Understanding Outcomes in Hepatocellular Carcinoma and Cirrhosis in England

Dr Robert John Driver
Student ID: 200017385

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Intellectual Property and Publication Statements

The work submitted is my own work, except where work has formed part of this jointly authored publication:

1. Driver RJ, Balachandrakumar V, Burton A, Shearer J, Downing A, Cross T, Morris E, Rowe IA. 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

   RD and IR had the original idea for the study and AB, AD, TC and EM contributed to its design and planning. RD, JS and VB performed the case note reviews. RD was responsible for data management, statistical analyses and wrote the first draft of the paper. IR reviewed the paper critically.

   Chapters 5 and 6 are based on this work.

2. Driver R, Burton A, Downing A, Marshall A, Morris, E, Rowe, I.OTU-10 Impact of cirrhosis severity on clinical outcomes in hepatocellular carcinoma in England. Gut 2019;68:A106

   IR and RD had the original idea for the study and AB, AM, AD and EM contributed to its design and planning. RD was responsible for data management, statistical analyses and presentation of the results.

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3. Driver R, Chizhande D, Jones R, Rowe IA. PTH-090 Survival after a diagnosis of hepatocellular carcinoma. Gut 2018;67:A123

   RD and IR had the original idea for the study and RJ contributed to its design. DC created the original dataset. RD was responsible for data management, statistical analyses and presentation of the results.

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4. Driver R, Chizhande D, Jones R, Rowe IA. PWE-076 Impact of cirrhosis severity on survival in hepatocellular carcinoma. Gut 2018;67:A110.

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   Chapters 5 and 6 are based on this work.

5. Burton, A., Tataru, D., Driver, R.J., Bird, T.G., Huws, D., Wallace, D., Cross, T.J., Rowe, I.A., Alexander, G., Marshall, A. and Rowe, I., 2021. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. JHEP Reports, 3(2), p.100232.

   AB acquired the data, performed analyses and drafted the manuscript. All authors contributed to the development of the study design, interpretation of the results, and critical revision of the manuscript.

   Chapters 7 and 8 are related to this work

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My own contributions, fully and explicitly indicated in the thesis, have been:

- searching, review and appraisal of literature
- development of the research questions
- preparation of the project proposal to Public Health England
- preparation of the ethics proposal
- case note review for the *Validation Study*
- writing of statistical code for algorithm development
- application to the Office for Data Release at Public Health England
- application for secure storage of data at the University of Leeds
- writing of statistical code for data analysis and presentation of results
- first author of all manuscripts and published abstracts
- design and drafting of thesis

The other members of the group and their contributions have been:

- development of the research questions (IR, AD, EM, AB)
- review of project proposal (HCC-UK/ NCRAS/ BASL partnership members)
- case note review (VB, JS)
- preparation of dataset for *Validation Study* (DC) and *National Study* (AB)
- adaptation of previous coding algorithms for statistical analysis, including funnel plots (AD, EM, RB, HF) and competing risk analyses (PL, MR, MC)
- review of thesis (IR, AD)

Abstract

Background:

Hepatocellular carcinoma (HCC) is a major cause of death globally and its incidence is rising. It usually occurs on a background of cirrhosis. Survival statistics are limited outside clinical trials and population-based studies are complex because patients have competing risks of liver- and cancer-related mortality. This thesis aimed to developed methods to assess cirrhosis severity from population-based electronic heath records (EHRs), in order to understand these clinical outcomes for patients with HCC, and to describe regional variation in treatment allocation across England.

Methods:

Algorithms were developed to determine cirrhosis severity from inpatient EHRs, using case note review from two NHS centres for validation. Competing risk was modelled using the presence of hepatic decompensation to identify liver-related outcomes. Using cancer registry data linked to the Hospital Episodes Statistics database, all patients diagnosed with HCC between 2007 and 2016 in England were identified. These patients were characterised using the algorithms and the predictors of HCC treatment allocation were identified. The impact of cirrhosis severity on overall survival and competing risk was investigated. Regional variation in the proportion of patients receiving different HCC treatments was described.

Results:

The sensitivity for cirrhosis detection from EHRs was 86% using the validated algorithm. Cirrhosis severity was the main predictor of overall survival following HCC treatment, and this difference correlated with an increase in liver-related mortality in competing risk analyses. Surgical treatments for HCC were more common in those regions with specialist services.

