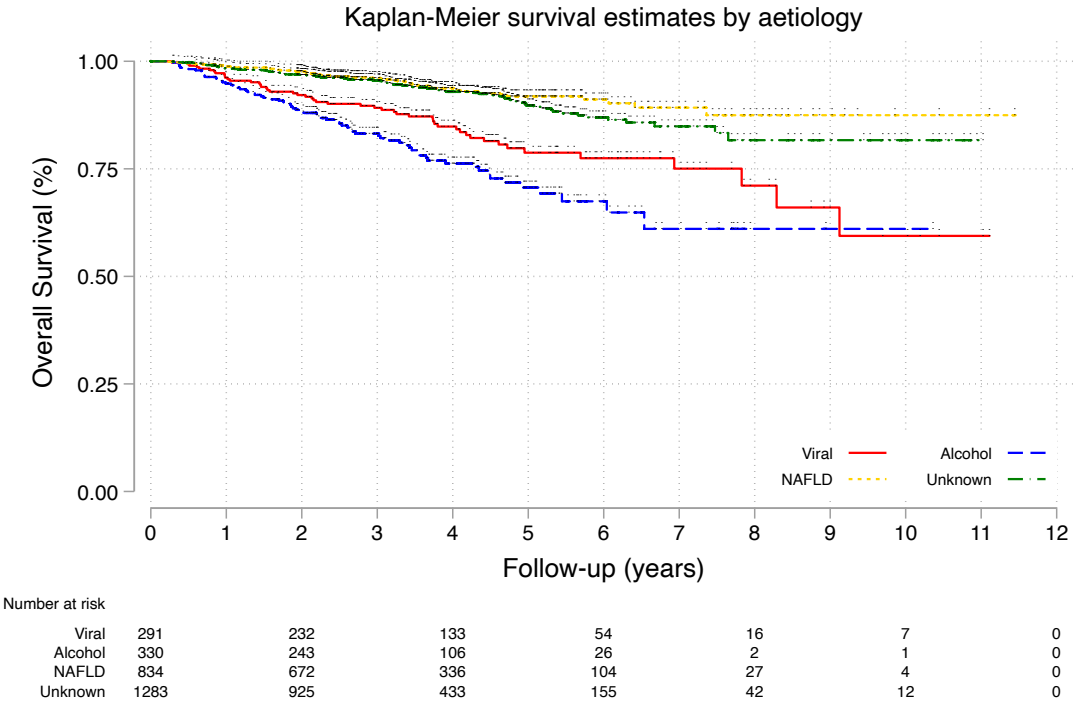


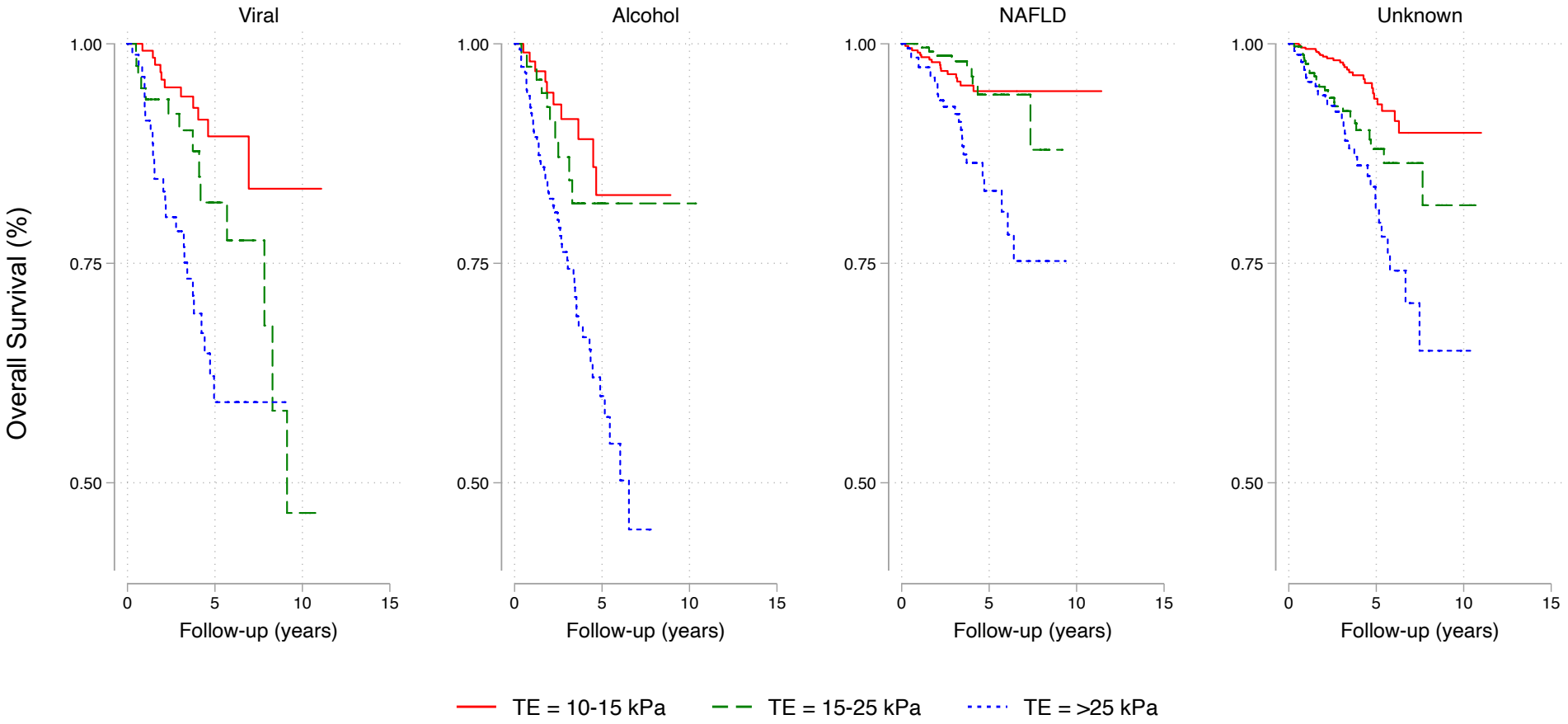
Figure 4.13. Survival estimates divided by aetiology



Number at risk

Viral	291	232	133	54	16	7	0
Alcohol	330	243	106	26	2	1	0
NAFLD	834	672	336	104	27	4	0
Unknown	1283	925	433	155	42	12	0

Figure 4.14. Survival estimates sub-divided by aetiology and liver stiffness



The factors associated with survival were analysed in univariable Cox models and are presented in **Table 4.4.** The results show that LSM, decreased synthetic function as indicated by ALBI grade and FIB-4 score, male gender and older age were all associated with a higher risk of death. In comparison to alcohol, all other aetiologies were at lower risk of death.

The effect of liver stiffness on overall survival was evaluated. In a multivariable analysis (**Table 4.5)** that adjusted for various factors including age, sex, ALBI score, FIB-4 and underlying aetiology, the hazard ratio (HR) for LSM was found to be 1.02.

Table 4.4. Exploratory univariable Cox proportional hazard regression analysis to determine impact on survival[27]

Variable	**HR**	**95% CI**	**p value**
Baseline liver stiffness (kPa)	1.03	1.03-1.04	<0.0001
ALBI score	4.24	3.58-5.01	<0.0001
FIB-4 score	1.10	1.09-1.12	<0.0001
Sex (male)	1.40	1.10-1.79	0.006
Age (years)	1.21	1.16-1.27	<0.0001
Aetiology			
Alcohol	-	-	-
Viral	0.65	0.45-0.94	0.02
NAFLD	0.23	0.16-0.32	<0.0001
Metabolic/Autoimmune	0.49	0.32-0.75	0.001
Unknown	0.25	0.18-0.35	<0.0001

[27] NAFLD; non-alcoholic fatty liver disease, HR; Hazard ratio, CI; Confidence interval

Table 4.5. Factors associated with survival in multivariable Cox proportional hazards model [28]

Variable	HR	95% CI	p value
Age (years)			
18-27	0.73	0.28-1.86	0.51
28-37	0.64	0.30-1.37	0.25
38-47	0.90	0.55-1.47	0.66
48-57	-	-	-
58-67	1.42	0.95-2.14	0.09
68-77	2.91	1.92-4.43	<0.0001
78+	2.62	1.30-5.29	0.007
Sex (Male)	1.51	1.11-2.06	0.008
Baseline liver stiffness (kPa)	1.02	1.01-1.03	<0.0001
ALBI score	2.47	1.93-3.15	<0.0001
FIB 4 score	1.04	1.01-1.06	0.008
Aetiology			
Alcohol	-	-	-
Viral	1.12	0.67-1.87	0.67
NAFLD	0.43	0.27-0.68	<0.0001
Metabolic/Autoimmune	0.80	0.46-1.37	0.41
Unknown	0.54	0.36-0.80	0.002

Major clinical outcomes

The impact of non-invasive fibrosis and functional testing on liver-related morbidity and mortality was investigated. The cumulative incidence of liver-related events, including varices, decompensation, transplantation, and death, at three years of follow-up was calculated and stratified based on baseline liver stiffness, FIB-4 score, and ALBI grade (**Table 4.6**). These results highlight the significance of non-invasive measures in predicting liver-related outcomes.

[28] NAFLD; non-alcoholic fatty liver disease, HR; Hazard ratio, CI; Confidence interval

Overall, the cumulative incidence of decompensation was 7.2% (95% confidence interval [CI], 6.2%–8.2%) at 3 years and 8.9% (95% CI, 7.7%–10.2%) at 5 years. Patients identified with ArLD had the highest cumulative incidence of decompensation at 5 years (19.2%, 14.8%–24.0%), and patients with NAFLD had the lowest (3.8%, 2.9%–5.0%). There was a clear association of the incidence of decompensation with baseline LSM. In those with LSM <15 kPa the incidence of decompensation at 5 years was 3.7% (95% CI, 2.7%–5.1%), rising to 8.6% (95% CI, 6.4%– 11.1%) in those with LSM 15–25 kPa and to 19.0% (95% CI, 15.8%–22.4%) in those with LSM >25 kPa.

The cumulative incidence of HCC was low: 1.6% (95% CI, 1.2%–2.2%) at 3 years and 2.5% (95% CI, 1.8%–3.3%) at 5 years. This incidence of HCC at 5 years was lower in patients identified with ArLD (3.8%; 95% CI, 2.1%–6.2%) and NAFLD (1.3%, 95% CI 0.7-2.2%) than those with viral hepatitis (5.7%; 95% CI, 3.2%–9.2%). Again, there was an association between LSM and the incidence of HCC; 1.7% (0.9%– 2.9%) of those with LSM <15 kPa, 2.4% (95% CI, 1.3%– 4.0%) of those with LSM 15–25 kPa, and 4.1% (95% CI, 2.6%–6.1%) of those with LSM >25 kPa developed HCC at 5 years.

Overall, the incidence of a first major clinical event in liver disease, either decompensation or the development of HCC was greatest in those with a LSM >25kPa **(Figure 4.17** and **Figure 4.18)**.

Figure 4.15. Cumulative incidence of varices according to liver stiffness

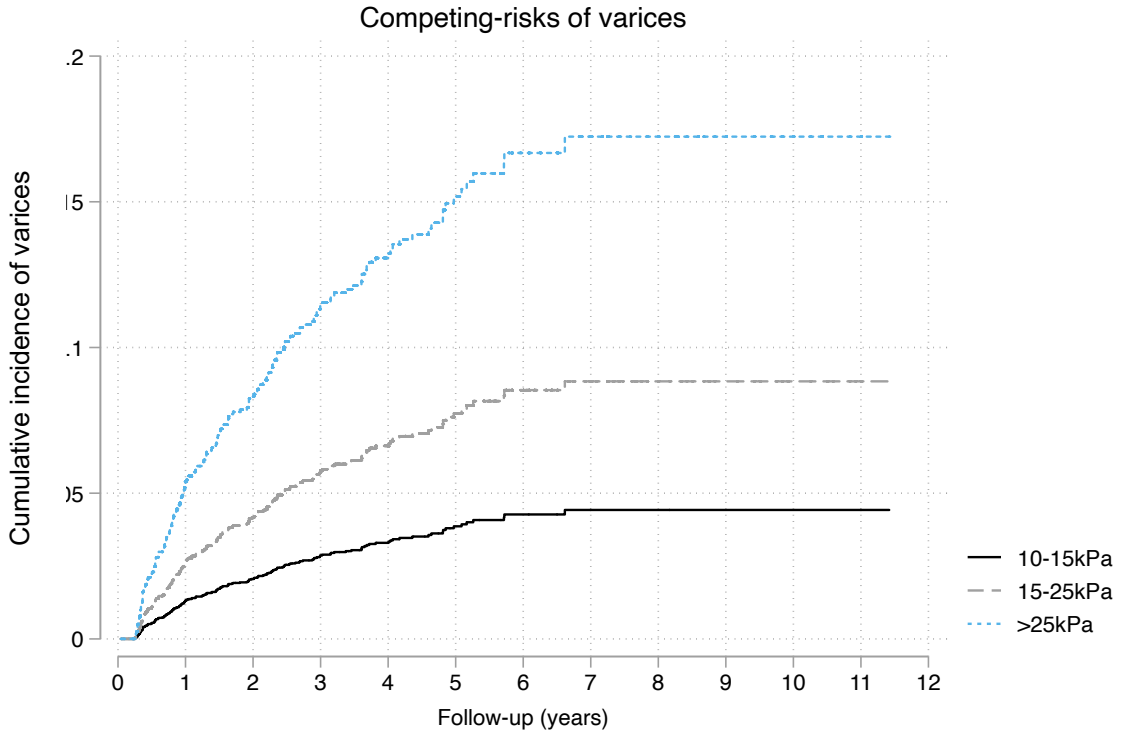


Figure 4.16. Cumulative incidence of bleeding varices according to liver stiffness

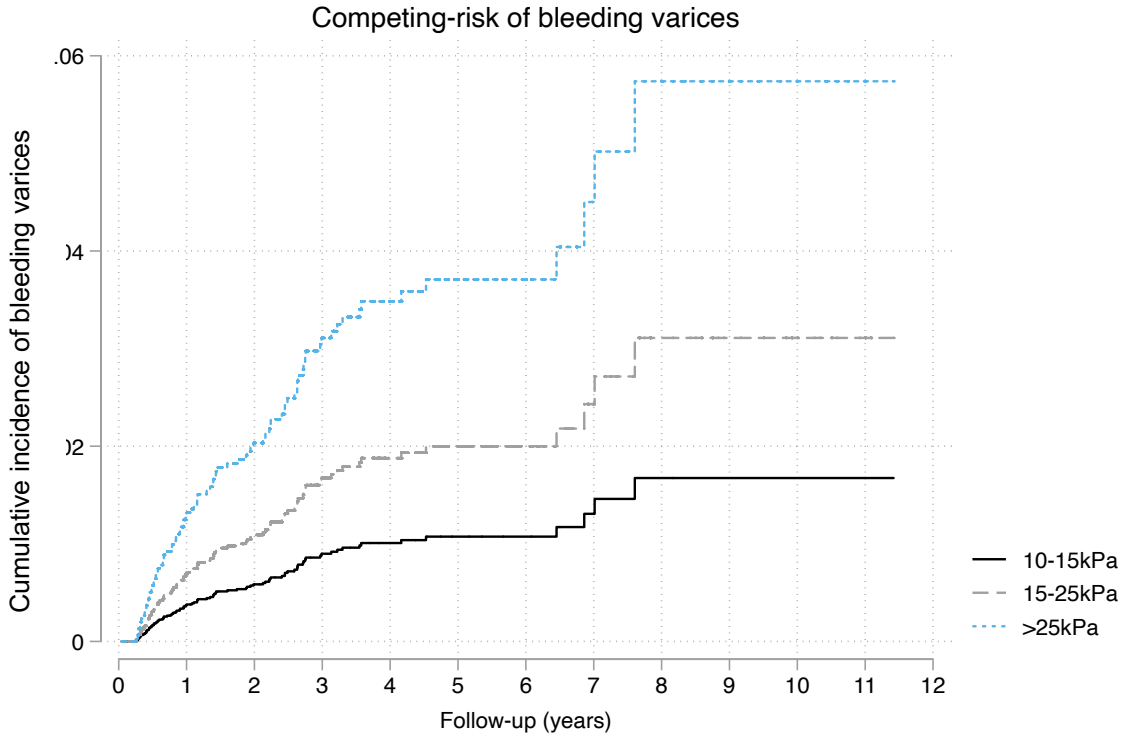


Figure 4.17. Cumulative incidence of decompensation according to liver stiffness

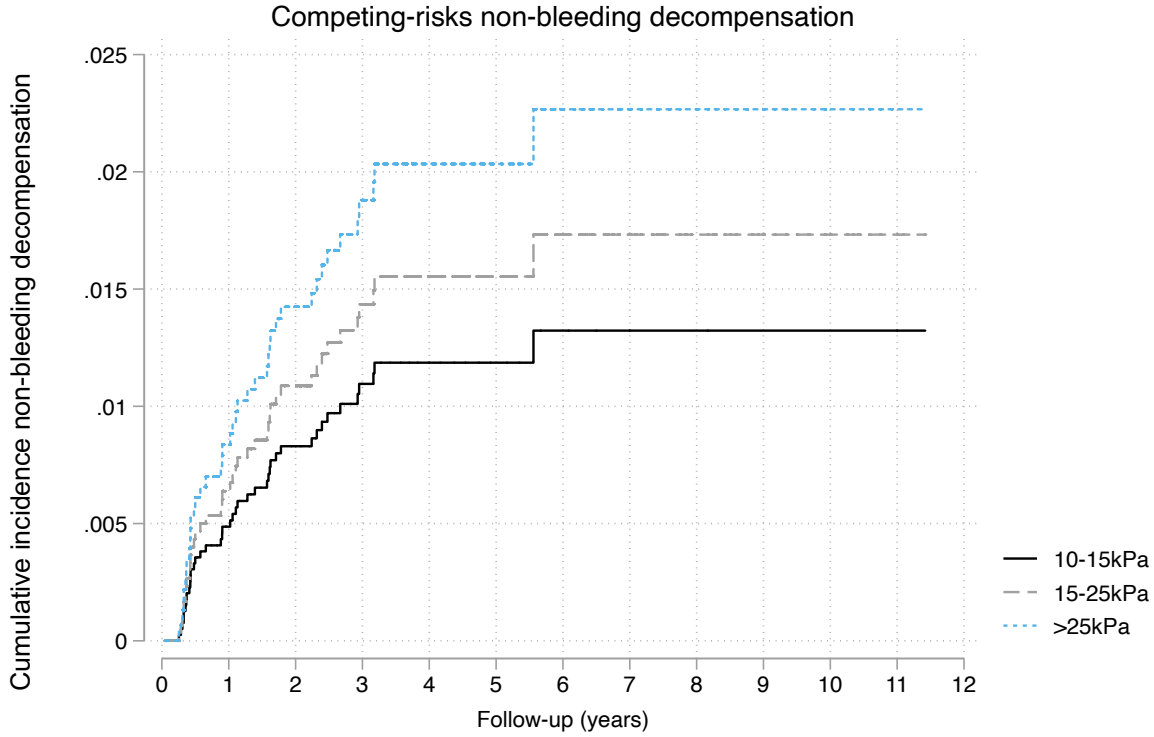


Figure 4.18. Cumulative incidence of hepatocellular carcinoma according to liver stiffness

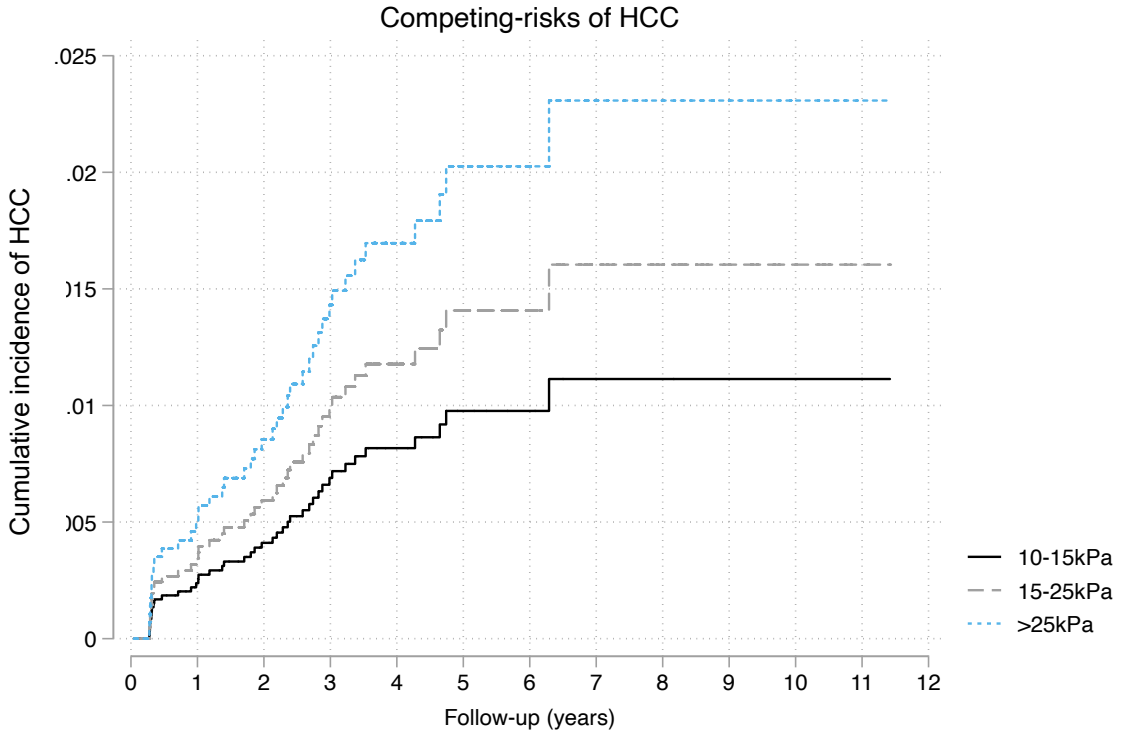


Table 4.6. Cumulative incidence rate at 3 years divided by liver stiffness, ALBI grade and FIB-4 per 100-person years.[29]

Cumulative incidence at 3 years								
	TE score			ALBI grade		FIB-4		
	10-15 kPa	15-25 kPa	>25 kPa	1	2 or 3	<1.3	1.3-2.67	>2.67
Varices (n)	0.71 (26)	2.69 (52)	6.52 (106)	1.78 (98)	7.15 (72)	0.35 (6)	1.39 (26)	6.40 (99)
95% CI	0.48-1.04	2.05-3.53	5.39-7.89	1.46-2.17	5.68-9.01	0.16-0.79	0.95-2.05	5.25-7.79
Bleeding varices (n)	0.44 (16)	0.71 (14)	1.62 (28)	0.72 (40)	1.40 (15)	0.30 (5)	0.63 (12)	1.28 (21)
95% CI	0.27-0.71	0.42-1.20	1.12-2.40	0.53-0.98	0.85-2.33	0.12-0.72	0.36-1.12	0.84-1.96
Non-bleeding decompensation (n)	0.49 (18)	1.47 (29)	4.57 (78)	0.84 (47)	6.83 (71)	0.36 (6)	0.74 (14)	4.07 (66)
95% CI	0.30—0.78	1.02-2.11	3.66-5.71	0.63-1.12	5.41-8.61	0.16-0.79	0.44-1.25	3.20-5.18
HCC (n)	0.32 (12)	0.71 (14)	1.61 (28)	0.57 (32)	1.77 (19)	0.12 (2)	0.42 (8)	1.58 (26)
95% CI	0.19-0.57	0.42-1.19	1.11-2.34	0.40-0.81	1.13-2.77	0.03-0.47	0.21-0.84	1.08-2.33
Liver transplant (n)	0.32 (12)	0.75 (15)	1.82 (32)	0.34 (19)	3.21 (35)	0.59 (10)	0.47 (9)	1.80 (30)
95% CI	0.18-0.57	0.45-1.25	1.31-2.57	0.22-0.53	2.31-4.47	0.32-1.10	0.25-0.91	1.26-2.57
Liver Death (n)	0.14 (5)	0.60 (12)	2.21 (39)	0.35 (20)	3.20 (35)	-	0.31 (6)	1.86 (31)
95% CI	0.06-0.32	0.34-1.06	1.62-3.03	0.23-0.55	2.30-4.46	-	0.14-0.70	1.31-2.64

[29] CI; confidence interval, HCC; hepatocellular carcinoma, TE; transient elastography

Competing risk regression

The cumulative incidence of first clinical events was calculated using a competing risk regression model. In this analysis non-liver events (cardiovascular and non-hepatic malignancy) were considered as competing events with the occurrence of varices, decompensation, and hepatocellular carcinoma. **Table 4.7** shows the variables assessed to determine their impact on clinical events during the follow-up period. TE and ALBI score were analysed as continuous variables rather than categorical.

LSM and FIB-4 were significantly associated with a diagnosis of varices, whilst LSM, ALBI score and FIB4 score at baseline were significantly associated with bleeding varices as a first clinical event. Only baseline ALBI score was significantly associated with non-bleeding decompensation. In comparison to persons with alcohol related liver disease, individuals with NAFLD were significantly less likely to have bleeding and non-bleeding varices, whilst those with viral hepatitis were more likely to have HCC. There was no statistically significant association with sex and age group in relation to competing risk of varices, bleeding, and non-bleeding decompensation. The impact of advancing liver disease (as described by non-invasive techniques) on extrahepatic morbidity and mortality was assessed (**Table 4.8**)**.** Increasing age was the only variable found to be significantly associated with the occurrence of both cardiovascular disease and non-hepatic malignancy whereas male sex was associated with incident cardiovascular disease. Neither non-invasive measures of increasing liver fibrosis nor liver disease was associated with cardiovascular disease or extrahepatic cancers in this study population, but ALBI score was also associated with the occurrence of non-liver death.

Table 4.7. Sub hazard ratios for competing liver events.[30]

Variable	sHR	95% CI	p value	sHR	95% CI	p value	sHR	95% CI	p value
	Varices			Bleeding varices			Non-bleeding decompensation		
Age (years)									
18-27	5.46	2.77-10.7	<0.0001	2.16	0.60-7.83	0.24	- -	- -	- -
28-37	1.47	0.66-3.25	0.35	0.90	0.25-3.19	0.87	1.83	0.46-7.28	0.39
38-47	1.09	0.57-2.07	0.80	1.02	0.47-2.25	0.95	1.33	0.42-4.22	0.63
48-57	-	-	-	-	-	-	-	-	-
58-67	1.11	0.70-1.77	0.65	1.28	0.67-2.45	0.45	1.23	0.45-3.40	0.69
68-77	0.93	0.53-1.64	0.80	0.69	0.27-1.77	0.45	0.93	0.27-3.18	0.91
78+	0.95	0.35-2.58	0.92	0.98	0.20-4.72	0.98	1.24	0.15-10.2	0.84
Sex (male)	0.86	0.61-1.22	0.41	1.12	0.64-1.96	0.69	1.49	0.64-3.43	0.35
TE score	1.02	1.01-1.03	<0.0001	1.02	1.00-1.03	0.01	1.01	0.99-1.02	0.34
ALBI score	1.26	0.89-1.78	0.20	2.62	1.74-3.95	<0.0001	1.69	1.01-2.84	0.06
FIB4 score	3.06	2.23-4.22	<0.0001	2.09	1.32-3.30	0.002	1.49	0.881-2.48	0.18
Aetiology									
Alcohol	-	-	-	-	-	-	-	-	-
Viral	0.91	0.42-1.98	0.82	1.53	0.72-3.23	0.27	1.45	0.38-5.57	0.59
NAFLD	1.93	1.10-3.39	0.02	0.32	0.14-0.75	0.009	1.32	0.44-3.97	0.63
Other	2.88	1.55-5.34	0.001	0.83	0.37-1.87	0.65	1.09	0.24-5.08	0.91

[30] sHR; sub-hazard ratio, CI; confidence interval, NAFLD; non-alcoholic fatty liver disease
– indicates baseline comparator. - - Indicates too few events to analyse

Table 4.8. Sub hazard ratios for competing non-liver events[31]

Variable	sHR	95% CI	p value	sHR	95% CI	p value	sHR	95% CI	p value	sHR	95% CI	p value
	HCC			Cardiovascular events			Non-hepatic malignancy			Non-liver death		
Age (years)												
18-27	- -	- -	- -	0.33	0.04-2.68	0.30	- -	- -	- -	1.05	0.36-3.08	0.93
28-37	1.16	0.24-5.60	0.85	0.22	0.03-1.75	0.15	- -	- -	- -	0.79	0.30-2.08	0.64
38-47	0.75	0.21-2.66	0.66	0.45	0.14-1.39	0.16	0.57	0.19-1.75	0.33	1.16	0.59-2.27	0.66
48-57	-	-	-	-	-	-	-	-	-	-	-	-
58-67	1.30	0.48-3.49	0.60	1.79	0.86-3.75	0.12	1.16	0.53-2.51	0.71	0.96	0.51-1.81	0.90
68-77	2.21	0.77-6.26	0.14	2.80	1.24-6.34	0.01	2.63	1.24-5.57	0.01	2.19	1.18-4.07	0.01
78+	- -	- -	- -	11.2	4.65-26.9	<0.0001	1.84	0.37-9.10	0.45	2.24	0.83-6.03	0.11
Sex (male)	1.79	0.68-4.70	0.24	3.77	1.91-7.43	<0.0001	1.40	0.76-2.58	0.28	1.25	0.80-1.97	0.33
TE score	1.00	0.98-1.02	0.92	0.98	0.96-1.00	0.02	0.99	0.97-1.02	0.55	1.01	1.00-1.02	0.14
ALBI score	1.20	0.55-2.62	0.65	0.92	0.49-1.75	0.80	0.53	0.27-1.07	0.08	2.72	1.90-3.89	<0.0001
FIB4 score	1.82	1.00-3.33	0.05	0.80	0.52-1.24	0.32	1.37	0.90-2.08	0.14	1.19	0.87-1.62	0.28
Aetiology												
Alcohol	-	-	-	-	-	-	-	-	-	-	-	-
Viral	2.87	1.01-8.11	0.05	0.70	0.26-1.88	0.47	0.33	0.09-1.19	0.09	0.74	0.28-1.97	0.55
NAFLD	0.48	0.13-1.74	0.26	0.75	0.38-1.51	0.42	0.47	0.23-0.98	0.04	0.54	0.25-1.17	0.12
Other	0.89	0.19-4.07	0.88	1.07	0.43-2.63	0.89	0.44	0.14-1.43	0.17	0.35	0.12-1.07	0.07

[31] sHR; sub-hazard ratio, CI; confidence interval, NAFLD; non-alcoholic fatty liver disease
– indicates baseline comparator. - - Indicates too few events to analyse

4.2.3 Discussion

Admissions and codes

Liver related diagnosis codes comprised seven out of the 'top ten' codes associated with in-patient admissions, suggesting that a large proportion of the admissions related to underlying liver disease rather than comorbidity. It is recognised that hospitalisation in patients with cirrhosis are usually a result of complications of portal hypertension, most commonly ascites (R18) (184). However, the codes which feature most frequently were diagnostic codes for liver disease (B18, K70, K74-K76), as opposed to codes for decompensation. One explanation may be that clinical coders attach the diagnostic liver disease code to an admission as a relevant condition which coexists at the time of admission, rather than the direct reason for admission. This highlights the importance of accurately identifying decompensation events to distinguish between liver-related and non-liver-related admissions.

The relatively high number of admissions per patient in the metabolic group is most likely frequent elective admissions for venesection in patients with haemochromatosis. This is supported by the most frequent code associated with in-patient admissions in the metabolic group being the code for 'disorder of iron metabolism'. This should be considered when using EHR data to determine outcomes and could be mitigated by separating emergency and urgent admissions from routine or elective admissions. The route of admission is a routinely collected data field within the HES database (85). This would also be of relevance for patients attending day case units for elective paracentesis, which may be coded as 'non-malignant ascites'.

The absence of a significant difference in the number of codes per admission between different diseases may appear counter-intuitive given the known association between NAFLD and extra-hepatic comorbidities. One possible explanation for this observation could be related to the way coded data are recorded in the EHR system, where certain comorbidities may not have been recorded in all cases or may have been recorded differently across different disease groups. Further investigation is needed to fully understand the reasons behind this observation and the potential impact on the accuracy of EHR-based studies of liver disease.

Codes for diabetes also occurred frequently, most notably within the NAFLD group in whom it was the most frequently occurring code, appearing in association with 709 in-patient admissions. Patients with cirrhosis are at increased risk of type 2 diabetes mellitus, irrespective of the underlying aetiology (185), and the presence of diabetes increases the risk of cirrhosis complications, death and hepatocellular carcinoma (186). In addition, studies have shown that cirrhotic patients with type 2 diabetes mellitus have a higher rate of hospital re-admission, extended length of stay and a higher rate of liver and non-liver related admissions (187). Using EHR data to observe the burden of diabetes-related admissions in the cirrhosis population may allow targeted interventions of those patients most at risk.

Codes for acute respiratory illness were common across all disease groups. This is in-keeping with previous studies which have shown that bacterial infections occur frequently in patients with cirrhosis and are a common cause for repeated hospital admissions and intensive care stays (188), and that mortality associated

with pneumonia is higher than other infectious diseases in patients with cirrhosis, particularly amongst those with ascites (189).

In this study, it is worth noting that the distinction between primary and secondary coding was not considered. In the HES dataset, each finished consultant episode derived from admitted patient care data can encompass a maximum of 20 ICD-10 codes, with one code designated as the primary diagnosis. The primary diagnosis represents the primary reason for the patient's healthcare encounter (97).

Secondary coding may include up to 19 additional ICD-10 codes, which capture additional information relevant to the patient's care but not necessarily representing the primary reason for hospitalisation. This can include comorbidities and concurrent conditions. The inclusion of secondary codes in the analysis is crucial as they help account for additional factors that may impact patient outcomes or contribute to the complexity of their care.

While the distinction between primary and secondary coding was not specifically addressed in this study, understanding, and utilising the full range of available codes in the HES dataset, including primary and secondary codes, can enhance the accuracy and depth of research findings. This is a consideration for future research using this data set.

Survival and clinical outcomes

Survival divided by disease and biochemical parameters as shown in the univariable and multivariable analysis followed the expected trajectory. The poorest survival was observed in those patients with viral and ArLD and higher LSM, whilst those patients with NAFLD were at a lower risk of death. This observation is in-keeping with disease registry studies in Europe and the United States, providing face validity to these findings (190, 191).

The outcomes illustrated in follow the expected pattern; as liver stiffness increases, so too does the risk of mortality. At five years of follow-up, approximately 25% of those with a LSM >25kPa have died, in comparison to 5% of those with a LSM between 10-15kPa. This supports the utility of TE, not only as a diagnostic tool in identifying ACLD but also in recognising those patients who are most at risk of death. This initial survival analysis was in-keeping with existing studies, with meta-analyses demonstrating that the risk of mortality has a ‘dose response’ relationship with LSM (48).

Increased mortality according to biochemical non-invasive measures was well defined in this analysis (**Figure 4.11** and **Figure 4.12)**. Those patients in whom there was insufficient data to calculate ALBI score had a similar survival outcome to the ALBI grade 1 individuals. This is likely due to the nature of this patient group, who had no further contact with secondary care following their initial TE. The data suggests that their synthetic function is most in-keeping with the ALBI grade 1 group. Survival estimates were stratified according to both liver stiffness and ALBI grade. The proportion of patients with ALBI grade 2 or 3 biochemistry

is higher amongst those patients with increased liver stiffness, and it is this group who appear at the greatest risk of mortality.

Risk stratification

The observation that combined non-invasive measures provide additional information is a striking concept and raises the possibility of a merged calculation which uses validated biochemical scores and liver stiffness to further risk stratify patients who are the highest risk of death and decompensation. The notion of combining ALBI and FIB-4 scores to create a predictive model for decompensation has been described previously (174), but not in combination with LSM. Comparable models have been used in cardiovascular disease for almost twenty years to estimate the ten-year risk of a fatal cardiovascular events, considering recognised risk factors such as smoking, age hypercholesterolaemia and geographical variation (192). This data suggests that liver stiffness, together with albumin and bilirubin are important predictors of outcomes in ACLD and can be used to inform stratification for follow up.

A suggested risk calculation based on these survival estimates is demonstrated in

Table 4.9. This simple prognostic tool could be easily deployed in the out-patient setting and would provide useful information for the clinician in terms of stratification for surveillance and screening based on risk of liver-related morbidity and mortality. It would also provide a visual illustration to patients help them understand their disease and the associated mortality risk. This is of particular

importance in cirrhotic patients given the widespread lack of understanding and knowledge about disease trajectory (193). In addition, risk scores can be used by non-liver clinicians and in primary care to help determine frequency of monitoring and to identify those patients who require referral to specialist services. This approach has been used with success in nephrology, with chronic kidney disease 'road maps' highlighting to primary care physicians who and when to refer (194).

Table 4.9. Non-invasive risk calculation based on liver stiffness and ALBI grade

Liver stiffness measurement (kPa)	Liver blood tests (ALBI)		Annual mortality risk (%)
	Grade 1	**Grade 2/3**	
<10	Low risk	<1	
10-15	<1	2	
15-25	2	3	
>25	3	10	

Findings in the context of current knowledge

The natural history of cirrhosis is most well described in relatively small cohorts of patients with biopsy proved disease (18, 195), frequently enriched for viral hepatitis than more common diseases such as ArLD and NAFLD. Predicted outcomes incorporating LSM and ALBI grade and FIB-4 score (**Table 4.6** and **Table 4.7**) are comparable to outcomes described in an inception cohort of patients with biopsy-proven compensated disease (31, 196). **Table 4.10** presents a direct comparison between these studies and this elastography cohort at 36 months following initial diagnosis (197).

Table 4.10. Comparison of clinical events observed in this cohort in comparison with previous study of biopsy proven cirrhosis.

Clinical event	Transient elastography cohort n=3029 (%)	Biopsy cohort N=202 (%)
Non-bleeding varices	230 (8)	35 (17)
Bleeding varices	65 (2)	2 (1)
Non-bleeding decompensation	167 (6)	17 (8)

A lower frequency of non-bleeding varices was observed in this cohort (8% vs.17%). This may relate in part to use of the Baveno IV criteria, for risk stratification of individuals who require variceal screening and less likely to be deployed in a patient with biopsy proven cirrhosis.

A lower incidence of both liver and non-liver complications was observed in patients with NAFLD, and it is recognised that there are differences between the natural history of liver disease of different aetiologies. For instance, the rate of liver-related complications in biopsied patients with hepatitis C virus infection is higher than in a similar population with NAFLD (198). Whilst it is recognised that cardiovascular events and extra-hepatic malignancy are the two leading causes of death in NAFLD (199, 200), this risk is most evident in patients undergoing liver biopsy for diagnosis and staging of liver disease in NAFLD. This group are likely to have a different prognosis to patients undergoing TE, and this may account for the differing rates of complications observed. Of note a recent retrospective population based case-control study, which used electronic primary care databases found a low prevalence of NAFLD and only a weak association between NAFLD and cardiovascular events when adjusted for known risk factors (201). One could postulate that the risk of incident cardiovascular events in

NAFLD may have been over-estimated due to selection bias in studies using biopsy proven cohorts.

The overall cumulative incidence of HCC in this cohort was low, but did increase with LSM, ALBI score and FIB-4 score. Whilst it is possible that the rate was underestimated in this analysis, the codes used to define HCC in the EHR have been validated in the literature and show good performance characteristics across different aetiologies (Sensitivity 94–96%; Specificity 93–98%) (121). In addition the same coding scheme as that used by Public Health England and the National Cancer Registration and Analysis Service was used here (63). Thus, it seems unlikely that many incident cases of HCC have been missed.

The incidence of HCC varies depending on underlying aetiology, ranging from <1.5% per year in patients with metabolic liver disease and NAFLD, between 0.2-1.8% per year in patients with ArLD cirrhosis and up to 3-5% per year in patients with cirrhosis secondary to viral hepatitis (202, 203). The low incidence rate of HCC observed may be due to the relatively high number of patients with NAFLD in comparison to viral hepatitis.

It should be noted that the rate described in this cohort is similar to that observed in a recent Danish registry-based cohort study of patients with ArLD cirrhosis (195). The authors of this study highlight the importance of death as a competing event when considering the true incidence of HCC, a factor which is not always considered in models estimating risk of HCC (204) and subsequent cost benefit analyses of HCC surveillance. The absolute benefits of surveillance where the incidence of HCC is low will be small (205, 206), and assessments of surveillance suggest cost-effectiveness at a threshold of 1.5% incidence per annum (207).

Those patients at the highest risk of developing HCC (high LSM, ALBI score and FIB-4) also have the poorest predicted mortality risk. Many of these patients will either decompensate and not be eligible for on-going surveillance or die from non-HCC causes. The data presented here lend weight to the recent arguments in favour of a randomised controlled trial of surveillance for HCC (208).

Limitations

There are limitations to this analysis worth consideration. The clinical context of elastography was not available, and factors which may affect the initial liver stiffness measurement such alcohol use and body mass index (BMI) could not be accounted for. A minority of patients had low non-invasive risk scores, suggesting a low probability of significant liver fibrosis. It may be because of this that several patients included were falsely considered to have advanced fibrosis.

The median follow-up period per patient was modest, which may have impacted upon the overall number of events observed. The patients included were drawn from the routine clinics of two large secondary care centres with associated tertiary care services, including transplantation. The description of natural history here may therefore not be applicable to other settings, particularly primary care though the relevance is likely greater than those studies using liver biopsy as the entry point.

In **Figures 4.9-4.12** the interaction of liver stiffness and non-invasive measures was visualised, showing that combing these two parameters improves prognostic ability. It is important to note that in the modelling process these interactions were not specifically accounted for, and thus the potential relationship may not have been fully captured. The absence of formal interaction modelling should be considered a limitation of this study, and future studies can explore more advanced methods to investigate and quantify the interactions among the variables of interest.

Whilst it was possible to identify admissions with liver-related complications and downstream mortality, the ascertainment of disease aetiology was incomplete in

a large proportion of individuals who had few or no hospital attendances. This was not unexpected given the validation findings described previously (**Page 78**), It is recognised that there is a degree of crossover between patients with ArLD and metabolic cofactors, and those with NAFLD who consume moderate amounts of alcohol (209), which will result in misclassification bias in some patients.

Completed case analyses was conducted in this analysis. This method has certain benefits; it is a straightforward approach which preserves observed data relationships and focuses solely on reliable information. It also avoids assumptions about missing data which may introduce bias. However, completed case analysis does have limitations. It results in a reduced sample size and the potential for lost information. This method risks introducing bias if completed cases are not representative of the whole population and if missing cases are non-random.

Alternative methods for handling missing data, such as multiple imputation, offer advantages over complete case analysis. Multiple imputations replace missing values with estimated values based on the available data (210), thereby mitigating the loss of information and potential bias associated with completed case analysis.

Although the current analysis did not adopt multiple imputation due to time constraints and limited expertise, future studies using this dataset should consider incorporating this method to address missing data. This approach allows for a more complete utilization of the available data, enhancing the statistical power and accuracy of the analysis.

It is not possible to identify BMI nor levels of alcohol consumption between different disease groups using EHR data alone, and the impact of disease modifiers such as antiviral treatment in patients with viral hepatitis cannot be automatically captured. Treatment of hepatitis B with significant liver fibrosis was offered universally in routine practice for the duration of the data collection, while direct acting antiviral treatments for hepatitis C emerged during the period. Patients with hepatitis C virus infection and significant liver fibrosis, as measured by transient elastography, were prioritised for treatment and since most patients had their first LSM in 2015 or later many of those patients with hepatitis C will have been treated and had a sustained virological response.

As only secondary care records were available, some events occurring in ambulatory patients will have been missed. Examples may include ascites or hepatic encephalopathy which is medically controlled and does not warrant in-patient admission. Although it is likely that this would represent a small number of events given the nature of the clinical events being analysed, and that the broad evaluation and conclusions would remain largely comparable. Similarly, whilst adjustments were made to the coding algorithms to exclude those patients with ICD-10 codes for decompensation prior to baseline TE, some cases may have been overlooked.

Finally, it is acknowledged that using the term ‘natural history’ to describe outcomes following a recorded secondary care encounter is not wholly accurate, the same being true of all observational studies which use selected populations of EHR data. Rather, this analysis describes outcomes in a cohort who have been pre-defined at baseline, a similar approach to other natural history studies of liver disease using biopsy proven cohorts.

Chapter 5

Screening and surveillance patterns in a UK population of patients with advanced chronic liver disease

5.1 Introduction

The incidence rate for primary liver cancer in the United Kingdom has risen over the past two decades, with an estimated 5,900 new cases being diagnosed each year. This trend is predicted to continue, with rates expected to rise by 38% over the next 15 years (211). Chronic viral hepatitis alongside alcohol misuse are the main risk factors worldwide (212), with the ongoing obesity epidemic and diabetes also contributing to the increasing incidence (213, 214). Whilst hepatocellular carcinoma (HCC) can occur in non-cirrhotic patients, the risk increases with clinically significant portal hypertension, with between 70-90% of all cases occurring in the context of established cirrhosis (215, 216).

Many patients are diagnosed with HCC at a late stage when treatment options are limited. Prognosis is improved when HCC is diagnosed at an early stage and curative treatment such as resection, ablation or liver transplantation can be considered (217). To facilitate detection, current European and American guidelines recommend that patients with cirrhosis, as well as some high-risk groups of patients including those with non-cirrhotic HBV, should be offered 6-monthly ultrasound scan (USS) surveillance to allow early diagnosis and initiation of curative treatment (218, 219). Whilst this guidance is supported by meta-analysis which suggest a survival advantage (220), the benefits of surveillance are not fully supported by randomised data and are inherently subjected to lead and length time bias (221). In addition, predictive modelling has shown that the absolute mortality benefit of surveillance is small (206).

The provision of HCC surveillance practices in the UK is poorly organised, owing mainly to the lack of database information and IT infrastructure supporting

automated 6-monthly recall for scans. A national survey published in 2015 showed that the 86% of UK hospitals did not have a database of patients attending surveillance nor any framework in place to allow audit or assessment (222). It is now well recognised that adherence to surveillance programmes in at-risk populations is sub-optimal, with database studies in North America and Europe demonstrating rates of regular surveillance of between 20-25% (223-225).

British, European, and American guidelines recommend that all patients identified as having advanced chronic liver disease (ACLD) should undergo endoscopic screening (36, 226, 227). Population base studies assessing adherence to these guidelines have shown varying levels of compliance (228-230).

This chapter uses EHR data to analyses the provision of ultrasound surveillance for HCC and variceal screening in a contemporary UK population.

5.2 Ultrasound surveillance

5.2.1 Patients and methods

Patient selection and population

Data regarding out-patient appointments was not available from the LTHT cohort. As a result, only data from the QEHB cohort was analysed. Patients were deemed eligible for surveillance if they fulfilled the following criteria:

i. Absence of a recorded HCC diagnosis prior to or within first six months of TE
ii. No evidence of decompensation documented within EHR prior to or within first six months of TE
iii. No recorded history of transplantation prior to or within two years of TE
iv. Liver stiffness measurement of ≥ 15kPa
v. Active follow-up in the hepatology outpatient department for a minimum of two years post-TE

Categorisation of follow-up

Active follow-up was defined as attending at least one hepatology clinic appointment annually for 2 years after the initial TE, with the first appointment being scheduled at least one month after the TE. The follow-up was divided into three categories:

i. **Regular follow-up** - Patients who attended at least one outpatient appointment per year for 2 years after TE

ii. **Inconsistent follow-up** - Patients who attended one outpatient appointment either in the first or second year after TE

iii. **No follow-up** - Patients who did not attend any outpatient appointments within 2 years after TE.

Categorisation of surveillance

Ultrasound scans (USS) were evaluated within two years of diagnosis of cirrhosis. The timing of the scan was adapted from the hierarchical system described by Thein *et* al (223). All scans occurring at least 4.5 months from the previous scan were deemed to be part of surveillance, with those occurring before this time considered additional likely for an acute indication. Scans included were limited either to 'US abdominal' or 'US liver'. Adherence to surveillance was ascribed as:

i. **Appropriate surveillance** - ≥ two USS for two years following TE at least 4.5 months apart

ii. **Incomplete surveillance** - either having one USS performed annually for two years following TE, or at least one USS conducted within two years of TE.

iii. **No surveillance** - No USS within two years of TE

Categorisation of comorbidity

The CCI was used to classify baseline comorbidity prior to TE and within the first 2 years of follow-up, details of which are included in **Appendix Pg 220 (Table**

10). For the purposes of this analysis the index was adapted to remove codes for ‘mild’ and ‘moderate’ liver disease and HCC. Patients were categorised by CCI into the following groups depending upon weight adjusted comorbidities:

i. No codes for comorbid disease
ii. One code for comorbid disease
iii. Two codes for comorbid disease
iv. Three or more codes for comorbid disease

Statistical analysis

All analysis was carried out using Stata/SE 15.1 Package (Single User License; Serial Number 401506311102) Once the surveillance cohort was identified, demographic details were extracted. This included age, underlying aetiology, and baseline biochemistry data. Clinical outcomes were analysed, included mortality, transplantation, and decompensation events during the follow-up period. Codes used to define these clinical events have been described previously and are included in the **Appendix Pg 211 (Table 7).**

Survival estimates according to patterns of surveillance and follow up in out-patient clinic were analysed and displayed using Kaplan-Meier curves. An ordered logistic regression model was used to estimate the relationship between surveillance and a set of independent variables. This method was used as patterns surveillance was categorised and ordered into three outcomes (none, inconsistent and appropriate), rather than combining two of these variables to enforce dichotomy (183).

Binomial logistic regression was used to determine predictors of receiving appropriate follow-up by modelling the relationship between a set of independent variables and the binary outcome. The model estimates the probability of the outcome occurring, and the predicted probability is used to classify the cases into one of the two outcome categories.

Variables of presumed clinical importance were chosen for inclusion in the regression model, including categorical variables of age, sex, and aetiology and CCI and continuous variables of LSM, ALBI score and FIB-4. Coding algorithms used are included in the **Appendix Pg 221-222.** A Cox proportional hazards regression analysis was used to assess the effect of surveillance on risk of mortality. This was initially unadjusted and then adjusted according to the variables described previously.