Conclusion:

Overall survival in HCC in England is comparable with published estimates from clinical trials. Survival is strongly influenced by underlying cirrhosis severity and this is associated with increased liver-related mortality. Careful consideration of the effect of previous hepatic decompensation is essential for treatment selection in HCC. Exploring barriers to receiving specialist treatment may improve the observed regional variation in treatment allocation.

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1 Glossary

Cirrhosis: Scarring of the liver.

Ascites: the accumulation of fluid in the abdomen, often caused by advanced cirrhosis or abdominal cancer.

Oesophageal varices: enlarged veins in the gullet caused by an increased pressure of blood flow returning to the liver in the presence of cirrhosis.

Child Pugh Score: clinical score used to assess cirrhosis severity and determine long-term prognosis. It comprises blood tests and clinical assessment of ascites and encephalopathy.

Model for End-Stage Liver Disease (MELD) score: clinical score used to assess cirrhosis severity. It was initially used to predict three month mortality, but is used internationally to prioritise patients with cirrhosis for liver transplantation.

Encephalopathy: confusion caused by the build-up of toxins in the blood, seen as a consequence of liver failure.
Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired mentation
Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
Grade 4 - Coma

Paracentesis: drainage of ascites from the abdomen

Portal Hypertension: increased pressure in the blood vessels returning blood to the liver from the gut

Liver transplant: the removal of a whole liver (which may contain cancer) from a patient and replacement with a donor liver.

Liver resection: surgical removal of part of a liver containing cancer

Ablation: a number of techniques involving local destruction of liver cancer using directed microwave or radio-frequency radiation or thermal techniques.

Trans-arterial chemoembolisation (TACE): the insertion of tiny beads containing chemotherapy via the blood vessels supplying the liver using guidewires under x-ray guidance. The beads are deposited locally to block the blood vessels supplying the tumour.

Sorafenib: an oral chemotherapy drug used to treat hepatocellular carcinoma.

2 General Introduction

2.1 Hepatocellular Carcinoma - Background

2.1.1 Epidemiology and Pathophysiology

Primary liver cancer represents 2% of all cancers diagnosed in the UK, with approximately 5,900 new cases each year (Cancer Research UK, 2016). Globally, it is the second most frequent cause of cancer-related death and the fifth most common cancer (Akinyemiju et al., 2017). The incidence is increasing both globally and in the UK, and approximately 90% of primary liver cancers are hepatocellular carcinoma (HCC). It is estimated that 70-90% of HCCs occur in the background of cirrhosis (El-Serag and Rudolph, 2007, D'Amico et al., 2006). Cirrhosis is the term used to describe scarring of the liver and it is caused by chronic inflammation (hepatitis) of any cause, including viral hepatitis and alcohol misuse. The incidence of cirrhosis in the UK is increasing and deaths related to liver disease have increased by 250% from 1971 to 2011, whereas deaths from other causes have decreased (Figure 1) (World Health Organisation, 2013).