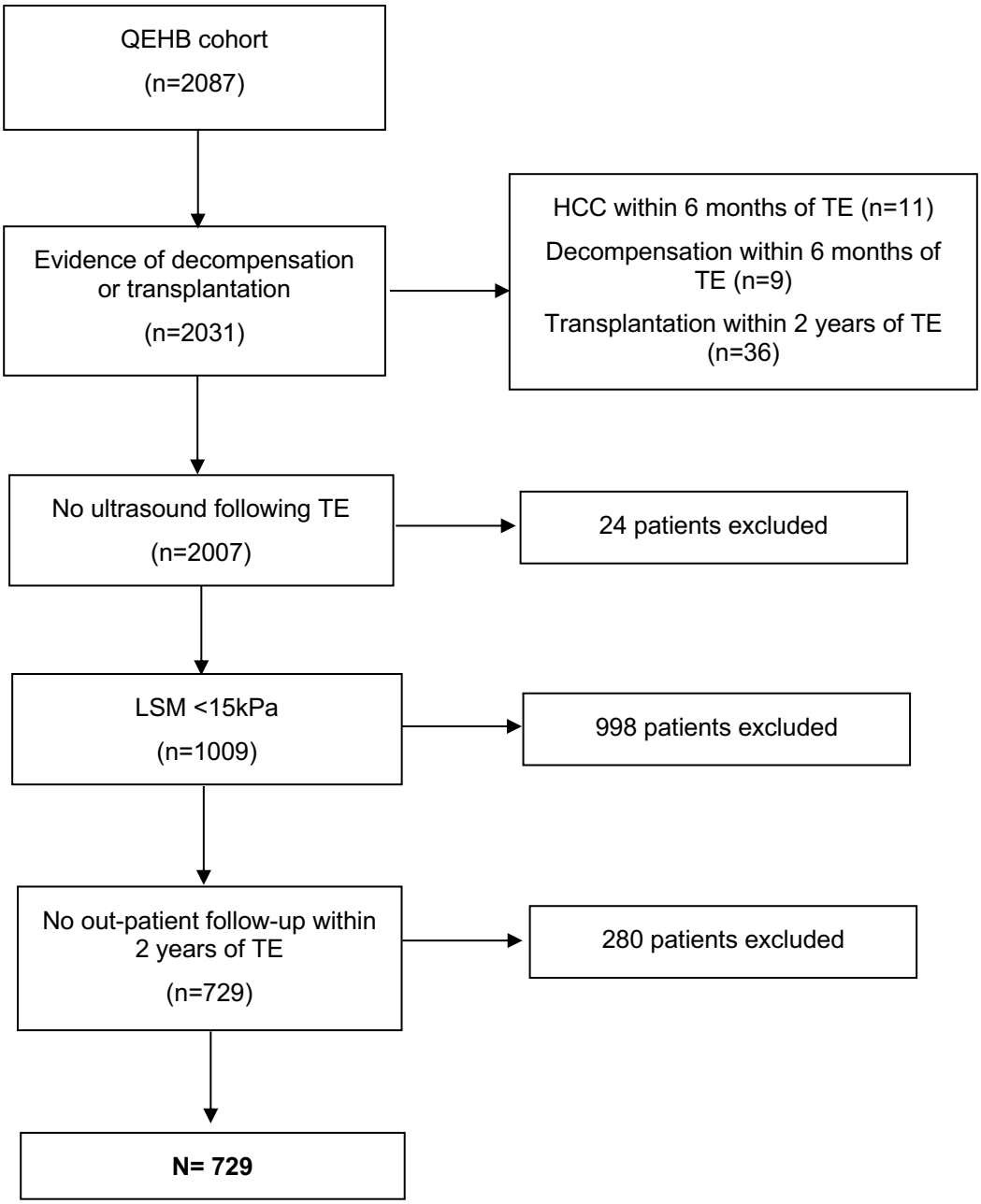
5.2.2 Results

Patient selection

The original QEHB cohort comprised of 2087 patients. The demographic information of the patients can be found in **Table 4.1.** The exclusion criteria were applied as depicted in **Figure 5.1.** Patients with decompensation, HCC or transplantation have been excluded *prior* to this analysis. A further 56 patients had one of these events within 6 months of TE. 24 patients had no ultrasounds following TE. 998 patients had a LSM <15kPa. 280 patients had no recorded out-patient appointments within 2 years following TE.

After taking these factors into consideration, a total of 729 patients were identified as suitable candidates for ultrasound surveillance and were used for further analysis.

Figure 5.1. Flow chart demonstrating identification of patients suitable for ultrasound surveillance



Patient characteristics

Demographic details of the 729 patients eligible for inclusion in the surveillance analysis are shown in **Table 5.1.** The median duration of follow up was 3.3 years. The most represented age group was 48 to 57 years old. 54% of the cohort were male. 28% of the cohort had NAFLD, 13% ArLD and 10% viral hepatitis. 56% of the cohort identified as White British.

The data necessary to calculate ALBI grade was available for 90% of the cohort. The majority of the cohort, 68%, was found to be ALBI grade 1 at baseline. The median ALBI score was -2.99. Data to determine FIB-4 index was available for 80% of the cohort and the median FIB-4 score was 3.57. Median TE score was 29.3 kPa. The CCI distribution of the cohort was as follows: 19% had a CCI score of 0, 20% had a CCI score of 1 or 2, and 40% had a CCI score greater than 3.

During the follow up period 14% of the patients in the surveillance cohort died, while 3.7% received a liver transplant. The most common first clinical event was non-bleeding varices, which occurred in 13% of the patients. This was followed by non-bleeding decompensation (4.5%) and cardiovascular events (4%). **Table 5.2** provides further details on the deaths and clinical events that took place.

Table 5.1. Demographic details for surveillance cohort[32]

Patient demographics	Surveillance cohort (n=729) (%)
Age (years), n (%)	
18-27	44 (6.2)
28-37	53 (7.3)
38-47	104 (14.3)
48-57	205 (28.1)
58-67	200 (27.4)
68-77	99 (13.6)
78+	23 (3.2)
Sex, n (%)	
Male	393 (53.9)
Female	336 (46.1)
Aetiology, n (%)	
NAFLD	207 (28.4)
Alcohol	96 (13.2)
Viral hepatitis	76 (10.4)
Autoimmune/cholestatic	87 (11.3)
Metabolic	16 (2.2)
Missing	253 (34.7)
Ethnicity, n (%)	
White	410 (56.2)
Mixed/Multiple ethnic groups	5 (0.7)
Asian/Asian British	89 (12.2)
Black/African/Caribbean/Black British	18 (2.5)
Other ethnic group/not known	207 (28.4)
Biochemistry	
Albumin (g/l, missing = 73)	43 (41, 47)
Bilirubin (µmol/L, missing = 73)	17 (8, 20)
Platelets ($x10^3/\mu l$, missing = 87)	173 (115, 218)
INR (missing =108)	1.2 (1, 1.2)
AST (iu/L, missing = 130)	73 (36, 84)
ALT(iu/L, missing =78)	74 (33, 84)
ALBI grade at baseline, n (%)	
1	515 (70.6)
2	134 (18.4)
3	7 (1.0)
Missing	73 (10)
FIB-4 Index at baseline, n (%)	
<1.45	101 (17.5)
1.45-3.25	192 (33.2)
>3.25	285 (49.3)
Unknown	151 (20.8)
Transient elastography (kPa), n (%)	
15-25	391 (53.6)
>25	338 (46.4)
Charlson comorbidity index	

[32] NAFLD; non-alcoholic fatty liver disease, INR; international normalised ratio, AST; aspartate transaminase, ALT; alanine transaminase

0	138 (18.9)
1	147 (20.2)
2	154 (21.1)
>3	290 (39.8)

Table 5.2. First clinical events of surveillance cohort

Clinical outcome	**Surveillance cohort n=729**
Death or transplantation	
Liver-related death	36 (4.9)
Non-liver related death	64 (8.8)
Liver transplantation	27 (3.7)
Clinical events	
Varices (non-bleeding)	98 (13.4)
Varices (bleeding)	10 (1.4)
Non-bleeding decompensation	33 (4.5)
Cardiovascular event	29 (4)
Non hepatic malignancy	14 (1.9)
Hepatocellular carcinoma	13 (1.8)

Incidence of HCC

During the follow-up period, a total of 26 patients (3.6%) were diagnosed with HCC. Thirteen of these diagnoses occurred as the first clinical event. **Table 5.3** provides further clinical information about these patients.

The median time from the start of the follow-up period to the diagnosis of HCC was 987 days. The most common underlying cause of HCC was viral hepatitis, affecting seven patients. Alcohol and NAFLD were each responsible for five cases. The underlying cause was unknown in six patients. The median LSM was 27kPa, ALBI score was -2.9, and FIB-4 score was 4.3. Over half of the patients diagnosed with HCC had a CCI score greater than 3, with 14 patients in this category.

Table 5.3. Table to show individual characteristics of patients diagnosed with HCC [33]

Sex	Age (years)	Aetiology	LSM (kPa)	ALBI	FIB-4	CCI	Length of time to HCC diagnosis (days)
Female	68-77	Unknown	23.7	-2.48	3.31	3	198
Male	58-67	Metabolic	23.5	-2.92	4.53	2	874
Female	68-77	NAFLD	29.1	-3.48	3.02	3	699
Female	38-47	Unknown	33.3	-2.77	-	0	1178
Male	48-57	Viral	33	-2.8	6.04	2	1544
Male	58-67	Metabolic	44.3	3.4	7.79	3	207
Male	28-37	Viral	26.3	-3.14	2.1	1	1560
Female	68-77	Viral	16	-2.9	-	3	2296
Male	58-67	Alcohol	27	-3.48	-	3	1030
Male	48-57	Viral	28.9	-	-	2	1140
Female	68-77	Alcohol	21.3	-3.68	1.56	3	861
Male	68-77	Unknown	33.8	-3.19	4.36	3	658
Male	78+	Unknown	15.1	-	-	3	907
Male	58-67	Alcohol	15.4	-2.89	1.6	3	564
Male	48-57	Viral	60	-2.43	7.14	1	1142
Female	58-67	NAFLD	45	-2.59	2.22	2	2479
Male	58-67	Metabolic	60	-1.76	10.68	3	1091
Male	48-57	Viral	21.3	-3.14	3.15	2	1731
Male	48-57	Alcohol	56.1	-	-	2	580
Male	68-77	Alcohol	48	-1.71	5.91	3	492
Male	68-77	NAFLD	22.1	-3.62	2.74	3	1204
Male	68-77	NAFLD	15.7	-2.66	3.97	3	252
Male	58-67	Unknown	46.1	-1.46	8.69	2	943
Male	48-57	Viral	46.4	-2.97	6.63	1	1289
Male	48-57	Unknown	23.2	-3.12	8.15	1	834
Male	58-67	NAFLD	19.8	-3	4.24	3	2556

[33] LSM; liver stiffness measurement, CCI; Charlson comorbidity index, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease

Adherence to surveillance and follow-up

Out of a total of 729 patients, 41% (301 patients) were undergoing appropriate surveillance ultrasounds, while 33% (238 patients) were receiving incomplete surveillance. 26% of patients (190) were not receiving regular surveillance at all. 29% (214 patients) were receiving regular follow-up while the remaining 71% (515 patients) were experiencing inconsistent follow-up. The characteristics of patients undergoing different patterns of surveillance are detailed in **Table 5.4.**

During the follow-up period, 26 patients were diagnosed with HCC. Out of these, 11 patients (42%) were receiving appropriate HCC surveillance, 12 (46%) were undergoing incomplete surveillance, and the remaining 3 (12%) had no surveillance. In terms of follow-up appointments, 7 patients (27%) were receiving regular follow-up, while the remaining 19 patients (73%) were receiving inconsistent follow-up.

Table 5.4. Table of descriptive characteristics of patients undergoing different surveillance patterns[34]

	Appropriate surveillance (n=301)	Incomplete surveillance (n=238)	No surveillance (n=190)
Age (years), n (%)			
18-27	9 (3)	23 (9.6)	13 (6.8)
28-37	15 (5)	23 (9.6)	15 (7.9)
38-47	46 (15.3)	31 (13)	27 (14.2)
48-57	90 (29.9)	57 (24)	58 (30.5)
58-67	88 (29.2)	69 (30)	43 (22.6)
68-77	45 (15)	29 (12.2)	25 (13.2)
78+	8 (2.7)	6 (2.5)	9 (4.7)
Sex			
Male	168 (55.8)	132 (55.5)	93 (49)
Female	133 (44.2)	106 (44.5)	97 (51.1)
Aetiology			
Viral	45 (15)	18 (7.6)	18 (9.5)
Metabolic	35 (11.6)	27 (11.3)	14 (7.4)
Autoimmune	6 (2)	9 (3.8)	1 (0.5)
Alcohol	47 (15.6)	27 (11.3)	22 (11.6)
NAFLD	72 (23.9)	74 (31.1)	61 (32.1)
Unknown	96 (31.9)	83 (34.9)	74 (39)
CCI			
0	52 (17.3)	54 (22.7)	32 (16.8)
1	64 (21.3)	38 (16)	45 (23.7)
2	65 (21.6)	52 (21.9)	37 (19.5)
>3	120 (39.9)	94 (39.5)	76 (40)
Follow-up			
Regular	107 (35.6)	81 (34)	26 (13.7)
Inconsistent	194 (64.5)	157 (66)	164 (86.3)

Survival estimates, predictors of surveillance and follow up

The median survival between patients receiving appropriate surveillance and those receiving incomplete, or no surveillance showed a statistically significant difference (p = 0.0377) as per the log-rank test, as shown in **Figure 5.2**. **Figure 5.3** also highlights the impact of follow-up patterns on survival, with patients regularly attending follow-up appointments showing greater survival (p = 0.0407). Additionally, the survival rate among patients divided by CCI group was also found to be statistically significant (p = 0.0089), as shown in **Figure 5.4.** An

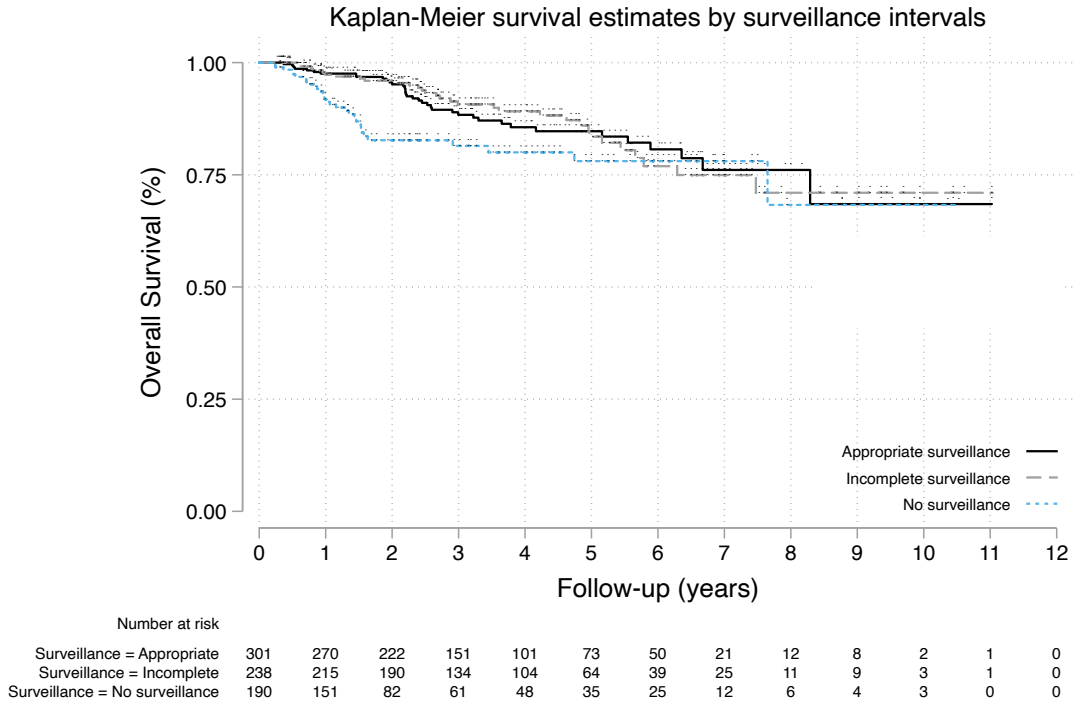
[34] NAFLD; non-alcoholic fatty liver disease, CCI; Charlson comorbidity index

ordered logistic regression was conducted to identify factors which influenced regular hepatoma surveillance, as shown in

Table 5.5. The results indicated that younger patients, those with a lower CCI score, and patients with NAFLD or an unknown aetiology were less likely to receive regular surveillance ultrasounds. Regular follow-up appointments were associated with increased odds of receiving regular surveillance ($p<0.001$). Binomial logistic regression did not reveal any significant predictors of regular follow-up (**Table 5.6).**

The unadjusted Cox regression model showed that the association between appropriate and incomplete surveillance and mortality risk was significant (HR = 0.59 and 0.56, respectively) as shown in **Table 5.7.** After adjusting for potential confounders, the association remained significant (HR = 0.36 and 0.28, respectively).

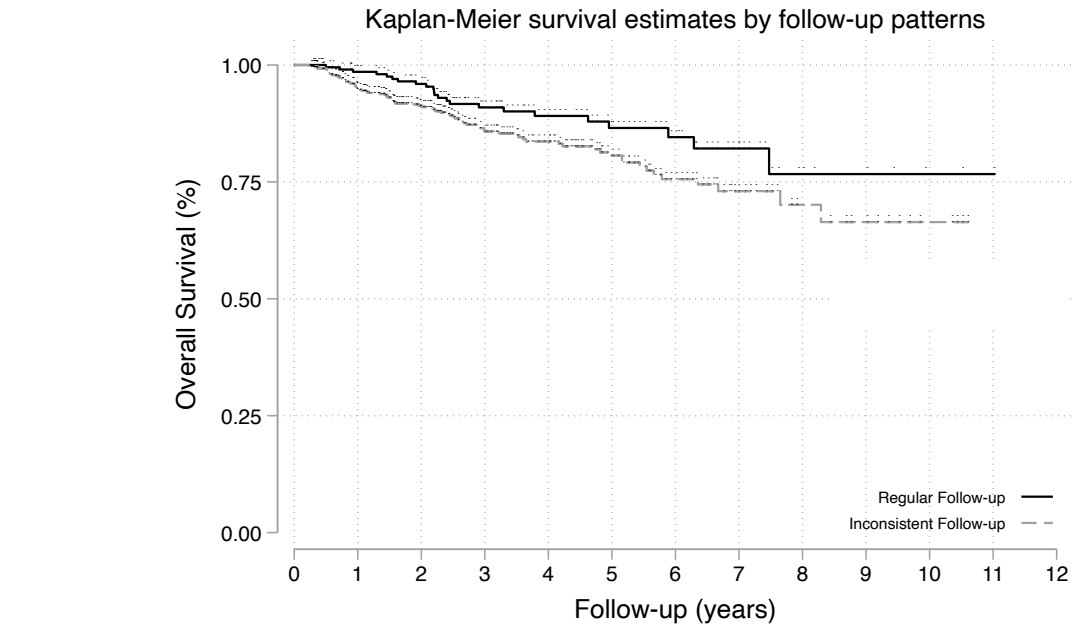
Figure 5.2. Survival estimates of patients receiving different patterns of surveillance



Number at risk

Surveillance = Appropriate	301	270	222	151	101	73	50	21	12	8	2	1	0
Surveillance = Incomplete	238	215	190	134	104	64	39	25	11	9	3	1	0
Surveillance = No surveillance	190	151	82	61	48	35	25	12	6	4	3	0	0

Figure 5.3. Survival estimates of patients receiving regular or inconsistent follow-up



Number at risk

Follow_up = Regular Follow-up	214	197	167	116	84	60	39	22	10	8	3	2	0
Follow_up = Inconsistent Follow-up	515	439	327	230	169	112	75	36	19	13	5	0	0

Figure 5.4. Survival estimates by Charlson comorbidity index

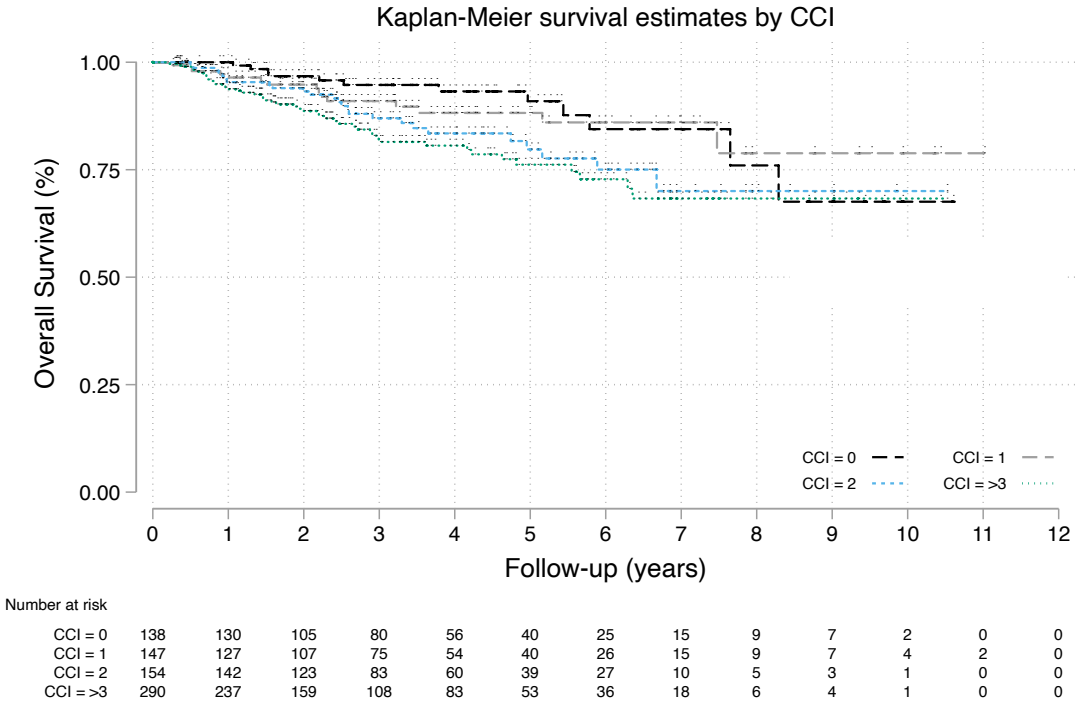


Table 5.5. Predictors of regular ultrasound surveillance by ordered logistic regression[35]

Variable	Odds ratio	95% CI	P value
Age			
18-27	0.35	0.15-0.78	0.010
28-37	0.41	0.19-0.87	0.020
38-47	0.53	0.27-1.03	0.061
48-57	-	-	-
58-67	1.41	0.85-2.36	0.185
68-77	1.12	0.59-2.15	0.723
78+	0.75	0.26-2.19	0.600
Sex (male)	1.01	0.74-1.40	0.946
LSM (kPa)	1.00	0.99-1.02	0.261
ALBI score	0.87	0.63-1.22	0.419
FIB-4 score	1.00	0.95-1.05	0.948
Aetiology			
Viral	-	-	-
Autoimmune	0.83	0.40-1.70	0.605
Metabolic	0.92	0.30-2.76	0.877
Alcohol	0.62	0.31-1.21	0.160
NAFLD	0.54	0.30-0.98	0.042
Unknown	0.48	0.26-0.87	0.015
CCI			
0	-	-	-
1	0.49	0.26-0.93	0.029

[35] CI; confidence interval, LSM; liver stiffness measurement, NAFLD; non-alcoholic fatty liver disease, CCI; Charlson comorbidity index

2	0.48	0.22-1.06	0.071
>3	0.40	0.17-0.94	0.034
Follow-up (regular)	2.16	1.53-3.06	<0.0001

Table 5.6. Predictors of regular follow up. Binomial logistic regression[36]

Follow-up			
Variable	**Odds ratio**	**95% CI**	**P value**
Age			
18-27	0.53	0.19-1.47	0.220
28-37	0.57	0.22-1.50	0.258
38-47	0.80	0.35-1.80	0.587
48-57	-	-	-
58-67	1.28	0.67-2.44	0.450
68-77	1.67	0.75-3.69	0.206
78+	1.82	0.52-6.36	0.346
Sex (male)	1.10	0.74-1.61	0.644
LSM (kPa)	1.00	0.98-1.01	0.768
ALBI score	1.15	0.77-1.73	0.492
FIB-4 score	0.91	0.83-0.99	0.028
Aetiology			
Viral	-	-	-
Autoimmune	1.33	0.58-3.05	0.499
Metabolic	0.28	0.03-2.35	0.240
Alcohol	1.50	0.69-3.22	0.304
NAFLD	0.98	0.49-1.96	0.955
Unknown	1.20	0.61-2.35	0.596
CCI			
0	-	-	-
1	0.82	0.37-1.80	0.618
2	0.51	0.19-1.40	0.192
>3	0.46	0.16-1.32	0.151

Table 5.7. Cox proportional hazard regression models for risk of mortality with appropriate, incomplete and no surveillance. HR; hazard ratio.[37]

	Unadjusted HR (95% CI)	**P value**	**Adjusted HR* (95% CI)**	**P value**
Appropriate surveillance	0.59 (0.36-0.95)	0.031	0.36 (0.20-0.65)	0.001
Incomplete surveillance	0.56 (0.34-0.93)	0.024	0.28 (0.15-0.52)	<0.0001
No surveillance	-	-	-	-

[36] CI; confidence interval, LSM; liver stiffness measurement, NAFLD; non-alcoholic fatty liver disease, CCI; Charlson comorbidity index

[37] * Adjusted for age, sex, liver stiffness, ALBI score, FIB-4 score, aetiology, Charlson comorbidity score and pattern of follow-up. HR; hazard ratio.

5.2.3 Discussion

In this study, the timing, and patterns of ultrasound surveillance for HCC and follow-up appointments for patients with compensated cirrhosis were analysed in a cohort of 729 patients. The patients were selected based on their suitability for surveillance, considering factors such as their synthetic function, markers of disease severity, and presence of comorbid conditions. The profile of patients diagnosed with HCC during the follow-up period was in line with previous research findings. The majority of these patients had either viral hepatitis or alcoholic liver disease, and a LSM of greater than 20kPa. 41% of the patients in this study were receiving appropriate ultrasound surveillance. Poor adherence to HCC surveillance is a well-documented issue, with previous studies reporting rates ranging from 8.8% to 46% (as detailed in **Table 5.8**) (231-236).

Table 5.8. Reported adherence rates to surveillance programmes[38]

Author (Year)	Study population	Number of patients, n	Surveillance rate (%)
Davila (2010) (232)	Patients diagnosed with HCC in Medicare databases	1873	Complete:17 Incomplete: 38
Davila (2011) (231)	Veterans Affairs registered patients diagnosed with hepatitis C	13,002	Complete: 12 Incomplete: 58.5 None: 29.5
Goldberg (2016) (234)	Commercially insured patients in United States	8916	Complete: 8.8 Incomplete: 55.4 None: 35.8
Farrell (2016) (233)	Patients with cirrhosis identified through radiology information system	804	Complete: 46 Incomplete: 54
Mittal (2016) (235)	Patients diagnosed with HCC in Veterans Affairs database	887	Complete: 46.5 None: 53.5
Tran (2017) (236)	Patients monitored at Stanford University Medical Centre, United States	2366	Complete: 24.4 Incomplete: 44
Yeo (2021) (237)	Patients enrolled in Truven Health MarketScan Research Database	82,427	Complete: 8.8 Incomplete: 20.5; 25.3 None: 45.4

[38] HCC; hepatocellular carcinoma

A recent meta-analysis found that pooled HCC surveillance rates varied depending upon the setting, ranging from 9.8% in population-based studies, to 29.5% in centre-based studies and 73.7% in those patients attending speciality clinics (238). The overall rate of surveillance was 24%, a minimal improvement in comparison to a systematic review conducted in 2012, which reported pooled surveillance rates of 18.4% (239).

There are many factors which influence adherence to surveillance recommendations. A national survey of UK hospitals showed that most centres arrange surveillance on an ad hoc basis, with no formal database in place to identify and monitor practice. Difficulty accessing radiology, cost and doubts over efficacy were cited as the most common barriers to implementation (222). Studies have also reviewed patient-reported barriers, the most frequently reported issues being difficulties with the scheduling process, cost (in US based cohorts) and problems with transportation to appointments (240).

It was striking that only 29% of individuals were receiving regular follow up with a specialist, despite having a LSM in-keeping with advanced fibrosis. The reasons for such poor follow-up are not known, but it is well recognised that patients with cirrhosis have poor understanding of their condition (241) and engagement with services. Data available through NHS Digital shows that patients did not attend (DNA) 7.1% of out-patient appointments in hepatology clinics between August 2019 and July 2020, higher than overall reported DNA rates for out-patient services and those within other specialties such as renal, cardiology and respiratory (5.7%, 4.9% and 1.76% respectively) (242). This data highlights the importance of improving patient education about the complications of cirrhosis and engagement in long-term follow-up.

This study found that the lack of surveillance was associated with a higher mortality risk, as demonstrated by both the survival analysis and Cox regression analysis. This finding aligns with the results of a systematic review by Singal et. al, which showed that patients receiving HCC surveillance had a significantly improved survival rate (pooled OR 1.90, 95% CI 1.67-2.17) (220). However, it is important to interpret this data with caution due to the limitations of retrospective observational cohort studies, such as inherent selection and lead time biases, which can overestimate the positive effects of screening on a population.

It is notable in this cohort that many of the patients not receiving surveillance ultrasounds died within the first two years of follow up. One could speculate that this is appropriate patient selection by the clinician, with those individuals at risk of decompensating and dying being removed from the surveillance programme, as they would not be eligible for curative therapy if an HCC was identified. The effect of selection and lead time biases was recognised in a systematic review by Kansagara and colleagues, which concluded that it was impossible to measure the true effect of screening on mortality based on the results of observational studies (243).

The main limitation to this analysis was that not possible to determine the reason why an ultrasound was being done. Whilst it was assumed that those at regular 6 monthly intervals were part of routine surveillance, it is conceivable that some of the scans were being done acutely for a separate indication. Additionally, the data are presented from a single tertiary care referral centre, and it is recognised that surveillance provision in centres with access to speciality care is higher than in population-based studies (238).

This data are in-keeping with previous observational studies which have shown that the provision of hepatoma surveillance in the UK remains poor, with over half of patients who were suitable for surveillance not receiving it. More recently there have been arguments put forward in favour of a randomised trial (208), which would provide insight into the true cost effectiveness, benefits and potential harms of a surveillance programme. To deliver this effectively in the UK on a national level, a robust infrastructure would be required, which allows for careful patient selection for entry into surveillance, and removal of patients when no longer suitable for curative treatment.

5.3 Variceal screening

5.3.1 Patients and methods

The same patient cohort used previously in this chapter were used to assess adherence to variceal screening (as outlined in **Section 4.2.1**). All patients with a valid LSM of 10kPa or higher were included in the analysis. Demographic data at baseline was also collected, including age at TE, gender, and ethnicity. Algorithms were applied to determine underlying aetiology, CCI and clinical events of interest. Data to determine ALBI and FIB-4 score and platelet count ($x10^3/\mu l$) were included.

The EHR data for each patient was reviewed to determine if the patient had an upper gastrointestinal endoscopy within one year of index TE. The OPCS procedural codes used to define an endoscopy are included in the **Appendix Pg 223 Table 11.** Codes denoting the presence of non-bleeding varices occurring within one year of TE were also noted, and if the patient did not have an accompanying procedural code it was assumed that the patient had undergone an endoscopy. Procedures which occurred within 30 days of an admission with codes for variceal bleeding was not considered to be part of screening. The medical record was not reviewed therefore, the grade of varices could not be determined.

Binomial logistic regression was used to determine predictors of undergoing screening endoscopy within one year. Variables of presumed clinical importance were chosen for inclusion in the regression model, including categorical variables of age, sex, and aetiology and continuous variables of LSM, ALBI score and FIB-4 index.

This study adheres to the guidelines set forth by the Baveno VI consensus which recommend using a LSM value of less than 20kPa with a platelet count greater than $150x10^3/\mu l$ as criteria for avoiding screening endoscopy in patients with suspected varices (52). Following this the expanded Baveno VI criteria was used; this refers to a continued risk prediction model which adjusts the thresholds to LSM less than 25kPa and platelet count greater than $110x10^3/\mu l$. The extended criteria has performed well in validation studies (53, 244). These criteria have also been validated within this cohort with good performance characteristics (245), the results of which are included in the **Appendix Pg 224-226** for reference.

The results of this analysis aimed to provide insight into the factors that influence adherence to variceal screening.

5.3.2 Results

Patient characteristics

Table 5.9. Demographic details comparing screening and non-screening cohorts.[39]

Patient demographics	Screening cohort (n=499) (%)	Non-screening cohort (n=2511) (%)
Age (years), n (%)		
18-27	22 (4.4)	151 (6.0)
28-37	42 (8.4)	245 (9.8)
38-47	71 (14.2)	459 (18.2)
48-57	124 (24.9)	668 (26.6)
58-67	123 (24.7)	626 (24.9)
68-77	98 (19.6)	297 (11.8)
78+	19 (3.8)	65 (2.6)
Sex, n (%)		
Male	297 (59.5)	1460 (58.1)
Female	202 (40.5)	1051 (41.9)
Aetiology, n (%)		
NAFLD	155 (31.1)	673 (26.8)
Alcohol	112 (22.4)	218 (8.9)
Viral hepatitis	56 (11.2)	235 (9.4)
Autoimmune/cholestatic	65 (13.0)	142 (5.7)
Metabolic	14 (2.8)	57 (2.3)
Missing	97 (19.4)	1186 (47.2)
Biochemistry		
Albumin (g/l, missing = 30; 262)	43 (39, 46)	44 (41, 47)
Bilirubin (µmol/L, missing = 30; 262)	12 (8, 19)	10 (7, 15)
Platelets ($x10^3/\mu l$, missing = 30; 287)	157 (113, 202)	200 (151, 248.5)
INR (missing =55; 443)	1 (1.1, 1.2)	1 (1, 1.1)
AST (iu/L, missing = 127; 697)	51.5 (35.5, 85.5)	47 (32, 75)
ALT(iu/L, missing =32; 282)	46 (29, 75)	53 (32, 84)
ALBI grade at baseline, n (%)		
1	341 (68.3)	1889 (75.2)
2	125 (25.1)	344 (13.7)
3	3 (0.6)	17 (0.7)
Missing	30 (6.0)	261 (10.4)
FIB-4 Index at baseline, n (%)		
<1.45	53 (10.6)	607 (24.2)
1.45-3.25	111 (22.2)	658 (26.2)
>3.25	206 (41.3)	503 (20.0)
Unknown	129 (25.9)	743 (29.6)
Transient elastography (kPa), n (%)		
10-15	107 (21.4)	1368 (54.5)
15-25	173 (34.7)	636 (25.3)
>25	219 (43.9)	507 (20.2)

[39] Continuous variables shown as median with interquartile range. Categorical variables shown as number and percentage. Missing data listed as screening followed by non-screening numbers. NAFLD; non-alcoholic fatty liver disease, AST; aspartate transaminase, ALT; alanine transaminase, INR; international normalised ratio

Demographic details are shown in **Table 5.9** A total of 3010 patients were eligible for inclusion, with 18 patients excluded due to the presence of codes for variceal bleeding within 30 days of initial endoscopy. Out of these eligible patients 16% (499 patients) had an upper gastrointestinal endoscopy within one year of TE, with 326 of these procedures (67%) occurring within the first six months of initial visit. In both cohorts there was a similar distribution of age, gender, and aetiology, although comparatively more missing data in the non-screening cohort. The median LSM in the screening cohort was 21.8kPa, whilst in the non-screening group it was lower at 14.3kPa. Similarly median FIB-4 score was higher in the screening cohort (2.97 vs 1.72).

Outcomes

Table 5.10. Predictors of screening endoscopy within one year. Binomial logistic regression.[40]

Variceal screening			
Variable	**Odds ratio**	**95% CI**	**P value**
LSM (kPa)	1.02	1.01-1.03	<0.0001
FIB-4 Index			
<1.45	-	-	-
1.45-3.25	1.49	0.99-2.23	0.05
>3.25	2.36	1.45-3.84	0.001
Platelets (x10^3/μl)			
>250	-	-	-
150-250	1.41	0.93-2.14	0.11
<150	1.73	1.05-2.86	0.03

[40] CI; Confidence internal, LSM; liver stiffness measurement

Binomial logistic regression found that increased LSM, FIB-4 score, and platelet count were all significantly associated with increased likelihood of undergoing prompt screening endoscopy. This information is presented in **Table 5.10** and illustrated in **Figure 5.5** and **Figure 5.6.**

Figure 5.5. Predicted probabilities with confidence intervals of screening endoscopy at different LSM thresholds

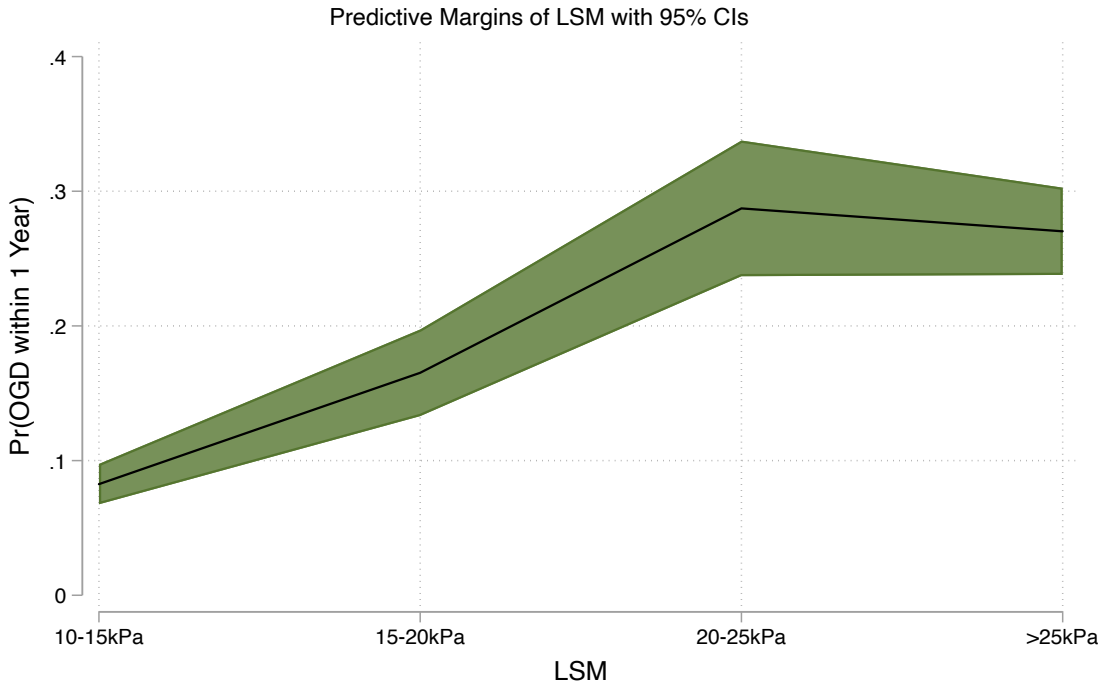
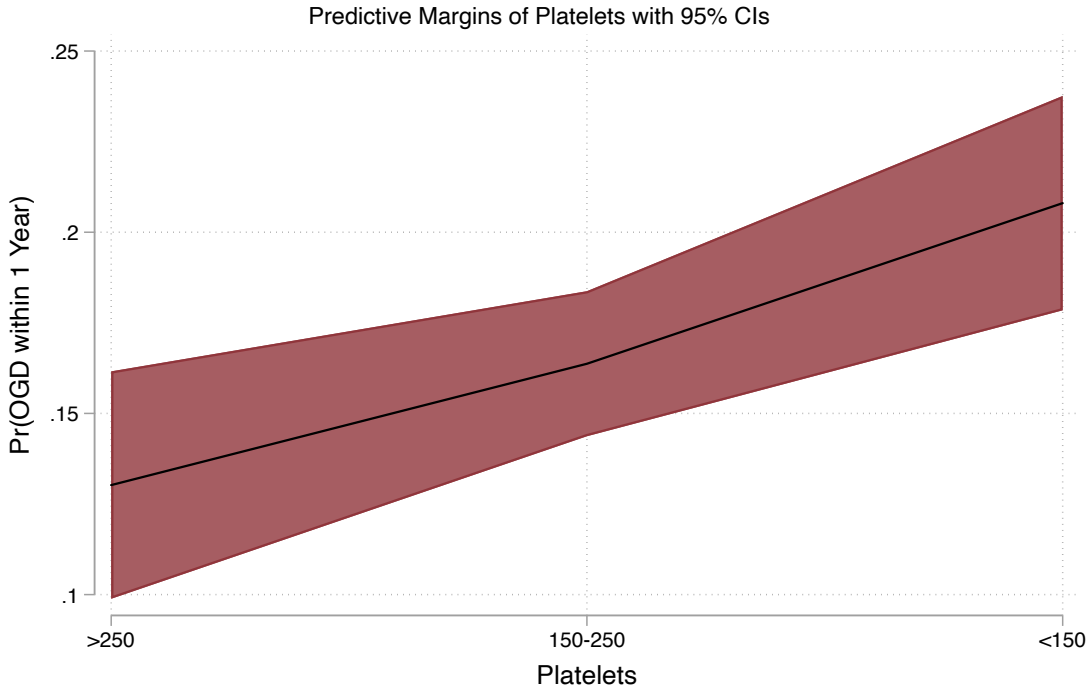


Figure 5.6. Predicted probabilities with confidence intervals of screening endoscopy at different platelet thresholds.



Of the patients who underwent screening endoscopy 89 (17.8%) were found to have non-bleeding varices, whilst 13 patients (2.7%) were subsequently admitted with variceal bleeding (excluding those occurring within 30 days). The median length of time between index endoscopy and variceal haemorrhage was 239 days (IQR 125, 294).

Overall, 1650 patients (54.8%) fulfilled the Baveno VI criteria. 129 of these patients had an endoscopy within one year of TE, which could have been safely avoided. When the extended Baveno VI criteria was applied, 2116 (70.3%) were identified, of which 234 patients underwent endoscopic screening within one year.

5.3.3 Discussion

Screening for oesophageal varices is recommended to improve outcomes for patients with cirrhosis (36). This data shows that adherence with these recommendations is poor, with only 17% of patients undergoing endoscopy within the first year of follow-up. Increased liver stiffness and FIB-4 score increased the likelihood of undergoing screening, likely a reflection of the clinician's higher index of suspicion of CSPH in these individuals. Over half of the cohort were low risk according to the Baveno VI criteria, which may account for the low rate of screening.

There are few studies which have evaluated adherence rates to varices surveillance recommendations. Two US studies reported high rates of screening within one year of between 80-94% in 119 and 179 patients respectively (229, 230). Given the small number of patients included in these single centre studies it is difficult to extrapolate these findings to a contemporary UK population. A more direct comparison can be made with validation studies of the Baveno VI criteria, which evaluated endoscopies within one year of transient elastography. A UK study excluded 1471 patients (79%) out of a possible 1862 patients with LSM >10kPa, as they had not undergone endoscopic surveillance within 12 months of TE (54), whilst a US validation cohort of 296 patients with a LSM >10kPa found that 135 patients (45%) had no screening endoscopy within one year (246). Similarly low rates can be observed in a recent population-based study of 82,427 privately insured patients with cirrhosis in the US, with more than 80% of patients having no endoscopy during the follow up period (237).

This study has certain limitations that need to be considered when interpreting the results. The medical record was not reviewed in this analysis; thus, it is not known how many patients declined endoscopic evaluation nor their reason for declining it. Nor was it possible to determine the grade of varices and the treatment implemented thereafter.

A modest threshold of 10kPa was used to define advanced fibrosis, accepting that this would misclassify a proportion of patients. However, as recent validation studies have proposed lower thresholds of <7kPa and >12kPa (Sensitivity 91%; Specificity 92%) for excluding and diagnosis compensated ACLD (168), it was felt that measurements above 10kPa was acceptable.

5.4 Conclusion

The first part of this chapter describes the natural history of compensated advanced chronic liver disease and identifies variation in rates of development of complications according to liver stiffness, severity of biochemical abnormalities and disease aetiology. The analysis shows that TE is strongly associated with outcomes in two large contemporary cohorts of patients. The utility of existing measures of liver fibrosis and liver function can, using EHR data, be exploited to provide large scale natural history information for patients with ACLD. This approach is of value in the development of large-scale effectiveness trials and cost-effectiveness analyses to understand the benefits of interventions and treatments in this growing patient population.

The second part of this chapter describes the provision of HCC surveillance and variceal screening. Only a minority of patients had undergone the recommended interventions. This data emphasises the short comings in the provision of surveillance and regular follow up which remain in UK practice and highlights the potential for a cirrhosis registry to support improved data collection and outcomes in patients with cirrhosis.

Chapter 6

Conclusions and Recommendations

6.1 Summary of findings

Liver disease, particularly cirrhosis, poses significant challenges in terms of understanding its progression and managing patient care effectively. To address these challenges, this work explores the potential of EHR data to observe outcomes in patients with cirrhosis aiming to improve the understanding and management of liver disease.

The use of EHR data offers several advantages in studying liver disease. EHRs provide a comprehensive and detailed record of patient encounters, including medical history, laboratory results, imaging findings, medication usage, and clinical notes. This wealth of information allows researchers to examine patient outcomes, identify risk factors, assess treatment effectiveness, and uncover patterns of care delivery.

To lay the foundations for this project, a rigorous systematic review of existing literature was conducted. A total of 1626 records were screened, and from this existing pool, 18 key studies were identified for evaluation. Building upon the insights gained from the literature review, a consensus code set consisting of nine essential ICD-10 codes was developed (**Table 2.10**). This code set serves as a standardised tool for accurately identifying cases of cirrhosis within EHR data.

The developed code set was validated in four diverse patient populations from Europe and North America, ensuring its applicability and reliability across different healthcare settings **(Section 3.3.2).**

The code set demonstrated improved performance characteristics compared to the commonly used code set reported in recent literature. In the UK the sensitivity of the consensus code set was improved from 44% to 61%, whilst in the US it improved from 89% to 100%. The PPV of the consensus code set was also encouraging, with 83% of cases positively identified in the UK and 89% in the US. This enhancement in accuracy and reliability strengthens the foundation for future EHR based research related to cirrhosis.

Additional validation was conducted to gain insights into the underlying causes of cirrhosis (**Sections 3.3.3 and 3.3.4).** To achieve this a hierarchical coding algorithm was developed and applied, resulting in an overall PPV of 63%. Algorithms to identify key clinical events of interest within EHR data were also developed. These algorithms demonstrated high levels of agreement, reaching 94% in the analysed cases. The ability to accurately identify and classify such critical clinical events is an essential aspect of liver disease research utilizing electronic data. The robust agreement achieved by the algorithms validates their effectiveness in capturing and categorising important clinical milestones in this patient population.

Data derived from EHR was used to analyse the natural history of liver disease in a large contemporary cohort of over 3000 patients with advanced fibrosis defined by transient elastography **(Section 4.2.2).** The impact of non-invasive fibrosis and functional testing on liver-related morbidity and mortality was investigated. The results of this analysis revealed compelling associations between key variables and patient outcomes. This showed that increasing liver stiffness, ALBI score, and disease aetiology are each associated with poorer outcomes. These findings provide valuable insights into the factors that contribute

to disease progression and help identify patients who are at higher risk of experiencing adverse liver-related events.

Based on these findings a suggested risk calculation was developed as presented in **Table 4.9** which serves as a practical tool that clinicians can employ to quickly assess and stratify patients based on their individual risk profiles. By incorporating relevant factors identified in the analysis, this risk calculation facilitates more efficient and informed decision-making, allowing clinicians to tailor interventions and allocate resources more effectively.

This project also examined patterns of screening and surveillance for complications of cirrhosis in accordance with current practice guidelines **(Sections 5.2.2 and 5.3.2).** The findings shed light on the current state of care delivery and revealed areas of concern that warrant attention. The results demonstrated suboptimal adherence to recommended guidelines for ultrasound surveillance for HCC. Alarmingly, only 41% of the patients included in the study were receiving the appropriate ultrasound surveillance, indicating a significant gap in the delivery of this crucial aspect of care. Similarly, the rate of endoscopy within the first year of follow-up, a vital component of surveillance for varices, was found to be low, with only 17% of patients undergoing this procedure. Improving the rates of ultrasound surveillance and endoscopic screening for varices is of paramount importance, due to the critical role these interventions play in preventing two of the most life-threatening complications of cirrhosis: the development of hepatocellular carcinoma and variceal bleeding.

Through the analysis of EHR data, potential gaps in care were identified and areas for improvement were identified in the management of patients with

advanced liver disease. This approach holds great potential for optimising patient care pathways and reducing adverse outcomes associated with cirrhosis.

It is important to contextualize this research within the broader landscape of liver disease care. The Lancet commission’s final report in 2020 highlighted the increasing burden of liver disease in the UK and the ongoing shortfalls in adequate care for patients admitted to hospital (68). To truly enhance the quality of care for patients with liver disease, there is a need for a national registry that provides a comprehensive overview of the disease's trajectory, enabling the development of prognostic models to mitigate risks and assess the efficacy of preventative interventions.

By leveraging the power of EHR data and advocating for a national registry, this research aims to drive improvements in the care and management of patients with liver disease, ultimately enhancing patient outcomes and addressing the current challenges in healthcare delivery.

6.2 The role of a disease registry

A disease registry is a centralised database that collects and organises clinical information relating to a specific disease or condition. The primary goal of a registry is to evaluate patient outcomes and gain a deeper understanding of the natural progression of a disease. By collecting epidemiological data from a large patient population, disease registries can identify eligible patients for large-scale clinical trials and cost-effectiveness evaluations. Additionally, they can be used to assess the effectiveness of novel therapeutic agents, monitor adherence to screening and surveillance strategies and to compare the quality of care provided across different centres.

Disease registries have been used successfully to map outcomes and responses to treatment in patients with a variety of medical conditions. One successful example is the Myocardial Ischaemic National Audit Project, a UK based programme which focusses on the management and outcomes of patients with myocardial infarction and unstable angina (247). This registry monitors variation in care and adherence to national guidelines and provides feedback to healthcare professionals to improve quality improvement initiatives. This project has been shown to improve quality of care for patients with ischaemic heart disease (248).

The EuroHeart (European Unified Registries for heart Care Evaluation and Randomised Trials) initiative, is an important collaboration between national registries within Europe (249). It aims to enhance the quality of heart disease care by establishing common data sets and standardised quality criteria across participating countries. By utilizing shared data standards, EuroHeart promotes consistency and comparability in the collection and analysis of heart disease

related data. One of the significant achievements of the EuroHeart project has been the publication of pan-European data standards (250). These standards serve as guidelines for collecting and evaluating data related to heart disease. Both the Myocardial Ischaemic National Audit Project and EuroHeart showcase how good quality data, harmonised code lists and international consensus can assess the effectiveness of different treatment approaches, identify best practices, and inform evidence-based decision-making.

However, despite the increasing burden of liver disease in the UK, there is currently no mandatory registry that documents the clinical course, complications, and treatment practices of patients with liver disease.

As the burden of liver disease grows and becomes more widely recognised by policymakers (251), the need for a disease registry using electronic database information becomes increasingly urgent. Such a registry would provide a valuable resource for clinicians and researchers to track and analyse key data points, including disease incidence, progression, treatment responses, and outcomes.

In 2013, National Confidential Enquiry into Patient Outcome and Death (NCEPOD) highlighted avoidable deaths in patients admitted with ArLD, with less than half of those receiving good quality care (252). Since then, it has become increasingly clear that the lack of comprehensive service and outcome data are a major shortcoming in the inpatient management of liver disease. Establishing a disease registry would be an ideal solution to address these deficiencies.

Non-invasive testing at baseline predicts outcomes and can be used to stratify risk in patients with compensated cirrhosis (253). With the increasing availability

of elastography data, there is now a well-defined entry point for research studies and quality improvement approaches aimed at optimising outcomes for these patients. While many of these studies are biopsy-controlled prospective studies with small cohorts, large population-based studies using national registry data are starting to emerge (254), highlighting the potential of EHR data to improve our understanding of the natural history of liver disease under the currently recommended standard of care.

By gathering and analysing data on patient outcomes and service provision, a registry could provide a detailed understanding of the current state of inpatient liver disease management. This could help to identify areas for improvement, guide the development of best practices, and facilitate the implementation of quality improvement initiatives. By tracking data over time, a registry could also help to identify trends in care delivery and provide valuable insights into the effectiveness of different management strategies.

This research project demonstrates that EHRs provide a wealth of valuable information. However, there are specific details that may be missing from EHRs but are crucial for a comprehensive disease registry. To establish a bespoke disease registry that complements EHR data, several aspects should be considered.

Firstly, EHRs primarily capture data from healthcare encounters but to achieve a complete picture, out-patient data is vital. This includes day case paracentesis, out-patient endoscopy attendance for variceal banding, and clinic attendances, all of which provide valuable information about patient care and disease management. It is recognised that there are challenges associated with out-

patient data. These encounters are often shorter visits, with less structured documentation, and high administrative workloads. The lack of standardised coding practices results in inconsistencies and gaps in coding. Nevertheless, including both in-patient and out-patient data is essential for a comprehensive understanding of liver disease, ensuring that a registry captures the diverse aspects of patient care.