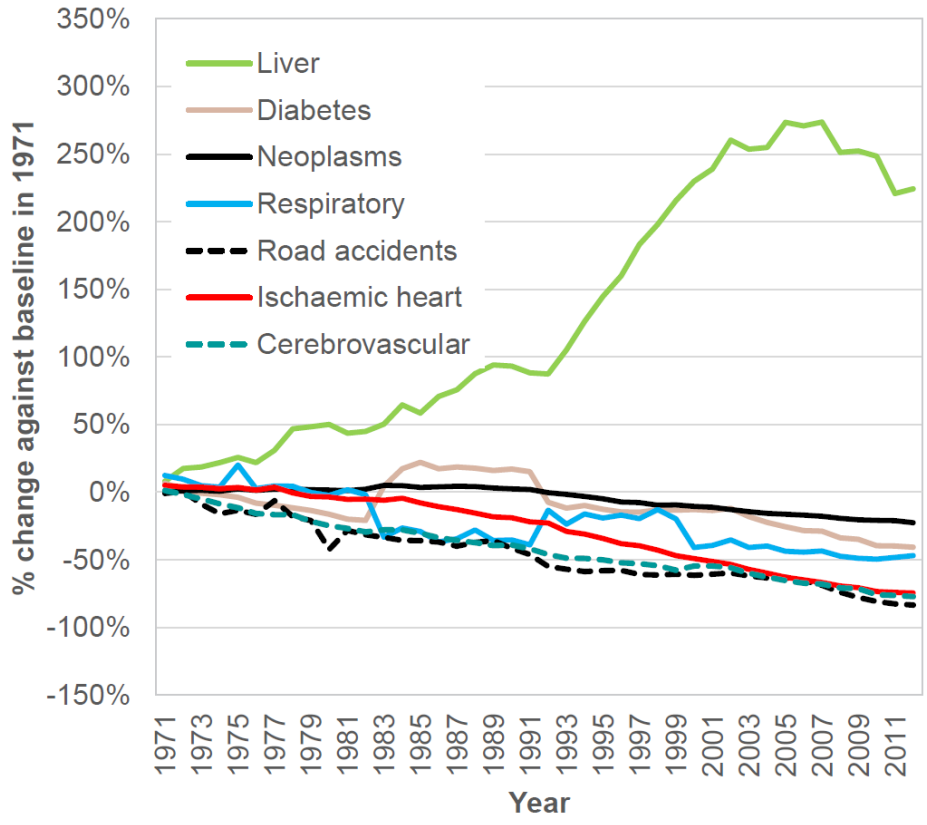

Figure 1. Trend in mortality from liver disease compared to trends in mortality from other causes, United Kingdom, 1971-2013

At a cellular level, the development of fibrosis (and the progression to cirrhosis) involves the replacement of normal liver tissue with scar tissue. The loss of healthy liver cells affects the normal function of the liver, which is associated with deficiency in protein synthesis and the development of jaundice, as the liver fails to process the breakdown products of red blood cells (bilirubin). These changes are detectable using blood tests and cirrhosis severity can be assessed using scores based on these, such as the Child Pugh classification (Pugh et al., 1973) and the Model for End-Stage Liver Disease (MELD) (Malinchoc et al., 2000). Fibrosis leads to an increase in liver stiffness, detectable non-invasively by transient elastography (Wong and Chan, 2010). More advanced scarring leads to an increase in the pressure of blood returning to the liver via the portal circulation, leading to the development of oesophageal varices and ascites (see Glossary), increasing liver-related morbidity and mortality.

The activation of proinflammatory cytokines and hepatocyte regeneration in cirrhosis form the basis of cellular transformation that leads to the development of HCC (Ramakrishna et al., 2013). The incidence of HCC has been shown to increase with more advanced cirrhosis (Ripoll et al., 2009), but different aetiologies of liver disease are associated with increased cancer risk. Globally, hepatitis B (HBV) is the most common risk factor associated with HCC (Beasley, 1988) and the increased HCC risk is greatest in regions were HBV is endemic such as Africa and East Asia. The presence of chronic hepatitis C infection (HCV) is another major risk factor for the development of HCC; a meta-analysis of case-control studies demonstrated a 17-fold increase in risk over HCV-negative controls (Donato et al., 2002). Worldwide estimates suggest that approximately 54% of HCC cases are linked to HBV infection and 31% can be attributed to HCV (Akinyemiju et al., 2017). HBV and HCV are oncogenic viruses, conferring additional risk of HCC development, which may also occur in the absence of cirrhosis. The increased global prevalence of HBV and HCV accounts for the increased incidence of HCC globally compared with the UK.

Alcohol is known to be a risk factor for HCC, but there is limited evidence of a direct carcinogenic effect beyond the link with the development of cirrhosis. Genetic haemochromatosis has been shown to be associated with the development of HCC (Ye et al., 2016), although it is most commonly seen in the presence of cirrhosis (Boige et al., 2003, Fracanzani et al., 2001). Excess iron deposition in the liver seen in haemochromatosis may promote oxidative stress that leads to malignant transformation in hepatocytes (Jayachandran et al., 2020).

There is an association between non-alcoholic fatty liver disease (NAFLD) and the development of HCC in individuals with cirrhosis (White et al., 2012). In addition, NAFLD has

been implicated in new cases of HCC in the absence of advanced fibrosis or cirrhosis (Mittal et al., 2016). Although the precise mechanism is unclear it is likely to relate to chronic inflammation and cytokine activation. Diabetes mellitus and obesity are also associated with NAFLD and have been shown to confer additional risk in HCC (Kulik and El-Serag, 2019, Schlesinger et al., 2013).