EHRs may not capture all relevant phenotypic information needed for a disease registry, in particular details regarding disease aetiology which was highlighted in this project. As disease aetiology can significantly influence disease progression, and outcomes it is an important data element to include in a registry and should therefore be collected separately.

The integration of laboratory data into EHRs offers significant benefits for streamlining registry data collection. However, it is important to address the issue of incomplete laboratory data to ensure comprehensive mapping of outcomes in patients with liver disease.

In this study it was noted that key laboratory data were often incomplete, such as AST values required for calculating FIB-4 scores. Whilst it is important to avoid time-consuming manual data entry, ensuring that laboratory results are captured at registry entry is an essential part of mapping outcomes in patients with liver disease. One approach to addressing this is to implement data capture mechanisms that prompt healthcare providers to enter specific laboratory results relevant to the registry. This could involve integrating decision support tools or reminders within the EHR system.

In addition to this, details regarding prescribed medications should be recorded separately. Whilst this was not explored specifically in this project, recording medications allows for a more comprehensive understanding of treatment responses and their impact on patient outcomes over time. Researchers can easily access and analyse medication data in a standardized format, ensuring consistency and facilitating comparative analyses across different patient cohorts. Moreover, a separate medication record in the registry allows for the inclusion of additional more detailed information that may not be routinely captured in EHRs. This can include details such as medication dosages, treatment durations, changes in medications over time, and reasons for medication adjustments or discontinuations.

Finally, to comprehensively assess liver disease risk factors and outcomes, capturing information about environmental exposures, occupational history, lifestyle factors such as body mass index and smoking status is crucial. These data elements may not be routinely collected in EHRs but are important for conducting population-level research and understanding the broader determinants of disease.

Ultimately, the establishment of a national liver disease registry would be a significant step forward in improving the quality of care and treatment outcomes for patients with liver disease in the UK and should be a top priority for policymakers and healthcare professionals alike.

Risk stratification

Liver disease is a complex heterogenous condition with multiple underlying causes and different treatment modalities. Clinicians face the challenge of not only detecting and classifying the disease and managing modifiable risk factors, but also determining the appropriate timing of therapeutic interventions and monitoring the response to therapy. These considerations are especially difficult when the underlying disease trajectory is not well-defined; although it is well known that a large proportion of the population is overweight and drink alcohol hazardously, only a minority of these patients will develop cirrhosis during their lifetime.

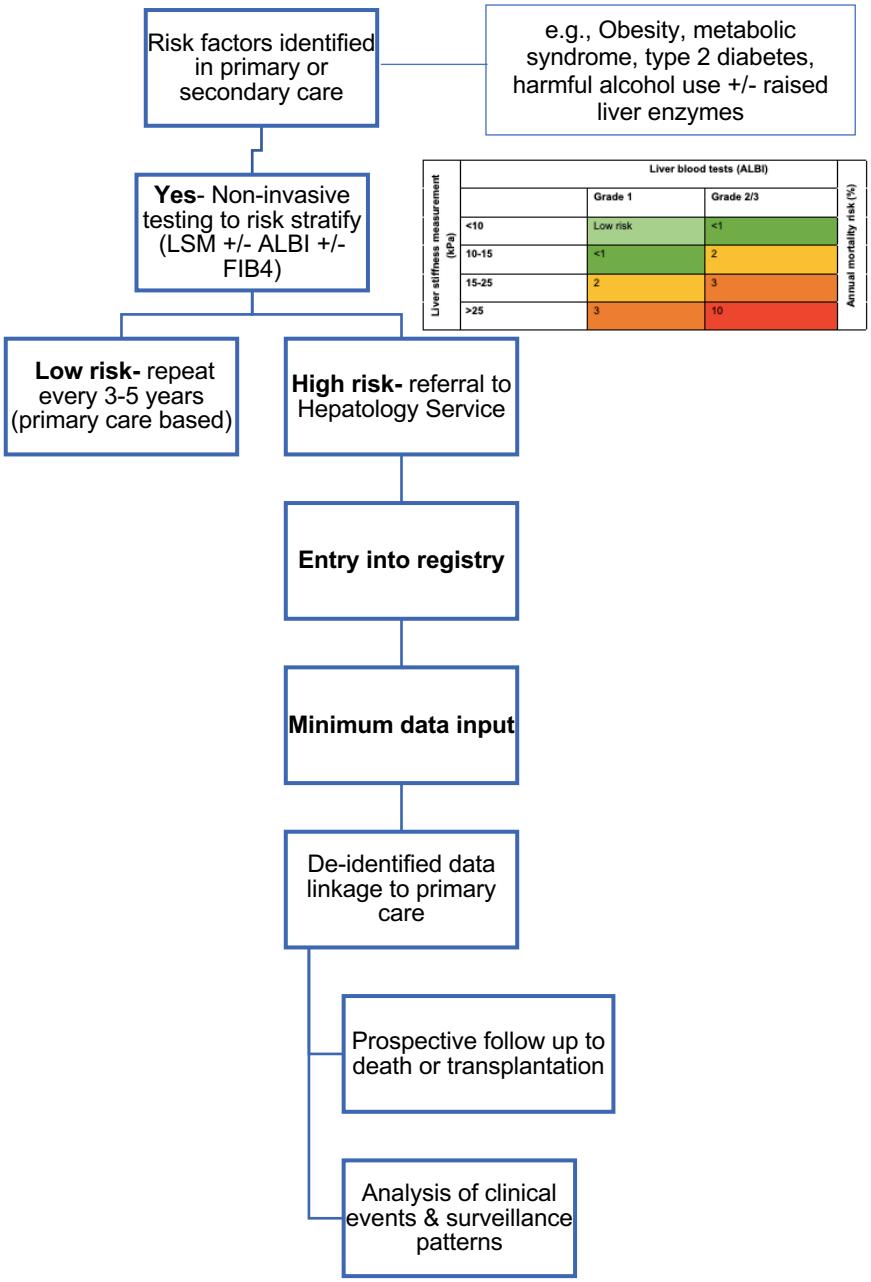
To improve the management of liver disease, clinicians need a better understanding of patient phenotypes based on demographics, clinical observations, and aggregated biochemical measurements. This approach can help identify patients who are most likely to be at risk of progression and enable clinicians to tailor follow-up accordingly.

The concept of ‘phenomapping’ using large datasets has been effectively used in cardiovascular medicine to classify disease groups and stratify patient risk (255). A model based on non-invasive testing, such as the one suggested in

Table 4.9, shows that a similar approach using EHR data can be used in liver disease to facilitate early detection of patients with advanced fibrosis. These risk stratification models can be integrated into referral pathways from the community to ensure that patients with the highest risk of liver related morbidity and mortality are referred to specialist clinics. Once patients with ACLD are identified, they can be enrolled in a registry that is supported by EHR data. A pathway for registry

entry, based on the Nottingham liver disease stratification pathway (256), is depicted in **Figure 6.1.**

Figure 6.1. Referral pathway of patient identification and entry into registry



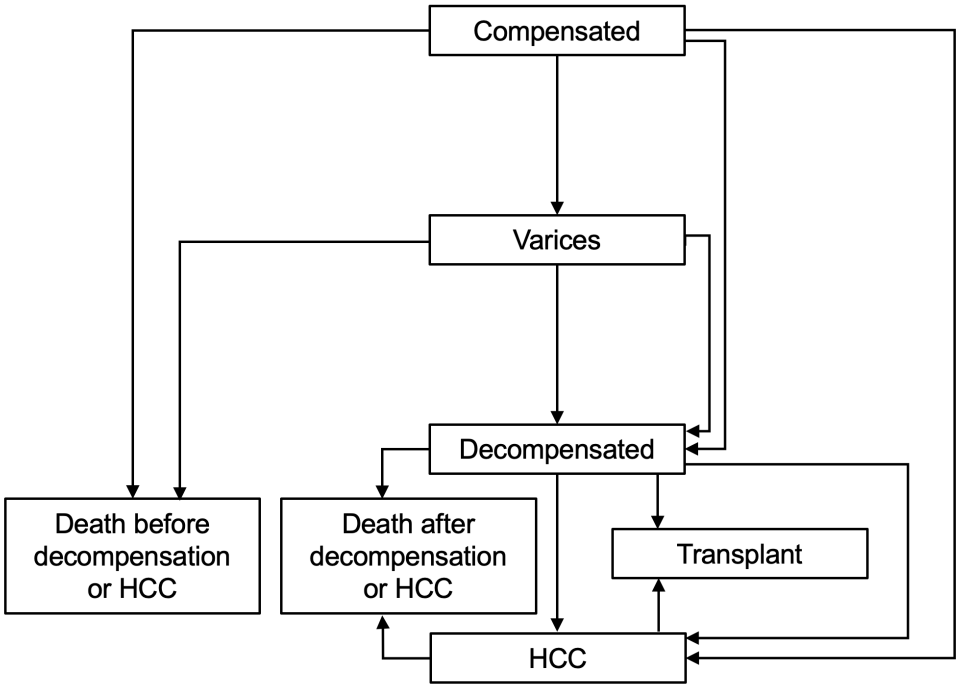
Defining the natural history

Recent natural history studies have employed multistate models of disease progression (31, 32), including proposed models that account for competing events and illustrate different transitional states from compensated ACLD, as shown in **Figure 6.2.**

Whilst most of these models have been developed using cohorts of patients with biopsy-proven cirrhosis from selected populations, the use of a registry that includes patients diagnosed by non-invasive measures could refine our understanding of the clinical course of cirrhosis from an earlier time point, allowing for more opportunities for intervention and adjustment of modifiable risk factors. By incorporating variables such as aetiology, liver stiffness, FIB-4, and ALBI score, modelling can be adjusted to better predict disease progression and outcomes.

Using multistate models can improve the identification of the target demographic for HCC surveillance, as it helps to determine which individuals are more likely to die a non-HCC death and thus may not benefit from ongoing surveillance. This modelling approach allows for the description of high and low-risk groups based on non-invasive measures, gender, and disease aetiology. A registry is an ideal tool for prospective follow up of these groups, providing a platform for designing and delivering randomised controlled trials. Indeed defining the target group is considered the first and most crucial step towards designing effective HCC surveillance programs (257).

Figure 6.2. Multistate model for the evaluation of the natural history of compensated advanced chronic liver disease.



Cost effectiveness analysis

EHR data has the potential to improve the cost effectiveness of liver disease management, by capturing long-term clinical outcomes in a contemporary population. Analogous approaches are already in place for cardiovascular disease, where bespoke data platforms have been used to map cardiovascular epidemiology and prognostic modelling. These models can be used to estimate lifetime healthcare costs, with which evidence-based decisions regarding funding and commissioning can be made (258). Despite the potential, the value of this method in liver disease is yet to be fully realised.

A sophisticated model based on contemporary diagnostics, which incorporates additional information on disease aetiology and liver function would provide a framework for improved cost-effectiveness analyses of existing and new

technologies, with patients stratified by baseline risk. This approach is particularly relevant to the NHS, where the cost of care for alcohol misuse and obesity alone is estimated at £9 billion per year (67).

The NICE guidelines recommend screening of all at-risk individuals for NAFLD (8), yet there is no valid cost-effectiveness analysis of this approach. Harnessing long-term EHR data offers the opportunity to improve understanding treatment benefits and to target screening for conditions such as NAFLD. This is crucial in the delivery of hepatology services with limited resources.

Quality improvement

The PHE Atlas of variation has highlighted the significant disparities in mortality from liver disease across different regions of England (63), which can be partially attributed to the inconsistent delivery of specialised care. In an effort to address this disparity, the RCP has endorsed the Improvement in Quality Liver Services (IQILS) programme, which aims to implement care quality standards through training and self-evaluation (259).

A national registry can play a crucial role in measuring the impact of these service improvements by working collaboratively with IQILS to provide objective feedback to participating centres. By collating data on adherence to surveillance guidelines, a bespoke web-based tool can identify potential areas that require development, which will drive improvements in the quality of care. This approach will help to ensure that all patients receive the same high-quality care regardless

of their geographical location, ultimately leading to a reduction in mortality rates from liver disease across the country.

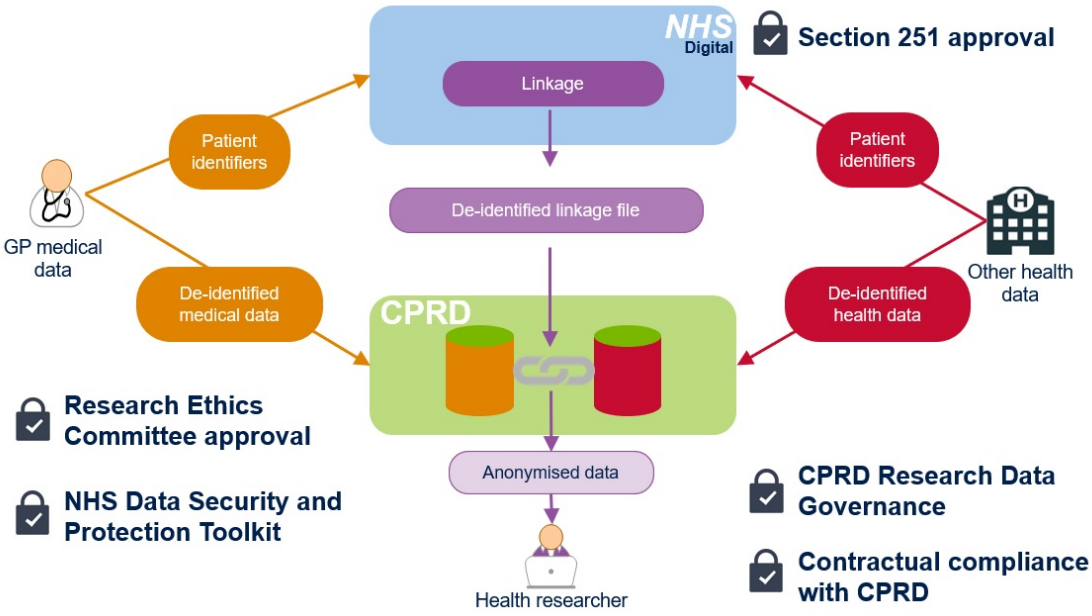
6.3 Practical considerations

Data linkage

To capture patients with early-stage disease, who are the target population for screening and surveillance strategies, it is preferrable to have linked data between primary and secondary healthcare providers. CPRD (**Page 52**) is a valuable resource that can facilitate this linkage, and previous studies have successfully utilised its' rich source of data to analyse trends and epidemiological impact of liver disease (123, 260). **Figure 6.3** (160) provides an illustration of the intricate process involved in linking CPRD data to research studies.

An alternative approach is to link primary care data can be linked via the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC). The RCGP RSC regularly extracts pseudo anonymised coded data from more than 1700 general practices in England (261). In 2017, the British Liver Trust (BLT) and RCGP Liver Priority Project published a set of recommended read codes, which have been validated for use in primary care electronic systems. These codes and the RCGP RSC database were utilised in the Lancet Commission reports (64), highlighting the strength of linked data to observe modifiable risk factors for liver disease, which are routinely recorded in primary care, such as body mass index and alcohol consumption.

Figure 6.3. Depiction of process and approvals required for retrieval of data via the CPRD (160)



Registry funding

Collaborating with either CPRD or RCGP RSC requires funding, which need to be considered in the development of a registry that exploits data from both primary and secondary care. This includes the costs associated with maintaining secure data platforms and supporting ongoing data input over extended periods of time. The Liver Priority Project recommended reviewing data and developing pathways for case finding, assessment, follow up and referral to optimise management of liver disease (262). A comprehensive linked registry that can evaluate and improve the delivery of care could address these unmet needs, providing robust justification for funding support.

In the first instance, grant funding can be considered whilst a registry is established. Research grants, such as the EASL Registry grant (263) and the Health Data Research grant (101) or a National Institute for Health Research

funded programme (264), industry collaborators or charitable bursaries such as Guts UK/Dr Falk and British Society of Gastroenterology research awards (265), could be potential funding sources. Once the value of the registry has been recognised, a fee for service can be requested from participating NHS Trusts.

Consent

Using EHR data for research raises concerns about patient consent. Whilst consent is not typically required to store routine clinical information in EHRs, using identifiable data for secondary purposes, including research and submission to registries, requires either obtaining informed consent from patients or obtaining specific legal exemption from the Confidentiality Advisory Group (CAG) under section 251 of the NHS Act 2006 (266).

For the CAG to grant approval, they must be satisfied that there is no practicable alternative option available. This implies that consent cannot be feasibly obtained by any other means and that both patient groups and the public find it acceptable for the potential benefits of data collection to outweigh the breach in confidentiality (151). An example is the National Cancer Registration and Analysis Service (NCRAS), which registers all diagnoses of cancer in England. The CAG has granted NCRAS permission under section 251 to collect confidential information about cancer patients without the need to seek consent (267).

There are strong arguments in favour of seeking section 251 exemption for a cirrhosis registry. Firstly, one of the primary purposes of the database is for audit

and service evaluation, to monitor performance between different centres and to drive improvements in the overall clinical care for patients with liver disease. Whilst this data may form a resource for research and identification of patients suitable for entry into clinical trials this is not its principal purpose.

Secondly, most of the analysis carried out on information provided by the database can be done without patient identifiable data, with only anonymised data leaving secure NHS Trust computers. The issue is understandably more contentious when patient identifiable data such as NHS numbers is required for data linkage.

Thirdly, with the increasing emphasis on community services and outreach clinics for diagnosing and monitoring liver disease, fewer patients will be attending specialist clinics in secondary care, making it challenging to obtain consent from all individuals non-invasively diagnosed with advanced fibrosis.

It should be noted that obtaining a section 251 exemption requires substantial patient and public involvement strategies, which have been identified as one of the most critical factors in successful applications (268). This process may be lengthy and challenging, but it is crucial to take the necessary steps to ensure the ethical and responsible use of patient data.

One example of the process for obtaining permission to use patient data for a registry is when the British Society of Gastroenterology applied to the CAG for permission to form a national Inflammatory Bowel Disease (IBD) registry in 2013. Despite concerns that obtaining consent should be practicable given regular clinician reviews, a 3-year period of exemption from patient consent was granted under section 251. During this time, the usefulness of data collection and linkage

was demonstrated, and efforts were made to seek written consent from patients (269). Like the IBD registry, it is likely that the CAG will consider an exemption for a national liver disease registry, given the regular bi-annual reviews of patients with cirrhosis. Ultimately, gaining patient consent may be required and worthwhile in the long-term to ensure that data obtained from a registry can be utilised in the most effective way possible to improve outcomes.

Minimum dataset

The data presented in this study highlights the potential of EHR data in observing outcomes in patients with liver disease. However, it is important to acknowledge that there were several limitations due to the lack of patient-level information. While many essential data fields are collected by EHR as part of routine clinical care, in-depth and standardised analysis of patients entering a registry requires the prospective collection of clinical information at cohort registration which cannot be derived directly from the EHR.

Since there is no existing registry for cirrhosis, creating the minimum dataset (MDS) is a crucial step prior to collection, processing, and analysis. This will address the shortfalls in real-world coded data identified by this study and ensure that the registry provides a comprehensive and reliable source of information for evaluating and improving the management of liver disease.

The study showed that the most challenging data field to determine using coded data was the aetiology of liver disease. Although the hierarchical system used in this study had good performance characteristics, it was mainly reliant on the

patient being admitted to the hospital to generate codes. The approach was less effective in those patients with overlapping aetiologies, such as viral hepatitis and alcohol as a co-factor, or ArLD and NAFLD. Therefore, inputting aetiology data at baseline will be essential to enable accurate comparison of clinical outcomes by disease group.

Although demographic details were largely available for patients in this study, there was often missing biochemical data, which limited the opportunity to calculate non-invasive risk scores. Therefore, to create a comprehensive minimum dataset (MDS), it will be necessary to prospectively collect essential clinical information, including baseline demographics, and biochemical data at the time of cohort registration.

Table 6.1 and **Table 6.2** provide a comprehensive guide for the initial Minimum Dataset (MDS) required to establish a registry for patients with liver disease. The essential data fields listed in **Table 6.1** are necessary for the registry's function, while the desirable data fields in **Table 6.2** would enhance the database's clinical utility.

Table 6.1. Recommended minimum dataset of essential data fields for entry into registry.[41]

Minimum Dataset Form		
Essential variables (at cohort registration)		
Item	**Response**	**Comment**
Personal identification	NHS number	Allow data linkage to primary care record and pseudo anonymisation
Pseudonymised unique identifier	-	-
Age at entry	Years	Age important risk factor for progression of liver disease and is a non-sensitive data field (as opposed to date of birth)
Date of entry into registry	dd/mm/yyyy	Registry entry point
Sex	Male/Female	Allow analysis of demographic distribution of liver disease
Transient elastography score	Liver stiffness measured in kPa	Non-invasive confirmation of advanced chronic liver disease
Transient elastography date	dd/mm/yyyy	-
Disease aetiology	Viral (Hepatitis B/C) Autoimmune Metabolic Alcohol NAFLD Other (specify) Unknown	Second aetiology to be recorded if appropriate
Baseline biochemistry	Albumin (g/l) Bilirubin (µmol/L) Platelets (x10^3/µl) INR AST (iu/L) ALT (iu/L) Sodium (mmol/L)	For calculation of non-invasive risk stratification scores including FIB4 and ALBI score, Baveno stage and UKELD

[41] NAFLD; non-alcoholic fatty liver disease, INR; international normalised ratio, AST; aspartate transaminase, ALT; alanine transaminase

Table 6.2. Recommended minimum dataset of desirable data fields for entry into registry.[42]

Minimum Dataset Form		
Desirable variables (at cohort registration)		
Item	**Response**	**Comment**
Ethnicity	Categorised according to PHE definitions	Important when considering inequality and deprivation quintiles
Postcode	Partial postcode	To assess geographical variation in service provision of liver disease
Weight at registration	Kilograms (measured at entry)	To allow calculation of body mass index at baseline
Height	Centimetres	As above
Alcohol consumption	Units/week	To analyse trends and impact of alcohol on disease progression
Relevant comorbidities	Type 2 diabetes Metabolic syndrome Cardiovascular disease Non-hepatic malignancy	To determine impact of non-liver morbidity on outcomes and disease progression
Relevant disease modifying treatments	Treatment for viral hepatitis which may impact upon	To account for impact of disease modifying treatment on disease progression
Transient elastography quality indices	IQR <30% Success rate >60%	Quality control of non-invasive diagnosis of ACLD
Relevant biochemistry	Hba1c Lipid profile	For assessment of extra-hepatic morbidity
Medications	Name, indication, dosage	

[42] PHE; Public Health England, IQR; Interquartile range, ACLD; advanced chronic liver disease

6.4 Future work

This research highlights the value of utilising electronic health record data in contemporary research practice in cirrhosis, reinforcing its potential for future use in developing a cirrhosis registry. The proposed consensus code set will be used to facilitate international collaboration and comparisons using route electronic data.

Liver stiffness, together with liver biochemistry measures taken at baseline, are critical predictors of outcomes in advanced chronic liver disease. This can be used to inform stratification for follow-up in patients with advanced chronic liver disease. Future efforts will aim to integrate this measure into routine clinical practice.

Prospective work can use routinely available EHR data to facilitate large-scale quality improved studies focussed on improving the delivery of hepatoma surveillance and refining the target patient population for surveillance.

Appendix

Table 1. ICD-10 Chapters and definitions (90).

Chapter	Category	Description
I	A00–B99	Certain infectious and parasitic diseases
II	C00–D48	Neoplasms
III	D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	E00–E90	Endocrine, nutritional, and metabolic diseases
V	F00–F99	Mental and behavioural disorders
VI	G00–G99	Diseases of the nervous system
VII	H00–H59	Diseases of the eye and adnexa
VIII	H60–H95	Diseases of the ear and mastoid process
IX	I00–I99	Diseases of the circulatory system
X	J00–J99	Diseases of the respiratory system
XI	K00–K93	Diseases of the digestive system
XII	L00–L99	Diseases of the skin and subcutaneous tissue
XIII	M00–M99	Diseases of the musculoskeletal system and connective tissue
XIV	N00–N99	Diseases of the genitourinary system
XV	O00–O99	Pregnancy, childbirth, and the puerperium
XVI	P00–P96	Certain conditions originating in the perinatal period
XVII	Q00–Q99	Congenital malformations, deformations, and chromosomal abnormalities
XVIII	R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified
XIX	S00–T98	Injury, poisoning and certain other consequences of external causes
XX	V01–Y98	External causes of morbidity and mortality
XXI	Z00–Z99	Factors influencing health status and contact with health services
XXII	U00–U99	Codes for special purposes

Table 2. OPCS-4 Chapters and definitions (95).

Chapter	Category	Description
A	A01-A84	Nervous system
B	B01-B41	Endocrine system and breast
C	C01-C90	Eye
D	D01-D28	Ear
E	E01-E98	Respiratory tract
G	G01-G82	Upper digestive tract
H	H01-H70	Lower digestive tract
J	J01-J77	Other abdominal organs-principally digestive
K	K01-K78	Heart
L	L01-L99 O01-O05 O15, O20	Arteries and veins
M	M01-M86	Urinary
N	N01-N35	Male genital organs
P	P01-P32	Lower female genital tract
Q	Q01-Q56	Upper female genital tract
R	R01-R43	Female genital tract associated with pregnancy, childbirth & puerperium
S	S01S70	Skin
T	T01-T97	Soft tissue
U	U01U54	Diagnostic imaging, testing and rehabilitation
V	V01-V68	Bones and joints of skull and spine
W	W01-W99, O06-O10, O17-O19, O21-O27, O29, O32	Other bones and joints
X	X01-X98	Miscellaneous operations
Y	Y01-Y99	Subsidiary classification of methods of operation
Z	Z01-Z99, O11-O14, O16, O28, O30-31, O33	Subsidiary classification of sites of operation

PROSPERO SYSTEMATIC REVIEW PROTOCOL

Validity of diagnostic coding in liver disease: a systemic review

Background and rationale

Liver disease is one of the leading causes of death in the United Kingdom (UK) and is recognised as a growing public health and economic burden worldwide. Over the past decade there have been many epidemiological studies relating to cirrhosis which use administrative databases and electronic health records. Electronic health records (EHR) collate longitudinal patient data generated throughout the course of routine clinical care. The majority of these databases rely upon the International Classification of Diseases codes, which assigns a primary diagnosis code and multiple secondary codes for each hospital admission or encounter. An admission may also contain details regarding procedures and investigations, which are coded using the Office of Population, Censuses and Surveys Classification of Interventions and Procedures (OPCS) classification codes.

Information stored within electronic health records has the potential to provide comprehensive data on large cohorts of patients with liver disease over a long duration of follow-up. As coded information is subject to inaccuracies and incompleteness, users must validate their findings against a pre-defined criterion. There are a number of codes relating to liver disease and its' complications which may be used alone or in combination to define the presence of cirrhosis. There have been several studies which evaluate the validity of diagnostic codes in identifying patients with cirrhosis, underlying aetiology, and decompensation. The aim of this systematic review is to evaluate the accuracy of diagnostic coding of cirrhosis in observational cohort studies using electronic health record databases. The review aims to compare and validate definitions of cirrhosis based upon sets of ICD-9 and ICD-10 codes across studies and countries.

Methods

Study design

Systematic review of the peer reviewed literature and conference abstracts.

Types of studies

Observational cohort studies assessing the validity of diagnostic and procedural codes to identify cirrhosis in adult patients.

Types of patients

Patients aged >18 years with information regarding in-patient hospital admissions stored in an electronic database captured as part of routine clinical care.

Types of interventions

Observational studies reporting the validity of diagnostic and procedural codes pertaining to cirrhosis only will be included in the review.

Types of outcome measures

The primary outcome measure will be the proportion of patients accurately identified as having cirrhosis when compared to the full medical record. This will include, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) reported for each of the ICD codes or combination of codes for a diagnosis of cirrhosis. A secondary outcome measure will be to determine the proportion of patients in whom the underlying liver disease aetiology can be correctly identified.

A secondary outcome measure will be to determine the proportion of patients in whom the occurrence of decompensation can be accurately identified.

Data sources

MedLine and EmBase Libraries

Search strategy

This will include the following terms: health services research or administrative data or hospital discharge data or ICD-9 or ICD-10 or ICD9 or ICD10 or ICD-9-CM or ICD-10- CM or international classification of diseases or medical record or health information or surveillance or physician claims or claims or hospital discharge or coding or codes or clinical coding or medical coding or diagnostic coding AND validity or validation or case definition or algorithm or agreement or accuracy or sensitivity or specificity or positive predictive value or negative predictive value or validity of results or reliability or reference values or reference range AND cirrhosis or hepatic cirrhosis or liver cirrhosis.

The search will be limited to articles published in English and human studies.

Selection of primary articles and conference abstracts

Studies will be evaluated for eligibility in a two-stage procedure. In the first stage all identified titles and abstracts will be reviewed. In the second stage a full text review will be performed on all studies which met the following eligibility criteria.

Inclusion/exclusion criteria

1. Study population including those >18 years of age.
2. Statistical estimates (sensitivity, specificity, positive predictive value, negative

   predictive) value will be reported or could be calculated from the available data.
3. An ICD-9 or ICD-10 code or combination of codes for cirrhosis which has been

   defined and validated.
4. A satisfactory validation standard e.g., full medical record review.

5. Studies using laboratory data to identify and define those patients with cirrhosis

will be excluded, as this data is not routinely available through EHR data alone.

6. Where conference abstracts and full manuscripts of the same trial are identified, data will be extracted from the full manuscript.

Reference lists of those studies included will be reviewed and subsequent studies included if they meet the above criteria but were not identified using the search strategy.

Data extraction and analysis

Data will be extracted and tabulated onto a standardised template. This will include the following information: study identifier and year of publication, site, start date and duration, sample size, ICD codes used. If statistical estimates were not reported in the original paper, estimates will be calculated from the available data.

Dissemination

The results of this systematic review will be shared with the scientific community at national and international liver meetings and will be submitted for publication in open access peer reviewed journals.

Figure 1. Search strategy for systematic review

# ▲	Searches	Results	Type	Actions	Annotations
1	exp Health Services Research/	198500	Advanced	Display Results | More	
2	administrative data.mp.	20070	Advanced	Display Results | More	
3	hospital discharge data.mp.	4115	Advanced	Display Results | More	
4	icd9.mp.	3797	Advanced	Display Results | More	
5	icd10.mp.	2151	Advanced	Display Results | More	
6	icd-9.mp.	43629	Advanced	Display Results | More	
7	icd-10.mp.	37067	Advanced	Display Results | More	
8	icd-9-CM.mp.	14751	Advanced	Display Results | More	
9	icd-10-CM.mp.	1405	Advanced	Display Results | More	
10	"International Classification of Diseases"/	20881	Advanced	Display Results | More	
11	medical record*.mp.	585896	Advanced	Display Results | More	
12	health information.mp.	57357	Advanced	Display Results | More	
13	surveillance.mp.	509642	Advanced	Display Results | More	
14	physician claims.mp.	768	Advanced	Display Results | More	
15	claims.mp.	123775	Advanced	Display Results | More	
16	hospital discharge.mp.	159460	Advanced	Display Results | More	
17	coding.mp.	447751	Advanced	Display Results | More	
18	codes.mp.	132489	Advanced	Display Results | More	
19	clinical coding.mp.	2906	Advanced	Display Results | More	
20	medical coding.mp.	252	Advanced	Display Results | More	
21	diagnostic coding.mp.	826	Advanced	Display Results | More	
22	(validity or validation or case definition or algorithm or agreement or accuracy or sensitivity or specificity or positive predictive value or negative predictive value or validity of results or reliability or reference values or reference range).af.	6273669	Advanced	Display Results | More	
23	cirrhosis.mp.	331419	Advanced	Display Results | More	
24	hepatic cirrhosis.mp.	9921	Advanced	Display Results | More	
25	exp Liver Cirrhosis/	264263	Advanced	Display Results | More	
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2142730	Advanced	Display Results | More	
27	22 and 26	268692	Advanced	Display Results | More	
28	23 or 24 or 25	331419	Advanced	Display Results | More	
29	27 and 28	2239	Advanced	Display Results | More	
30	limit 29 to english language	2184	Advanced	Display Results | More	
31	limit 30 to humans	1975	Advanced	Display Results | More	
32	remove duplicates from 31	1626	Advanced	Display Results | More	

Figure 2. QUADAS Tool.

Table extracted directly from Whiting, P., et al., The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol, 2003. 3: p. 25.

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

Table 3. ICD-9 codes used to identify liver disease.

When appropriate listed as code category to indicate that all sub-codes were used by that author.

Code	Number of sub-codes	Description	Number of authors using code
155	3	Malignant neoplasm of digestive organs and peritoneum	1
155.0		Hepatocellular carcinoma	2
V42.7		Liver- Organ or tissue replacement	2
070.2		Viral hepatitis B with hepatic coma	1
070.21		Acute hepatitis B with delta with hepatic coma	1
070.22		Chronic viral hepatitis without delta	1
070.23		Chronic viral hepatitis B with delta	1
070.3		Acute hepatitis B without delta without hepatic coma	1
070.31		Acute hepatitis B with delta without coma	1
070.41		Acute hepatitis C with hepatic coma	1
070.42		Acute delta (super) infection of hepatitis B carrier	1
070.44		Chronic viral hepatitis C	1
070.49		Other unspecified acute viral hepatitis	1
070.51		Acute hepatitis C without hepatic coma	1
070.54		Chronic viral hepatitis C	1
070.59		Other acute or chronic hepatitis	1
070.6		Unspecified viral hepatitis with hepatic coma	1
070.7		Unspecified viral hepatitis C without hepatic coma	1
070.71		Unspecified viral hepatitis C with hepatic coma	1
070.90		Unspecified viral hepatitis without hepatic coma	1
273.4		Alpha-1-Antitrypsin deficiency	1
275.1		Wilson's disease	1
453.0		Budd Chiari syndrome	1
456.0		Oesophageal varices with bleeding	8
456.1		Oesophageal varices without mention of bleeding	7
456.2	2	Oesophageal varices in diseases classified elsewhere	7
530.7		Mallory-Weiss syndrome	1
530.82		Oesophageal haemorrhage (excluding variceal)	1
567.0		Disorder of peritoneum in infectious diseases	1
567.21		Generalised acute peritonitis	1
567.23		Spontaneous bacterial peritonitis	3
567.89		Other peritonitis	1

571.0		Alcoholic fatty liver	2
571.10		Alcoholic hepatitis without ascites	1
571.2		Alcoholic cirrhosis of the liver	10
571.3		Alcoholic liver damage, unspecified	1
571.4	4	Chronic hepatitis (excludes viral)	2
571.40		Chronic hepatitis, unspecified	1
571.41		Chronic persistent hepatitis, not otherwise specified	1
571.42		Autoimmune hepatitis	1
571.5		Cirrhosis of liver without mention of alcohol	11
571.6		Biliary cirrhosis	6
571.8		Other chronic non-alcoholic liver disease	1
572.2		Hepatic coma	8
572.3		Portal hypertension	7
572.4		Hepatorenal syndrome	7
572.8		Other sequelae of chronic liver disease	3
573.0		Chronic passive congestion of the liver	1
573.1		Liver disorders in diseases classified elsewhere	1
573.9		Liver disease, unspecified	1
576.1		Cholangitis	1
578.0		Haematemesis	1
578.1		Melaena	1
578.9		Haemorrhage of GI tract	1
782.4		Jaundice, unspecified	1
789.5		Ascites	6
789.59		Non-malignant ascites	3
996.82		Liver-complications of transplanted organs	1

Table 4. ICD-10 codes used to identify liver disease.

* Denotes ICD-O3 (Oncology classification)

Code	Number of subcodes	Description	Number of authors using code
B15.0		Hepatitis A with hepatic coma	2
B16.0		Acute hepatitis B with delta-agent with hepatic coma	2
B16.2		Acute hepatitis B without delta-agent with hepatic coma	2
B17.1		Acute hepatitis C with hepatic coma	1
B19	2	Unspecified viral hepatitis with hepatic coma	2
C22.0/81703*		Liver cell carcinoma	3
C22.1/81803*		Intrahepatic bile duct carcinoma	1
C22.2		Hepatoblastoma	1
C22.7		Other specified carcinomas of the liver	1
C22.8		Malignant neoplasm of liver, primary, unspecified	2
C22.9		Liver neoplasm, unspecified	3
I85	2	Oesophageal varices	6
I85.9		Oesophageal varices without bleeding	2
I86.4		Gastric varices	4
I98.2		Oesophageal varices without bleeding elsewhere	2
I98.3		Oesophageal varices with bleeding elsewhere	2
K22.6		Mallory Weiss Syndrome	1
K22.8		Other unspecified diseases of oesophagus	1
K65.2		Spontaneous bacterial peritonitis	1
K70.1		Alcoholic hepatitis	2
K70.2		Alcoholic fibrosis and sclerosis of liver	1
K70.3		Alcoholic cirrhosis of liver	6
K70.4		Alcoholic hepatic failure	4
K70.9		Alcoholic liver disease, unspecified	1
K71.7		Toxic liver disease with fibrosis and cirrhosis of liver	3
K72	3	Hepatic failure, not elsewhere classified	1
K72.1		Chronic hepatic failure	5
K72.9		Hepatic failure, unspecified with coma	4
K74	7	Fibrosis and cirrhosis of liver	1
K74.3		Primary biliary cirrhosis	1
K74.4		Secondary biliary cirrhosis	3

K74.5		Biliary cirrhosis, unspecified	3
K74.6		Other and unspecified cirrhosis of liver	5
K76.6		Portal hypertension	6
K76.7		Hepatorenal syndrome	2
K92.0		Haematemesis	2
K92.1		Melaena	2
K92.2		Gastric haemorrhage, unspecified	2
R17		Unspecified jaundice	1
R18.0		Ascites	2
R18.8		Other ascites	2
T86.40		Unspecified complication of liver transplant	2
T86.41		Liver transplant rejection	2
T86.42		Liver transplant failure	1

Table 5. OPCS and CCP codes used to identify liver disease.

Some of the included codes are specific to a national extension of the ICD coding dictionary. These codes are included separately.

Code	Description	Number of authors using code
J06.1	Trans jugular intrahepatic insertion of stent into portal vein	2
J06.2	Trans jugular intrahepatic insertion of stent graft into portal vein	2
T46.1	Paracentesis abdominis for ascites	2
T46.2	Drainage of ascites NEC	2
G10.4	Local ligation of varices of oesophagus	2
G10.8	Other specified open operation on varices of oesophagus	1
G10.9	Unspecified open operations on varices of oesophagus	2
G14.4	Fibre-optic endoscopic injection sclerotherapy to varices of oesophagus	2
G17.4	Endoscopic injection sclerotherapy to varices of oesophagus using rigid oesophagoscope	2
G43.4	Fibreoptic endoscopic sclerotherapy to lesion of upper gastrointestinal tract	1
G43.7	Fibre-optic endoscopic rubber band ligation of upper gastrointestinal tract varices	1
Z76804	Liver transplant candidate	1
Z944	Liver transplant status	1
62.40/62.41/62.49	Transplant procedural code	1
66.91	Liver dysfunction procedural code	1
10.06	Insertion of Sengstaken tube	1

Table 6. CPT codes used to identify liver disease.

Some of the included codes are specific to a national extension of the ICD coding dictionary. These codes are included separately.

Code	Description
47135/47136	Liver transplantation procedures
0FY00Z0	Allogenic Transplantation of Liver
0FY00Z1	Syngeneic Transplantation of Liver
0FY00Z2	Zooplastic Transplantation of Liver
37140/37160/37180/37181/37182/37183	Portal decompression procedure
43204/43205	Endoscopy
43243/43244	Oesophagogastroduodenoscopy
43400/43401	Repair procedure of oesophagus
42.91	Ligation of oesophageal varices
44.91	Ligation of gastric varices
96.06	Insertion of Sengstaken tube
06L30CZ	Occlusion of oesophageal vein with extra-luminal device
06L30DZ	Occlusion of oesophageal vein with intra-luminal device
06L30ZZ	Occlusion of oesophageal vein, open approach
06L33CZ	Occlusion of oesophageal vein with extra-luminal device, percutaneous approach
06L33DZ	Occlusion of oesophageal vein with intra-luminal device, percutaneous approach
06L33ZZ	Occlusion of oesophageal vein, percutaneous approach
06L34CZ	Occlusion of oesophageal vein with extra-luminal device, percutaneous endoscopic approach
06L34ZZ	Occlusion of oesophageal vein, percutaneous endoscopic approach
06L20ZZ	Occlusion of gastric vein, open approach
06L23ZZ	Occlusion of gastric vein, percutaneous approach
06L24ZZ	Occlusion of gastric vein, percutaneous endoscopic approach
0DL57DZ	Occlusion of oesophagus with intra-luminal device via natural or artificial opening
0DL58DZ	Occlusion of oesophagus with intra-luminal device via natural or artificial opening, endoscopic
49080/49081	Abdominal paracentesis
54.91	Percutaneous abdominal drainage
0D9S30Z/0D9S3ZZ	Drainage of greater omentum, percutaneous approach
0D9S4ZZ	Drainage of greater omentum, percutaneous endoscopic approach

0D9T30Z/0D9T3ZZ	Drainage of lesser omentum, percutaneous approach
0D9T40Z/0D9T4ZZ	Drainage of lesser omentum, percutaneous endoscopic approach
0D9V3ZZ	Drainage of mesentery, percutaneous approach
0D9V40Z/0D9V4ZZ	Drainage of mesentery, percutaneous endoscopic approach
0D9W30Z/OD9W3ZZ	Drainage of peritoneum, percutaneous approach
0D9W40Z/0D9W4ZZ	Drainage of peritoneum, percutaneous endoscopic approach
0W9F30Z/0W9F3ZZ	Drainage of abdominal wall, percutaneous approach
0W9F40Z/0W9F4ZZZ	Drainage of abdominal wall, percutaneous endoscopic approach
0W9G30Z/0W9G3ZZ	Drainage of peritoneal cavity, percutaneous approach
0W9G40Z/0W9G4ZZ	Drainage of peritoneal cavity, percutaneous endoscopic approach
0W9J30Z/0W9J3ZZ	Drainage of pelvic cavity, percutaneous approach

Table 7. Diagnosis and procedure codes used to determine clinical events of interest.[43]

Diagnoses	ICD-10 Codes	OPCS codes
Aetiology		
Viral hepatitis	B18.0, B18.1, B18.2 B18.8, B18.9, B19.0, B19.9	---
Autoimmune	K74.3, K75.4, K83.0	---
Metabolic	E83.1, E83.0, E88.0	---
Alcohol	F10, G62.1, G31.2, G72.1, I42.6, K29.2, K70, K85.2, X45, Y15, T51.0, T51.1, T51.9, X65, R78.0	---
NAFLD	K76.0, K78.8, E11, E12, E13, E14	---
Clinical event		
Varices	I85.9, I86.4, I98.2	G10.4, G10.8, G10.9, G14.4, G17.4, G43.4, G43.7
Decompensation	R18, R17, K76.7, K65.2, I85.0, I98.3, K72.9 K92.0 K92.1, K92.2, K25-28	T46.1, T46.2, G10.4, G10.8, G10.9, G14.4, K06.1, J06.2, G17.4, G43.4, G43.7
Liver transplantation	---	J01
Hepatocellular carcinoma	C22	J02, J03, J10, J12
Cardiovascular event	I21, I22, I23, I24, I25, I50, I20, I72, I46, I63.9, I64	---
Non-hepatic malignancy	C0, C1, C20, C21, C23, C24, C25, C26, C3-C9, C25, C26	---
Kramer code set	K74.6, K70.3, K74.4, K74.5*	

[43] *Kramer code set converted from ICD-9 to ICD-10 equivalent. NAFLD; non-alcoholic fatty liver disease, ICD; international classification of diseases, Office of Population Censuses and Surveys

Algorithm to determine presence of codes within the consensus code set (Stata)

An application to submit this information in the Research Data Leeds Repository has been made and will be made available as an open access resource following publication of the thesis (application submitted June 2023).

```
//Identifying cirrhosis
//codes for consensus codeset //
drop if id==.
gen cirrhosis = strpos(aet, "K74.6")>0 | ///
                                strpos(aet, "K70.3")>0 | ///
                                strpos(aet, "I85.0")>0 | ///
                                strpos(aet, "I85.9")>0 | ///
                                strpos(aet, "I98.2")>0 | ///
                                strpos(aet, "I98.3")>0 | ///
                                strpos(aet, "K76.6")>0 | ///
                                strpos(aet, "K76.7")>0 | ///
                                strpos(aet, "K72.9")>0
```

Hierarchical algorithm to determine aetiology (Stata)

```
drop if id ==.

//1. Identifying different aetiology based on codes//
gen viral = strpos(aet, "B18.0")>0 | ///
                                strpos(aet, "B18.1")>0 | ///
                                strpos(aet, "B18.2")>0 | ///
                                strpos(aet, "B18.8")>0 | ///
                                strpos(aet, "B18.9")>0 | ///
                                strpos(aet, "B19.0")>0 | ///
                                strpos(aet, "B19.9")>0

gen autoimmune = strpos(aet, "K74.3")>0 | ///
                                        strpos(aet, "K75.4")>0 | ///
                                        strpos(aet, "K83.0")>0

gen metabolic = strpos(aet, "E83.1")>0 | ///
                                        strpos(aet, "E83.0")>0 | ///
                                        strpos(aet, "E88.0")>0

gen alcohol = strpos(aet, "F10")>0 | ///
                                        strpos(aet, "G62.1")>0 | ///
                                        strpos(aet, "G31.2")>0 | ///
                                        strpos(aet, "G72.1")>0 | ///
                                        strpos(aet, "I42.6")>0 | ///
                                        strpos(aet, "K29.2")>0 | ///
                                        strpos(aet, "K70")>0 | ///
                                        strpos(aet, "K85.2")>0 | ///
                                        strpos(aet, "X45")>0 | ///
                                        strpos(aet, "Y15")>0 | ///
                                        strpos(aet, "T51.0")>0 | ///
                                        strpos(aet, "T51.1")>0 | ///
                                        strpos(aet, "T51.9")>0 | ///
                                        strpos(aet, "X65")>0 | ///
```

```
                                        strpos(aet, "R78.0")>0

gen nafld = strpos(aet, "K76.0")>0 | ///
                                        strpos(aet, "K78.8")>0 | ///
                                        strpos(aet, "E11")>0 | ///
                                        strpos(aet, "E12")>0 | ///
                                        strpos(aet, "E13")>0 | ///
                                        strpos(aet, "E14")>0

//2. Creates hierarchical diagnosis system//
replace autoimmune = 2 if autoimmune==1
replace metabolic = 3 if metabolic==1
replace alcohol = 4 if alcohol==1
replace nafld= 5 if nafld==1


egen concatdiag = concat(viral metabolic autoimmune alcohol nafld)

replace concatdiag = subinstr(concatdiag, "0", "", .)

gen newdiagnosis=.

replace newdiagnosis = 1 if regexm(concatdiag, "1")
replace newdiagnosis = 2 if regexm(concatdiag, "^2")
replace newdiagnosis = 3 if regexm(concatdiag, "^3")
replace newdiagnosis = 4 if regexm(concatdiag, "^4")
replace newdiagnosis = 5 if regexm(concatdiag, "^5")
```

Table 8. Diagnosis and procedure codes used to define Baveno stages.

Algorithm designed in step wise approach from Baveno 2-4. If none of the above codes occurred, it was assumed that the patient was Baveno stage 1.

Baveno Stage	ICD-10 Codes	OPCS codes
2	I85.9, I86.4, I98.2	G10.4, G10.8, G10.9, G14.4, J06.1, J06.2, G17.4, G43.4, G43.7
3	R17, R18, K76.7, K65.2	T46.1, T46.2
4	I85.0, I98.3, K92.0, K92.1, K92.2	G10.4, G10.8, G10.9, G14.4, J06.1, J06.2, G17.4, G43.4, G43.7
1	If none of the above codes are present	

Algorithm to determine Baveno staging/disease severity (Stata)

An application to submit this information in the Research Data Leeds Repository has been made and will be made available as an open access resource following publication of the thesis (application submitted June 2023).

```
//1. Removes those patients who did not have any admissions after TE//
//intervaldays refers to the number of days between the TE and an admission//
sort id
drop if intervaldays=="NULL"
destring intervaldays, generate(int_days1)
drop intervaldays

//2. Identifies events occurring before and after TE//
gen event=.
replace event=0 if int_days1 <0
replace event=1 if int_days1 >=0
gen decomp_pre=.
replace decomp_pre=1 if event==0 & decomp==1
replace decomp_pre=0 if event==1 & decomp==1
by id: egen decomppre_n=max(decomp_pre)
drop if decomppre_n==1

//3. Remove patients with decompensation prior to TE//
gen decomp = strpos(episodediagnosis, "I85.0")>0 | ///
                                strpos(episodediagnosis, "I98.3")>0 | ///
                                strpos(episodediagnosis, "R18.X")>0 | ///
                                strpos(episodediagnosis, "T46.2")>0 | ///
                                strpos(episodediagnosis, "K72.9")>0


//4. Combine codes occurring in the same episode (defined by intervaldays)
to form new variable epicode//

gen epicode = code[_n]
forvalues j =1/20  {
replace epicode = epicode + code[_n+`j'] if (intervaldays[_n]== ///
intervaldays[_n+`j']& id[_n]==id[_n+`j'])
}

//5. remove the duplicate codes in the same episode //

drop if (intervaldays[_n]==intervaldays[_n-1] & id[_n]==id[_n-1])

keep id  fibroscan_score sex daystodeath dateofdeath ///
                        intervaldays epi_date epicode fibroscandate ///
                        end_date max_days end_date age_te

//6. New baveno code (bav). It does not include ascites/ paracentesis on its own
Baveno =1 if patient is cirrhotic and there are no other codes that suggest decompensation //

gen baveno=.

/* baveno = 2 if non-bleeding varices, or treatment for varices, or portal
hypertension */
replace bav = 2 if (strmatch(epicode,"*I85.9*") | ///
                        strmatch(epicode,"*G10.4*")| strmatch(epicode,"*G10.8*")| ///
                        strmatch(epicode,"*G10.9*")| strmatch(epicode,"*G14.4*")| ///
                        strmatch(epicode,"*I85.9*")| strmatch(epicode,"*I86.4*")| ///
```

```
                    strmatch(epicode,"*I98.2*")| ///
                    strmatch(epicode,"*J06.1*")| strmatch(epicode,"*J06.2*")| ///
                    strmatch(epicode,"*G17.4*")| strmatch(epicode,"*G43.4*")| ///
                    strmatch(epicode,"*G43.7*"))

/* baveno = 3 if ascites or paracentesis */
replace bav = 3 if (strmatch(epicode,"*R18.X*") | strmatch(epicode,"*R17*") | ///
          strmatch(epicode,"*T46.1*")| strmatch(epicode,"*T46.2*") | ///
        strmatch(epicode,"*K76.7*") | strmatch(epicode,"*K65.2*"))

/* baveno = 4 if bleeding varices, or UGI bleed PLUS treatment for varices
of UGI bleed PLUS varices  or UGI bleed PLUS portal hypertension*/
replace bav = 4 if (strmatch(epicode,"*I85.0*") | ///
          strmatch(epicode,"*I98.3*")| ///
          ((strmatch(epicode,"*K92.0*")| strmatch(epicode,"*K92.1*")| ///
                  strmatch(epicode,"*K92.2*")) & ///
                 (strmatch(epicode,"*G10.4*")| strmatch(epicode,"*G10.8*")| ///
                  strmatch(epicode,"*G10.9*")| strmatch(epicode,"*G14.4*")| ///
                  strmatch(epicode,"*J06.1*")| strmatch(epicode,"*J06.2*")| ///
                  strmatch(epicode,"*G17.4*")| strmatch(epicode,"*G43.4*")| ///
                  strmatch(epicode,"*G43.7*"))))

replace bav = 4 if (strmatch(epicode,"*K25.*")| strmatch(epicode,"*K26.*")| ///
                  strmatch(epicode,"*K27.*")| strmatch(epicode,"*K28.*")| ///
                 strmatch(epicode,"*K72.9"))


//7. Identifies first event to occur during follow-up//
sort id
by id: gen long obsno = _n
by id : gen countnonmissing = sum(!missing(bav_non)) if !missing(bav_non)
bysort id (countnonmissing) : gen firstnonmissing = bav_non[1]
rename firstnonmissing first_event
drop obsno countnonmissing
replace first_event=0 if first_event==.

/* identify the start time of follow-up  */

gen starttime = fibro_date

/* identify time to any event - total follow-up */
rename maxdate intervaldays
generate transtime = intervaldays if first_event[_n]>first_event[_n-1] & ///
id[_n]==id[_n-1]
replace transtime = intervaldays if id[_n]!=id[_n-1]
replace transtime=. if first_event==0 & transtime>0
```

Algorithm used for competing risk analysis (Stata)

```
//status_new//
//0= no event//
//1= varices//
//2= non liver death
//3= non bleeding decomp//
//4= bleeding decomp//
//6= hcc//
//7= cvd//
//8= non hep malig//


        //**CI ANALYSIS*//


//CI of first event varices//
stset time, failure(status_new== 1) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==2 3 4 6 7 8)

//CI of first event bleeding varices//
stset time, failure(status_new== 3) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==2 1 4 6 7 8)

//CI of first event non bleeding decomp//
stset time, failure(status_new== 4) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==3 1 2 6 7 8)

//CI of first event hcc//
stset time, failure(status_new== 6) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==3 1 2 4 7 8)

//CI of first event cvd//
stset time, failure(status_new== 7) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==3 1 2 4 6 8)

//CI of first event non-hep//
stset time, failure(status_new== 8) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==3 1 2 4 6 7)

//CI of first event non-liver death//
stset time, failure(status_new== 2) id(id)
stcrreg ib4.age i.sex_n te_exact i.aet_n albi_score fib4, compete(status_new==3 1 9 4 6 7)


      //*CI GRAPHS*//

//CI of first event varices//
stset time2, failure(status_new== 1)
stcrreg te_score age_group sex_n aet_n albi_score, compete(status_new== 2 3 4 6 7 8)
stcurve, cif at0(te_score=0) at1(te_score=1) at2(te_score=2) ///
ytitle("CI of varices", size (small)) ///
xtitle("Follow-up (years)", size (small)) ///
xscale(range(0 12)) ///
xlabel(0(1)12)

//CI of first event bleeding varices//
stset time2, failure(status_new== 3)
stcrreg te_score age_group sex_n aet_n albi_score, compete(status_new== 2 1 4 6 7 8)
stcurve, cif at0(te_score=0) at1(te_score=1) at2(te_score=2) ///
ytitle("CI of bleeding varices", size (small)) ///
xtitle("Follow-up (years)", size (small)) ///
xscale(range(0 12)) ///
```

```
xlabel(0(1)12)

//CI of first event non bleeding decomp//
stset time2, failure(status_new== 4)
stcrreg te_score age_group sex_n aet_n albi_score, compete(status_new== 3 1 2 6 7 8)
stcurve, cif at0(te_score=0) at1(te_score=1) at2(te_score=2) ///
ytitle("CI of non-bleeding decompensation", size (small)) ///
xtitle("Follow-up (years)", size (small)) ///
xscale(range(0 12)) ///
xlabel(0(1)12)

//CI of first event hcc//
stset time2, failure(status_new== 6)
stcrreg te_score age_group sex_n aet_n albi_score, compete(status_new== 3 1 2 4 7 8)
stcurve, cif at0(te_score=0) at1(te_score=1) at2(te_score=2) ///
ytitle("CI of non-bleeding HCC", size (small)) ///
xtitle("Follow-up (years)", size (small)) ///
xscale(range(0 12)) ///
xlabel(0(1)12)
```

Table 9. Definition of most frequently occurring codes associated with admissions

ICD-10 code	Description
B18	Chronic viral hepatitis
C50	Malignant neoplasm of breast
C70	Malignant neoplasm of eye, brain, or other part of CNS
C22	Malignant neoplasm of liver and intrahepatic bile ducts
E10	Insulin-dependent diabetes mellitus
E11	Non-insulin-dependent diabetes mellitus
E83	Disorder of iron metabolism
E88	Alpha-1-antitrypsin deficiency
F10	Mental and behavioural disorders due to use of alcohol
I85	Oesophageal varices with/without bleeding
I98	Oesophageal varices without bleeding in diseases classified elsewhere
J44	Chronic obstructive pulmonary disease with acute lower respiratory tract infection
J45	Asthma
K70	Alcoholic fatty liver
K74	Fibrosis and cirrhosis of the liver
K75	Other specified inflammatory liver disease
K76	Other diseases of the liver
M06	Rheumatoid arthritis
R18	Ascites

Table 10. Codes used to define Charlson comorbidity index.[44]

Charlson comorbidity	ICD-10 Codes	Points contributing to CCI Score
Myocardial infarction	I21, I22, I25.2	1
Congestive cardiac failure	I09.9, I11.0, 013.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0	1
Peripheral vascular disease	I70, I71, I73.1, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	G45, G46, H34.0, I60-I69	1
Dementia	F00-F03, F05.1, G30, G31.1	1
COPD	I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3	1
Rheumatic/connective tissue	M05, M06, M31.5, M32, M33, M35.3, M36	1
Peptic ulcer disease	K25-K28	1
Uncomplicated diabetes	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1,E14.6, E14.8, E14.9	1
Complicated diabetes	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	2
Hemiplegia	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.1-G83.4, G83.9	2
Chronic kidney disease	I12.0, I13.1, N03.2-N03.7,N05.2, N05.3-N05.7, E12.2, N18, N19, N25.0, Z49.0-Z49.2, N94.0, Z99.2	2
Malignancy (excluding HCC)	C0, C1, C20, C21, C23-C26, C30-C34, C37-C40, C40, C50,C60, C70-C76, C81-C85, C88, C90	2
Metastatic cancer	C77, C78, C79, C80	6
AIDS/HIV	B20, B21, B22, B24	6

[44] COPD; Chronic obstructive pulmonary disease, AIDS; Acquired immunodeficiency disorder, HIV; Human Immunodeficiency Virus, HCC; hepatocellular carcinoma.

Algorithm used to determine if patient receiving ultrasound surveillance

An application to submit this information in the Research Data Leeds Repository has been made and will be made available as an open access resource following publication of the thesis (application submitted June 2023).

```
//1. Determine how many have had/not had uss during FU//
by id: egen surveillance=max(epi_type)

//2. Identify patients with at least 2y follow-up//
gen end_date = max_days/365
gen end_avg = round(end_date,0.5)
gen avg_2y = 1 if end_avg >=2

//3. Identify USS within 2 years of TE//
gen uss_2y = 1 if uss_days <=730

//4. At least 2y FU & at least 1 USS within 2y//
gen uss2y_endFU=1 if avg_2y==1 & uss_2y==1

//5. Identifies if gap between uss less than 4.5 months//
gen uss_4m = 1 if int_uss2 >4.5

//6. Identifies if gap between uss is greater than 1y//
gen uss_12m =1 if avg_uss <12

//7. Identifies patients with only one uss in 2y//
sort id ussdate_n
by id: gen seqno= _n
by id: egen max_seqno=max(seqno)

by id: egen median_uss = median(int_uss2)
gen avg_median = round(median_uss,0.5)


//8. Hierarchical timing of hcc//
//1= >2 USS annually for 2y >4.5 apart (2 screen) //
//2= 1 screen annually for 2y (1 screen per year for first 2y) //
//3= at least 1 screen within 2y period (inconsistent) //
//4= no surveillance within first 2y (no screen)//
//excludes anything beyond 2y following te//

//1//
gen uss_surv=.
replace uss_surv=1 if uss_4m==1 & uss_12==1 & max_seqno >1 & ///
                                              avg_median >=4 & avg_median < 8 & ///
                                              uss2y_endFU==1

by id: egen uss_surv_n= max(uss_surv)

//2//
replace uss_surv_n=2 if uss_surv_n==. & uss_4m==1 & uss_12==1 & max_seqno >1 & ///
                                          seqno >1 & avg_median2y >=8  & avg_median2y <=12
& ///
                                              uss2y_endFU==1

replace uss_surv_n=2 if uss_surv_n==. & surveillance==1 & uss2y_endFU==1 & ///
```

```
                                        avg_median2y <=12 & seqno <2 & avg_uss>4

by id: egen uss_surv_2= max(uss_surv_n)

//3//
replace uss_surv_2=3 if uss_surv_2==. & uss_4m==1 & uss_12==. & max_seqno >1 & ///
                                                    uss2y_endFU==1
replace uss_surv_2=3 if uss_surv_2==. & uss2y_endFU==1

by id: egen uss_surv_3= max(uss_surv_2)

//4//
replace uss_surv_3=4 if uss_surv_3==.
```

Table 11. Office of Population Censuses and Surveys codes and definitions used to define upper gastrointestinal endoscopy within 12 months of transient elastography.

Code	Definition
G10.4	Local ligation of varices of oesophagus
G10.8	Other specified open operations on varices of oesophagus
G10.9	Unspecified open operations on varices of oesophagus
G14.4	Fibreoptic endoscopic injection sclerotherapy to varices of oesophagus
G17.4	Endoscopic injection sclerotherapy to varices of oesophagus using rigid oesophagoscope
G43.4	Fibreoptic endoscopic sclerotherapy to lesion of upper gastrointestinal tract
G43.7	Fibreoptic endoscopic rubber band ligation of upper gastrointestinal tract varices
G45.1	Fibreoptic endoscopic examination of upper gastrointestinal tract and biopsy of lesion of upper gastrointestinal tract
G45.4	Fibreoptic endoscopic examination of upper gastrointestinal tract and staining of gastric mucosa
G45.8	Other specified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract
G46.8	Other specified therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract
G46.9	Unspecified therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract
G16.1	Diagnostic fibreoptic endoscopic examination of oesophagus and biopsy of lesion of oesophagus
G16.8	Other specified diagnostic fibreoptic endoscopic examination of oesophagus
G16.9	Unspecified diagnostic fibreoptic endoscopic examination of oesophagus
G10.5	Open injection sclerotherapy to varices of oesophagus

Internal validation of Baveno VI and extended Baveno VI criteria

Demographic details of the cohort are included in **Table 12.**The validation cohort comprised of 205 patients with a valid LSM ≥10kPa with a and an upper gastrointestinal endoscopy within 12 months of TE. Gastroesophageal varices were defined as low-risk varices (LRV, < grade 2) or high-risk varices (HRV, small with red signs, ≥ grade 2 + any gastric varices).

Table 12. Demographic details of validation cohort [45]

Characteristics	Total n=205 (%)	HRV n=29	No HRV n= 176
Age (years)	56.7 ± 12.7	59 ± 10.9	56 ± 13.0
Male (%)	132 (64)	20 (69)	112 (64)
Female (%)	73 (36)	9 (31)	64 (36)
Aetiology			
NAFLD (%)	88 (43)	11 (38)	77 (44)
ArLD (%)	57 (28)	11 (38)	46 (26)
Hepatitis C (%)	32 (15)	3 (10)	29 (16)
Hepatitis B (%)	9 (4)	1 (3)	8 (5)
Miscellaneous (%)	19 (9)	3 (10)	16 (9)
MELD score (median)	7	9	7
LSM (kPa) (median)	24.8	46.2	21.5
Laboratory results			
Platelets (cells $x10^3/\mu l$)	177 ± 81.6	113 ± 31.5	188 ± 82.5
Creatinine (μmol/L)	69 ± 25.8	65 ± 21.1	69 ± 26.5
Bilirubin (μmol/L)	15 ± 11.8	21 ± 14.6	15 ± 11.1
INR	1.1 ± 0.3	1.2 ± 0.2	1.0 ± 0.3
Sodium (mmol/L)	139 ± 2.9	139 ± 2.9	139 ± 2.9

48 patients (23%) met Baveno VI criteria (LSM <20kPa and platelet count >150 $x10^3/\mu l$) of whom five patients (10%) had any varices, all of which were LRV (**Figure 3**). Of the 157/205 (77%) cases that did not meet the Baveno VI criteria, 62/157 (39%) had any varices of which 29/205 (14%) were HRV. 88 patients (43%) met the expanded Baveno VI criteria (LSM <25kPa and platelet count >110 $x10^3/\mu l$) of whom eleven patients (13%) had any varices, two (2%) of which were

[45] NAFLD; non-alcoholic fatty liver disease, ArLD; alcohol-related liver disease, INR; international normalised ratio, HRV; high risk varices

HRV (**Figure 4**). Of the 117/205 (57%) cases that did not meet the expanded Baveno VI criteria, fifty-six patients (48%) had any varices of which 27/205 (13%) were HRV. Sensitivity characteristics are shown in **Table 13.**

Figure 3. Flow chart of patients in cohort as defined by the Baveno VI criteria

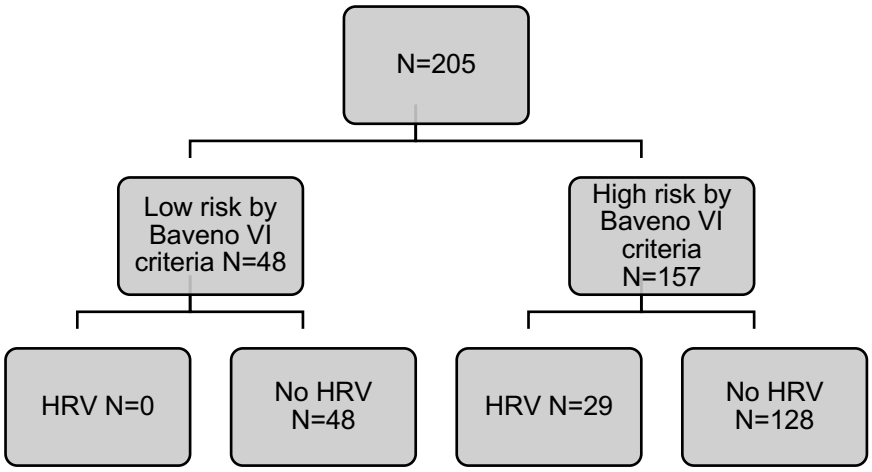


Figure 4. Flow chart of patients in cohort as defined by the Expanded Baveno VI criteria

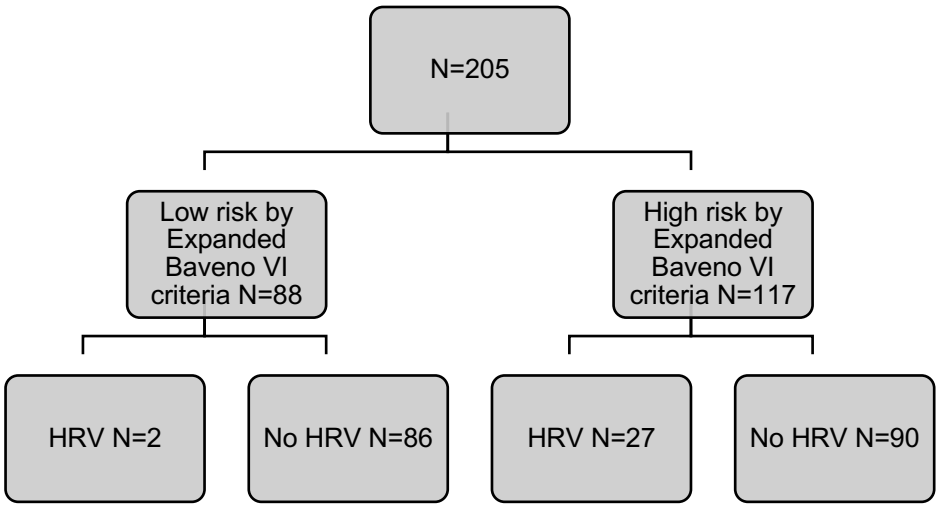


Table 13. Comparison of risk stratifying criteria in number of endoscopies avoided[46]

	Endoscopies avoided	HRV missed	Sensitivity	NPV
Baveno VI criteria	48 (23%)	0	1.00	1.00
Expanded Baveno VI criteria	88 (43%)	2 (2.3%)	0.93	0.98

[46] HRV; high risk varices, NPV: negative predictive value

References

1. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371(9615):838-51.

2. Lefkowitch JH. Morphology of alcoholic liver disease. Clin Liver Dis. 2005;9(1):37-53.

3. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet. 1995;346(8981):987-90.

4. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55(6):2005-23.

5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.

6. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013;57(4):1357-65.

7. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-402.

8. National Institute for Health and Care Excellence. Non-alcoholic fatty liver disease (NAFLD): assessment and management. July 2016. 2016.

9. World Health Organisation. Hepatitis B 2019 [Available from: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b (Accessed 21/07/2020).

10. Williams R, Alexander G, Aspinall R, Bosanquet J, Camps-Walsh G, Cramp M, et al. New metrics for the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2017;389(10083):2053-80.

11. All-Party Parliamentary Group on liver Health Inquiry Report. Eliminating Hepatitis C in England. March 2018.

12. Pinzani M, Rombouts K, Colagrande S. Fibrosis in chronic liver diseases: diagnosis and management. J Hepatol. 2005;42 Suppl(1):S22-36.

13. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. The New England journal of medicine. 2005;353(21):2254-61.

14. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;5(3):419-24.

15. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133(2):481-8.

16. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009;50(5):923-8.

17. Gomez EV, Rodriguez YS, Bertot LC, Gonzalez AT, Perez YM, Soler EA, et al. The natural history of compensated HCV-related cirrhosis: a prospective long-term study. J Hepatol. 2013;58(3):434-44.

18. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.

19. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38(3):266-72.

20. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology. 2004;40(3):652-9.

21. Garcia-Pagan JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. The New England journal of medicine. 2010;362(25):2370-9.

22. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology. 1987;7(1):122-8.

23. Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006;4(11):1385-94.

24. Wijdicks EF. Hepatic Encephalopathy. The New England journal of medicine. 2016;375(17):1660-70.

25. Amodio P, Del Piccolo F, Petteno E, Mapelli D, Angeli P, Iemmolo R, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol. 2001;35(1):37-45.

26. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. The American journal of gastroenterology. 2001;96(9):2718-23.

27. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci. 1986;31(5):468-75.

28. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999;30(5):890-5.

29. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int. 2012;32(9):1407-14.

30. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010;51(5):1675-82.

31. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol. 2018;68(3):563-76.

32. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015;62(1):292-302.

33. Bravo AA, Sheth SG, Chopra S. Liver biopsy. The New England journal of medicine. 2001;344(7):495-500.

34. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology. 1994;20(1 Pt 1):15-20.

35. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003;38(6):1449-57.

36. National Institute for Health and Care Excellence. Cirrhosis in over 16s: assessment and management (6 July 2016).

37. Benedito J, Carcel J, Clemente G, Mulet A. Cheese maturity assessment using ultrasonics. J Dairy Sci. 2000;83(2):248-54.

38. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013;34(2):169-84.

39. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol. 2017;67(2):399-411.

40. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol. 2008;48(5):835-47.

41. Foucher J, Castera L, Bernard PH, Adhoute X, Laharie D, Bertet J, et al. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan in a prospective study of 2114 examinations. Eur J Gastroenterol Hepatol. 2006;18(4):411-2.

42. Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology. 2012;55(1):199-208.

43. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134(4):960-74.

44. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol. 2011;54(4):650-9.

45. Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int. 2013;33(1):62-71.

46. You MW, Kim KW, Pyo J, Huh J, Kim HJ, Lee SJ, et al. A Meta-analysis for the Diagnostic Performance of Transient Elastography for Clinically Significant Portal Hypertension. Ultrasound Med Biol. 2017;43(1):59-68.

47. Robic MA, Procopet B, Metivier S, Peron JM, Selves J, Vinel JP, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol. 2011;55(5):1017-24.

48. Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in

patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(12):1573-84 e1-2; quiz e88-9.

49. de Ledinghen V, Vergniol J, Barthe C, Foucher J, Chermak F, Le Bail B, et al. Non-invasive tests for fibrosis and liver stiffness predict 5-year survival of patients chronically infected with hepatitis B virus. Aliment Pharmacol Ther. 2013;37(10):979-88.

50. Vergniol J, Foucher J, Terrebonne E, Bernard PH, le Bail B, Merrouche W, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology. 2011;140(7):1970-9, 9 e1-3.

51. Shili-Masmoudi S, Wong GL, Hiriart JB, Liu K, Chermak F, Shu SS, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. Liver Int. 2019.

52. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743-52.

53. Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology. 2016;64(6):2173-84.

54. Maurice JB, Brodkin E, Arnold F, Navaratnam A, Paine H, Khawar S, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. Journal of Hepatology.65(5):899-905.

55. Bae J, Sinn DH, Kang W, Gwak GY, Choi MS, Paik YH, et al. Validation of the Baveno VI and the expanded Baveno VI criteria to identify patients who could avoid screening endoscopy. Liver Int. 2018;38(8):1442-8.

56. Office for National Statistics. NOMIS, Official Labour Market Statistics. Mortality Statistics- underlying cause sex and age 2019 [10/06/2020].

57. Public Health England. Liver Disease: All our health. 2022.

58. Publich Health England. The 2nd Atlas of variation in risk factors and healthcare for liver disease in England. 2017.

59. Office for National Statistics. Deaths registered in England and Wales 2018 2019 [

60. Digital N. Hospital Episode Statistics, Admitted Patient Care - England, 2014-15 2015 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/hospital-episode-statistics-admitted-patient-care-england-2014-15.

61. Annual Report of the Chief Medical Officer Surveillance Volume. On the State of the Public's Health. 2012.

62. All Party Parliamentary Hepatology Group (APPHG) Inquiry into Improving Outcomes in Liver Disease. Liver Disease: Today's Complaceny, Tomorrow's Catastrophe. March 2014.

63. Public Health England. The 2nd Atlas of variation in risk factors and healthcare for liver disease in England. September 2017.

64. Williams R, Alexander G, Armstrong I, Baker A, Bhala N, Camps-Walsh G, et al. Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2018;391(10125):1097-107.

65. Williams R, Alexander G, Aspinall R, Batterham R, Bhala N, Bosanquet N, et al. Gathering momentum for the way ahead: fifth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2018;392(10162):2398-412.

66. Williams R, Ashton K, Aspinall R, Bellis MA, Bosanquet J, Cramp ME, et al. Implementation of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2015;386(10008):2098-111.

67. Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in

health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384(9958):1953-97.

68. Williams R, Aithal G, Alexander GJ, Allison M, Armstrong I, Aspinall R, et al. Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK. Lancet. 2020;395(10219):226-39.

69. Institute for Public Policy Research. Divided and Connected: Regional inequalities in the North, the UK and the developed world. 2019.

70. Vaughn-Sandler V, Sherman C, Aronsohn A, Volk ML. Consequences of perceived stigma among patients with cirrhosis. Dig Dis Sci. 2014;59(3):681-6.

71. NHS Digital. Statistics on Alcohol, England 2019 [PAS].

72. Collaborators GBDRF, Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287-323.

73. Foundation for Liver Research Endorsed by the Lancet Commission on Liver Disease. Financial case for action on liver disease: Escalating costs of alcohol misuse, obesity and viral hepatitis. July 2017.

74. NHS Digital. Statistics on obesity, physical activity and diet, England, 2020 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/england-2020/part-3-adult-obesity-copy.

75. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274-85.

76. Public Health England. Liver disease profiles: statistical commentary, February 2020. [Available from:

https://www.gov.uk/government/publications/liver-disease-profiles-february-2020-update/liver-disease-profiles-statistical-commentary-february-2020.

77. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577-86.

78. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.

79. Public Health England. Hepatitis B: migrant health guide. 2017.

80. National Institute for Health and Care Excellence. Hepatitis B and C testing: people at risk of infection. 2012.

81. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol. 2008;48(2):335-52.

82. Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. Eur J Public Health. 2012;22(2):187-92.

83. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(3):161-76.

84. McEwan P, Bennett H, Ward T, Webster S, Gordon J, Kalsekar A, et al. The cost-effectiveness of daclatasvir-based regimens for the treatment of hepatitis C virus genotypes 1 and 4 in the UK. Eur J Gastroenterol Hepatol. 2016;28(2):173-80.

85. NHS Digital. Hospital Admitted Patient Care Activity 2018-2019 September 2019 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19.

86. NHS Digital. The HES Processing Cycle and HES Data Qualiy. Version 4.0 Final 26/09/2016. In: HES Data Quality Team, editor. 2016.

87. Ratib S, West J, Fleming KM. Liver cirrhosis in England - An observational study: Are we measuring its burden occurrence correctly? BMJ Open. 2017;7 (7) (no pagination)(e013752).

88. Jepsen P, Vilstrup H, Sorensen HT. Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study. BMC gastroenterology. 2008;8:3.

89. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet. 2006;367(9504):52-6.

90. World Health Organisation. International statistical classification of diseases and related health problems: tenth revision, 2nd ed. 2004.

91. World Health Organisation [Available from: http://apps.who.int/classifications/icd10/browse/2010/en (Accessed 24th September 2018).

92. NHS Digital [Available from: https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/10 (Accessed 24th September 2018).

93. American Medical Association [Available from: https://www.ama-assn.org/practice-management/cpt-current-procedural-terminology (Accessed 24th September 2018).

94. Digital N. OPCS Classification of Interventions and Procedures [26/06/2020]. Available from: https://www.datadictionary.nhs.uk/web_site_content/supporting_information/clinical_coding/opcs_classification_of_interventions_and_procedures.asp?shownav=1.

95. Clinical Classifications Service NHS Digital. National Clinical Coding Standards OPCS-4. Accurate data for quality information. April 2017.

96. Thorn JC, Turner E, Hounsome L, Walsh E, Donovan JL, Verne J, et al. Validation of the Hospital Episode Statistics Outpatient Dataset in England. Pharmacoeconomics. 2016;34(2):161-8.

97. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). Int J Epidemiol. 2017;46(4):1093-i.

98. Franklin M, Thorn J. Self-reported and routinely collected electronic healthcare resource-use data for trial-based economic evaluations: the current state of play in England and considerations for the future. BMC Med Res Methodol. 2019;19(1):8.

99. Lugg-Widger F, Angel L, Cannings-John R, Hood K, Hughes K, Moody G, et al. Challenges in accessing routinely collected data from multiple providers in the UK for primary studies: Managing the morass. International Journal of Population Data Science. 2018;3.

100. Department of Health & Social Care. The future of healthcare: our vision for digital, data and technology in health and care. October 2018.

101. Medical Research Council. Health Data Research UK (HDR UK) [Available from: https://mrc.ukri.org/about/institutes-units-centres/uk-institute-for-health-and-biomedical-informatics-research/.

102. Health Data Research UK. Gut Reaction- The Health Data Research Hub for Inflammatory Bowel Disease [Available from: https://www.hdruk.ac.uk/help-with-your-data/our-hubs-across-the-uk/gut-reaction/.

103. Kramer JR, Davila JA, Miller ED, Richardson P, Giordano TP, El-Serag HB. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Alimentary Pharmacology and Therapeutics. 2008;27(3):274-82.

104. Re VL, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic

decompensation events in the Veterans Aging Cohort Study. Pharmacoepidemiology and Drug Safety. 2011;20(7):689-99.

105. Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singal AG. Use of administrative claims data for identifying patients with cirrhosis. Journal of Clinical Gastroenterology. 2013;47(5):E50-E4.

106. Goldberg D, Lewis JD, Halpern SD, Weiner M, Lo Re IV. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. Pharmacoepidemiology and Drug Safety. 2012;21(7):765-9.

107. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. PLoS One. 2015;10(8):e0135834.

108. Khokhar B, Jette N, Metcalfe A, Cunningham CT, Quan H, Kaplan GG, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. BMJ Open. 2016;6(8):e009952.

109. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

110. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.

111. Chang EK, Yu CY, Clarke R, Hackbarth A, Sanders T, Esrailian E, et al. Defining a Patient Population With Cirrhosis: An Automated Algorithm With Natural Language Processing. J Clin Gastroenterol. 2016;50(10):889-94.

112. Hachem CY, Kramer JR, Kanwal F, El-Serag HB. Hepatitis vaccination in patients with hepatitis C: Practice and validation of codes at a large veterans administration medical centre. Alimentary Pharmacology and Therapeutics. 2008;28(9):1078-87.

113. Lu M, Chacra W, Rabin D, Rupp LB, Trudeau S, Li J, et al. Validity of an automated algorithm using diagnosis and procedure codes to identify decompensated cirrhosis using electronic health records. Clinical Epidemiology. 2017;9:369-76.

114. Mapakshi S, Kramer JR, Richardson P, El-Serag HB, Kanwal F. Positive Predictive Value of International Classification of Diseases, 10th Revision, Codes for Cirrhosis and Its Related Complications. Clinical Gastroenterology and Hepatology. 2018.

115. Rabin D, Chacra W, Gordon S, Yang J, Rupp L. Use of billing and procedure codes to predict stage of liver disease in patients with chronic viral hepatitis. American Journal of Gastroenterology. 2013;1):S147.

116. Rakoski MO, McCammon RJ, Piette JD, Iwashyna TJ, Marrero JA, Lok AS, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. Hepatology. 2012;55(1):184-91.

117. Singal AG, Ma Y, Nehra M, Gopal P, Amarasingham R. The validity of administrative codes for identifying patients with cirrhosis. Hepatology. 2011;1):586A.

118. Kanwal F, Kramer JR, Buchanan P, Asch SM, Assioun Y, Bacon BR, et al. The quality of care provided to patients with cirrhosis and ascites in the Department of Veterans Affairs. Gastroenterology. 2012;143(1):70-7.

119. Fialla AD, De Muckadell OBS, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: A population-based cohort study. Scandinavian journal of gastroenterology. 2012;47(6):702-9.

120. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.

121. Lapointe-Shaw L, Georgie F, Carlone D, Cerocchi O, Chung H, Dewit Y, et al. Identifying cirrhosis, decompensated cirrhosis and hepatocellular

carcinoma in health administrative data: A validation study. PLoS One. 2018;13(8):e0201120.

122. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived rom ICD-9-CCM administrative data. Medical care. 2002;40(8):675-85.

123. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. The American journal of gastroenterology. 2014;109(2):190-8.

124. Driver RJ, Balachandrakumar V, Burton A, Shearer J, Downing A, Cross T, et al. Validation of an algorithm using inpatient electronic health records to determine the presence and severity of cirrhosis in patients with hepatocellular carcinoma in England: an observational study. BMJ Open. 2019;9(7):e028571.

125. Kanwal F, Kramer JR, Buchanan P, Asch S, Assioun Y, Gary J, et al. The quality of care provided to patients with cirrhosis and ascites. Hepatology. 2011;1):408A.

126. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-9.

127. Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, et al. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651-60.

128. Singal AG, Rahimi RS, Clark C, Ma Y, Cuthbert JA, Rockey DC, et al. An automated model using electronic medical record data identifies patients with cirrhosis at high risk for readmission. Clinical Gastroenterology and Hepatology. 2013;11(10):1335-41.

129. Elsevier Scopus Website. [Available from: https://www.elsevier.com/solutions/scopus?dgcid=RN_AGCM_Sourced_300005030.

130. Centers for Medicare & Medicaid Services. General Equivalence Mappings: ICD-9-CM to and from ICD-10-CM and ICD-10-PCS [Available from:

https://www.cms.gov/medicare/coding/icd10/downloads/icd-10_gem_fact_sheet.pdf.

131. Centers for Medicare & Medicaid Services. 2018 ICD-10 CM and GEMs [Available from: https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs.

132. Bengtsson B, Askling J, Ludvigsson JF, Hagstrom H. Validity of administrative codes associated with cirrhosis in Sweden. Scandinavian journal of gastroenterology. 2020;55(10):1205-10.

133. Bernatsky S, Lix L, O'Donnell S, Lacaille D, Network C. Consensus statements for the use of administrative health data in rheumatic disease research and surveillance. The Journal of rheumatology. 2013;40(1):66-73.

134. Hanly JG, Thompson K, Skedgel C. The use of administrative health care databases to identify patients with rheumatoid arthritis. Open access rheumatology : research and reviews. 2015;7:69-75.

135. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. PLoS One. 2014;9(3):e92286.

136. Digital N. Terminology and Classifications: SNOMED CT [Available from: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct.

137. NHS Information Centre. Hospital Episode Statistics (HES): Improving the quality and value of hospital data. 2011.

138. Walley T, Mantgani A. The UK General Practice Research Database. Lancet. 1997;350(9084):1097-9.

139. Dominitz JA, Boyko EJ, Koepsell TD, Heagerty PJ, Maynard C, Sporleder JL, et al. Elevated prevalence of hepatitis C infection in users of United States veterans medical centers. Hepatology. 2005;41(1):88-96.

140. Das SR, Kinsinger LS, Yancy WS, Jr., Wang A, Ciesco E, Burdick M, et al. Obesity prevalence among veterans at Veterans Affairs medical facilities. Am J Prev Med. 2005;28(3):291-4.

141. Rimland JM, Abraha I, Luchetta ML, Cozzolino F, Orso M, Cherubini A, et al. Validation of chronic obstructive pulmonary disease (COPD) diagnoses in healthcare databases: a systematic review protocol. BMJ Open. 2016;6(6):e011777.

142. The 2nd Atlas of variation in risk factors and healtcare for liver disease in England. 2017.

143. HDRUK Phenotype Library. [Available from: https://phenotypes.healthdatagateway.org.

144. HDRUK Phenotype Library. Liver fibrosis, sclerosis and cirrhosis [Available from: https://phenotypes.healthdatagateway.org/phenotypes/PH140/version/280/detail/.

145. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Husain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. The Lancet Digital Health. 2019;1(2):e63-e77.

146. Leeds Teaching Hospitals NHS Trust. Leeds Liver Unit [Available from: https://www.leedsth.nhs.uk/a-z-of-services/leeds-liver-unit/.

147. UK Government Digital Service. List of ethnic groups [Available from: https://www.ethnicity-facts-figures.service.gov.uk/ethnic-groups.

148. Tapper EB, Zhang P, Garg R, Nault T, Leary K, Krishnamurthy V, et al. Body composition predicts mortality and decompensation in compensated cirrhosis patients: A prospective cohort study. JHEP Rep. 2020;2(1):100061.

149. de Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology. 2005;43(1):167-76.

150. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2005;43(1):167-76.

151. Department of Heath. NHS Confidentiality Code of Practice. 2003.

152. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (United Kingdom General Data Protection Regulation) (Text with EEA relevance), (2016).

153. Spencer SA, Davies MP. Hospital episode statistics: improving the quality and value of hospital data: a national internet e-survey of hospital consultants. BMJ Open. 2012;2(6).

154. Kramer JR, Davila JA, Miller ED, Richardson P, Giordano TP, El-Serag HB. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Alimentary Pharmacology & Therapeutics.27(3):274-82.

155. Chaudhry Z, Mannan F, Gibson-White A, Syed U, Ahmed S, Majeed A. Research Outputs of England's Hospital Episode Statistics (HES) Database: Bibliometric Analysis. J Innov Health Inform. 2017;24(4):949.

156. Royal College of Physicians. Engaging clinicians in improving data quality in the NHS: iLab project summary. 2006.

157. Insights From Advanced Analytics At The Veterans Health Administration. Health Affairs. 2014;33(7):1203-11.

158. Varela LO, Knudsen Sr, Carpendale MST, Eastwood C, Quan H. Comparing ICD-Data Across Countries: A Case for Visualization? 2019 IEEE Workshop on Visual Analytics in Healthcare (VAHC). 2019:60-1.

159. NHS Digital. HES Data Dictionary. Outpatients. April 2018.

160. Clinical Practice Research Datalink. [Available from: https://www.cprd.com/home.

161. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a

population-based cohort study. The American journal of gastroenterology. 2015;110(8):1149-58.

162. Philip G, Djerboua M, Carlone D, Flemming JA. Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data. PLOS ONE. 2020;15(2):e0229218.

163. Husain N, Blais P, Kramer J, Kowalkowski M, Richardson P, El-Serag HB, et al. Nonalcoholic fatty liver disease (NAFLD) in the Veterans Administration population: development and validation of an algorithm for NAFLD using automated data. Aliment Pharmacol Ther. 2014;40(8):949-54.

164. Myers RP, Shaheen AAM, Fong A, Wan AF, Swain MG, Hilsden RJ, et al. Validation of Coding Algorithms for the Identification of Patients with Primary Biliary Cirrhosis Using Administrative Data. Canadian Journal of Gastroenterology. 2010;24:237860.

165. Molodecky NA, Myers RP, Barkema HW, Quan H, Kaplan GG. Validity of administrative data for the diagnosis of primary sclerosing cholangitis: a population-based study. Liver Int. 2011;31(5):712-20.

166. Niu B, Forde KA, Goldberg DS. Coding algorithms for identifying patients with cirrhosis and hepatitis B or C virus using administrative data. Pharmacoepidemiol Drug Saf. 2015;24(1):107-11.

167. Corey KE, Kartoun U, Zheng H, Shaw SY. Development and Validation of an Algorithm to Identify Nonalcoholic Fatty Liver Disease in the Electronic Medical Record. Dig Dis Sci. 2016;61(3):913-9.

168. Papatheodoridi M, Hiriart JB, Lupsor-Platon M, Bronte F, Boursier J, Elshaarawy O, et al. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. J Hepatol. 2021;74(5):1109-16.

169. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What Is It and What Can It Tell Us? The New England journal of medicine. 2016;375(23):2293-7.

170. Leeds Teaching Hospitals NHS Trust. Annual Report and Accounts 2017/18: Incorporating the Annual Quality Account.

171. University Hospitals Birmingham NHS Foundation Trust. Annual Report and Accounts 2017/18.

172. Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology. 2013;57(3):1182-91.

173. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-8.

174. Guha IN, Harris R, Berhane S, Dillon A, Coffey L, James MW, et al. Validation of a Model for Identification of Patients With Compensated Cirrhosis at High Risk of Decompensation. Clin Gastroenterol Hepatol. 2019;17(11):2330-8 e1.

175. Peng Y, Qi X, Tang S, Deng H, Li J, Ning Z, et al. Child-Pugh, MELD, and ALBI scores for predicting the in-hospital mortality in cirrhotic patients with acute-on-chronic liver failure. Expert Rev Gastroenterol Hepatol. 2016;10(8):971-80.

176. Zou D, Qi X, Zhu C, Ning Z, Hou F, Zhao J, et al. Albumin-bilirubin score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis: A retrospective study. Turk J Gastroenterol. 2016;27(2):180-6.

177. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25.

178. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7(10):1104-12.

179. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007;46(1):32-6.

180. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

181. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676-82.

182. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.

183. StataCorp. Stata 17 Base Reference Manual. College Station, TX: Stata Press.2021.

184. Powell EE, Skoien R, Rahman T, Clark PJ, O'Beirne J, Hartel G, et al. Increasing Hospitalization Rates for Cirrhosis: Overrepresentation of Disadvantaged Australians. EClinicalMedicine. 2019;11:44-53.

185. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Am J Med. 2007;120(10):829-34.

186. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. Aliment Pharmacol Ther. 2005;22 Suppl 2:24-7.

187. Ahn SB, Powell EE, Russell A, Hartel G, Irvine KM, Moser C, et al. Type 2 Diabetes: A Risk Factor for Hospital Readmissions and Mortality in Australian Patients With Cirrhosis. Hepatol Commun. 2020;4(9):1279-92.

188. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60(6):1310-24.

189. Hung T-H, Tseng C-W, Hsieh Y-H, Tseng K-C, Tsai C-C, Tsai C-C. High mortality of pneumonia in cirrhotic patients with ascites. BMC gastroenterology. 2013;13(1):25.

190. Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. Clinical course and mortality by etiology of liver cirrhosis in Sweden: a population based, long-term follow-up study of 1317 patients. Aliment Pharmacol Ther. 2019;49(11):1421-30.

191. Orman ES, Roberts A, Ghabril M, Nephew L, Desai AP, Patidar K, et al. Trends in Characteristics, Mortality, and Other Outcomes of Patients With Newly Diagnosed Cirrhosis. JAMA Netw Open. 2019;2(6):e196412.

192. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.

193. Volk ML, Fisher N, Fontana RJ. Patient knowledge about disease self-management in cirrhosis. The American journal of gastroenterology. 2013;108(3):302-5.

194. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl, . 2013;3(1-150).

195. Jepsen P, Kraglund F, West J, Villadsen GE, Sorensen HT, Vilstrup H. Risk of hepatocellular carcinoma in Danish outpatients with alcohol-related cirrhosis. J Hepatol. 2020;73(5):1030-6.

196. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 2014;39(10):1180-93.

197. D'Amico G, Abraldes JG, Rebora P, Valsecchi MG, Garcia-Tsao G. Ordinal Outcomes Are Superior to Binary Outcomes for Designing and Evaluating Clinical Trials in Compensated Cirrhosis. Hepatology. 2020;72(3):1029-42.

198. Bhala N, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology. 2011;54(4):1208-16.

199. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138-53.

200. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61(5):1547-54.

201. Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. BMJ. 2019;367:l5367.

202. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5 Suppl 1):S35-50.

203. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-50.

204. Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol. 2019;71(3):523-33.

205. Roskilly A, Rowe IA. Surveillance for hepatocellular cancer. Clin Med (Lond). 2018;18(Suppl 2):s66-s9.

206. Taylor EJ, Jones RL, Guthrie JA, Rowe IA. Modeling the benefits and harms of surveillance for hepatocellular carcinoma: Information to support informed choices. Hepatology. 2017;66(5):1546-55.

207. Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. Am J Med. 1996;101(4):422-34.

208. Jepsen P, West J. We need stronger evidence for (or against) hepatocellular carcinoma surveillance. Journal of Hepatology.

209. Ajmera VH, Terrault NA, Harrison SA. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review. Hepatology. 2017;65(6):2090-9.

210. Rubin DB. Multiple Imputation for nonresponse in surveys. : Hoboken, NJ: John Wiley & Sons.; 2004.

211. Cancer Research UK. [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-Zero.

212. El-Serag HB. Hepatocellular carcinoma. The New England journal of medicine. 2011;365(12):1118-27.

213. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126(2):460-8.

214. Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2007;5(8):938-45, 45 e1-4.

215. Shim JJ, Oh CH, Kim JW, Lee CK, Kim BH. Liver cirrhosis stages and the incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving antiviral therapy. Scandinavian journal of gastroenterology. 2017;52(9):1029-36.

216. Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2011;9(1):64-70.

217. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;150(4):835-53.

218. European Association For The Study Of The L, European Organisation For R, Treatment Of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.

219. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358-80.

220. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med. 2014;11(4):e1001624.

221. Cucchetti A, Trevisani F, Pecorelli A, Erroi V, Farinati F, Ciccarese F, et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. J Hepatol. 2014;61(2):333-41.

222. Cross TJS, Villanueva A, Shetty S, Wilkes E, Collins P, Adair A, et al. A national survey of the provision of ultrasound surveillance for the detection of hepatocellular carcinoma. Frontline Gastroenterol. 2016;7(2):82-9.

223. Thein HH, Campitelli MA, Yeung LT, Zaheen A, Yoshida EM, Earle CC. Improved Survival in Patients with Viral Hepatitis-Induced Hepatocellular Carcinoma Undergoing Recommended Abdominal Ultrasound Surveillance in Ontario: A Population-Based Retrospective Cohort Study. PLoS One. 2015;10(9):e0138907.

224. Palmer LB, Kappelman MD, Sandler RS, Hayashi PH. Surveillance for hepatocellular carcinoma in a Medicaid cirrhotic population. J Clin Gastroenterol. 2013;47(8):713-8.

225. Edenvik P, Davidsdottir L, Oksanen A, Isaksson B, Hultcrantz R, Stal P. Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice? Liver Int. 2015;35(7):1862-71.

226. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922-38.

227. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015;64(11):1680-704.

228. Flemming JA, Saxena V, Shen H, Terrault NA, Rongey C. Facility- and Patient-Level Factors Associated with Esophageal Variceal Screening in the USA. Dig Dis Sci. 2016;61(1):62-9.

229. Moodley J, Lopez R, Carey W. Compliance with practice guidelines and risk of a first esophageal variceal hemorrhage in patients with cirrhosis. Clin Gastroenterol Hepatol. 2010;8(8):703-8.

230. Sharma A, Ball K, Markert RJ, Krishnamurthy P. Adherence to Screening, Primary Prophylaxis, and Surveillance for Esophageal Varices in a U.S Veterans' Population: 964. American Journal of Gastroenterology. 2018;113:S542-S3.

231. Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med. 2011;154(2):85-93.

232. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology. 2010;52(1):132-41.

233. Farrell C, Halpen A, Cross TJ, Richardson PD, Johnson P, Joekes EC. Ultrasound surveillance for hepatocellular carcinoma: service evaluation of a radiology-led recall system in a tertiary-referral centre for liver diseases in the UK. Clin Radiol. 2017;72(4):338 e11- e17.

234. Goldberg DS, Valderrama A, Kamalakar R, Sansgiry SS, Babajanyan S, Lewis JD. Hepatocellular Carcinoma Surveillance Among Cirrhotic Patients With Commercial Health Insurance. J Clin Gastroenterol. 2016;50(3):258-65.

235. Mittal S, Kanwal F, Ying J, Chung R, Sada YH, Temple S, et al. Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: A United States cohort. J Hepatol. 2016;65(6):1148-54.

236. Tran SA, Le A, Zhao C, Hoang J, Yasukawa LA, Weber S, et al. Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis. BMJ Open Gastroenterol. 2018;5(1):e000192.

237. Yeo YH, Hwang J, Jeong D, Dang N, Kam LY, Henry L, et al. Surveillance of patients with cirrhosis remains suboptimal in the United States. J Hepatol. 2021;75(4):856-64.

238. Wolf E, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis: A Systematic Review and Meta-Analysis. Hepatology. 2021;73(2):713-25.

239. Singal AG, Yopp A, C SS, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med. 2012;27(7):861-7.

240. Farvardin S, Patel J, Khambaty M, Yerokun OA, Mok H, Tiro JA, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. Hepatology. 2017;65(3):875-84.

241. Goldsworthy MA, Fateen W, Thygesen H, Aldersley MA, Rowe IA, Jones RL. Patient understanding of liver cirrhosis and improvement using multimedia education. Frontline Gastroenterol. 2017;8(3):214-9.

242. NHS Digital. Provisional Monthly Hospital Episode Statistics for Admitted Patient Care, Outpatient and Accident and Emergency data April 2021 - July 2021 2021 [Available from: https://app.powerbi.com/view?r=eyJrIjoiMjc3MWU5NDAtNTE5OS00NzEyLTg3MzEtNzEzYWFjNDlkMWQzIiwidCI6IjUwZjYwNzFmLWJiZmUtNDAxYS04ODAzLTY3Mzc0OGU2MjllMiIsImMiOjh9 (accessed 12th October 2021).

243. Kansagara D, Papak J, Pasha AS, O'Neil M, Freeman M, Relevo R, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. Ann Intern Med. 2014;161(4):261-9.

244. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology. 2017;66(6):1980-8.

245. Shearer J, Chizhande D, Jones R, Rowe IA. Non-invasive prediction of oesophageal varices in patients with cirrhosis secondary to non-alcoholic fatty liver disease. J Hepatol. 2018;69(5):1202-3.

246. Jangouk P, Turco L, De Oliveira A, Schepis F, Villa E, Garcia-Tsao G. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. Liver Int. 2017;37(8):1177-83.

247. Myocardial Ischaemia/MINAP (Heart Attack audit). [Available from: https://www.nicor.org.uk/myocardial-ischaemia-minap-heart-attack-audit/.

248. Hall M, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, et al. Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non-ST-Elevation Myocardial Infarction, 2003-2013. JAMA. 2016;316(10):1073-82.

249. EuroHeart: European Society of Cardiology. [Available from: https://www.escardio.org/Research/euroheart.

250. Aktaa S, Batra G, James SK, Blackman DJ, Ludman PF, Mamas MA, et al. Data standards for transcatheter aortic valve implantation: the European Unified Registries for Heart Care Evaluation and Randomised Trials

(EuroHeart). European Heart Journal - Quality of Care and Clinical Outcomes. 2022.

251. Davies SC Annual Report of the Chief Medical Officer. Volume 1, 2011, On the State of the Public's Health. Department of Health, London. www.gov.uk/government/publications/cmo-annual-report-2011-volume-one-on-the-state-of-the-public-s-health

252. NCEPOD. "Measuring the Units"-a review of patients who died with alcoholic related liver disease. National Confidential Enquiry into Patient Outcome and Death (UK); 2013:1-25. 2013.

253. Rasmussen DN, Thiele M, Johansen S, Kjaergaard M, Lindvig KP, Israelsen M, et al. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. J Hepatol. 2021;75(5):1017-25.

254. Hagstrom H, Talback M, Andreasson A, Walldius G, Hammar N. Ability of Noninvasive Scoring Systems to Identify Individuals in the Population at Risk for Severe Liver Disease. Gastroenterology. 2020;158(1):200-14.

255. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation. 2015;131(3):269-79.

256. Chalmers J, Wilkes E, Harris R, Kent L, Kinra S, Aithal GP, et al. The Development and Implementation of a Commissioned Pathway for the Identification and Stratification of Liver Disease in the Community. Frontline Gastroenterol. 2020;11(2):86-92.

257. Matthews C, Cross TJS. Before we can find an evidence base for HCC surveillance, we need to define our target demographic. J Hepatol. 2021;75(6):1494-5.

258. Asaria M, Walker S, Palmer S, Gale CP, Shah AD, Abrams KR, et al. Using electronic health records to predict costs and outcomes in stable coronary artery disease. Heart. 2016;102(10):755-62.

259. Royal College of Physicians. Improving Quality in Liver Services [Available from: https://www.iqils.org/About-accreditation.

260. Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. Alimentary Pharmacology & Therapeutics. 2010;32(11-12):1343-50.

261. Royal College of General Practitioners. RCGP Research and Surveillance Centre (RSC) [Available from: https://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx.

262. Royal College of General Practitioners. Recommendations for commissioning bodies to improve the early detection of chronic liver disease in UK primary care [Available from: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/liver-disease-toolkit/recommendations-for-commissioning-bodies-to-improve-the-early-detection-of-chronic-liver-disease.aspx.

263. EASL Registry Grant. [Available from: https://easl.eu/research-funding/registry-grants/.

264. National INstitute for Health Research. Supporting liver diseases research [Available from: https://www.nihr.ac.uk/explore-nihr/specialties/liver.htm.

265. Guts UK. Guts UK/BSG Trainee Awards [Available from: https://gutscharity.org.uk/research/grants-and-awards/guts-uk-bsg-trainee-research-grants/.

266. NHS Digital. Section 251 and the application of national data opt-outs 2019 [Available from: https://digital.nhs.uk/services/data-access-request-service-dars/how-the-national-data-opt-out-affects-data-released-by-nhs-digital/national-data-opt-out-guidance-for-researchers/4-section-251-and-the-application-of-national-data-opt-outs.

267. Public Health England. National Cancer Registration and Analysis Service (NCRAS) 2016 [Available from: https://www.gov.uk/guidance/national-cancer-registration-and-analysis-service-ncras.

268. Cross L, Carson LE, Jewell A, Heslin M, Osborn D, Downs J, et al. Guidance for researchers wanting to link NHS data using non-consent approaches: a thematic analysis of feedback from the Health Research Authority Confidentiality Advisory Group. Int J Popul Data Sci. 2020;5(1):1355.

269. IBD Registry. The UK Inflammatory Bowel Disease (IBD Registry) Information for the Caldicott Guardians of NHS organisations in England. October 2015.