Males have a higher rate of HCC than females globally (Wands, 2007); this may relate to the acquisition of risk factors, as well as genetic and hormonal factors (Naugler et al., 2007). In particular, androgen receptor signalling has been implicated the pathogenesis of HCC (Ma et al., 2014). In the United States, HCC rates are twice as high in Asians compared with African Americans, whose rates are twice as high as in white populations (El-Serag and Rudolph, 2007). Some of these differences are likely to be related to the rates of acquisition of risk factors, such as HBV infection.

2.1.2 Diagnosis

In view of the increased risk of HCC in cirrhosis, international guidelines recommend the surveillance of patients with cirrhosis with ultrasound scanning (EASL, 2018, Bruix et al., 2016). The aim of surveillance is the detection of HCC at an early stage, which is more likely to be amenable to curative treatment. The identification of a focal abnormality in the liver on ultrasound imaging requires further characterisation before a diagnosis of HCC can be established.

Historically, a targeted liver biopsy was performed in order to make a histopathological diagnosis of HCC. However, there are risks of complications with this approach; patients with cirrhosis are at an increased risk of bleeding due to deranged clotting and there is an associated risk of seeding of cancer from the needle track (Stigliano et al., 2007). In current clinical practice, a diagnosis of HCC in cirrhosis is more commonly made radiologically using established non-invasive criteria (Elsayes et al., 2019, EASL, 2018). Characteristic appearances on computed tomography (CT) or magnetic resonance imaging (MRI) scanning have become widely adopted for the diagnosis of HCC in the presence of underlying cirrhosis. A diagnosis is made by the identification of the early uptake of intravenous contrast by liver nodules in the arterial phase on CT/ MRI scanning and washout in the portal venous phase. The development of new blood vessels in HCC leads to this characteristic appearance, suggesting that cancers are more biologically advanced to be detectable radiologically.

2.1.3 Staging

For the purpose of national registration, the TNM staging system is used in the setting of malignancy to classify a cancer in terms of tumour size and local invasion (T), spread to lymph nodes (N) and metastatic spread (M) (Brierley et al., 2017). Although this classification exists for HCC (Table 1), it is not widely used clinically and does not appear in international guidelines.

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1a	Solitary tumour 2 cm or less in greatest dimension with or without vascular invasion
T1b	Solitary tumour more than 2 cm in greatest dimension without vascular invasion
T2	Solitary tumour with vascular invasion more than 2 cm dimension or multiple tumours, none more than 5 cm in greatest dimension
T3	Multiple tumours any more than 5 cm in greatest dimension
T4	Tumour(s) involving a major branch of the portal or hepatic vein with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder or with perforation of visceral peritoneum
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis - This includes metastasis to non-regional lymph nodes, including periaortic, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes.

Table 1. TNM Classification of liver tumours

The TNM classification is less useful for the assessment of prognosis in HCC because of the absence of information related to underlying cirrhosis severity and patient fitness; HCC is unlike other solid tumours because the majority of patients are at risk of both liver- and cancer-related mortality. Also, assessment of microvascular invasion can only be accurately assessed pathologically, either from resected surgical specimen or a biopsy (which is infrequently performed) (EASL, 2018).

The purpose of staging in HCC is to guide prognosis and treatment. The most widely-adopted staging system is the Barcelona Clinic Liver Cancer (BCLC) classification (Figure 2), which is outlined in the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the management of HCC (EASL, 2018). The advantage of this system over the TNM classification is that it also considers the severity of underlying cirrhosis and fitness of

the patient, using the Eastern Cooperative Oncology group (ECOG) performance status (Oken et al., 1982). This grades a patient's functional status from 0 (no symptoms) to 4 (bedbound). In addition to the cancer stage, these factors influence both treatment decisions and overall survival.

The BCLC staging system incorporates the Child Pugh classification of cirrhosis severity (Pugh et al., 1973). This well-established score incorporates blood test markers of liver function as well as complications relating to portal hypertension (Table 2 and Glossary). Portal hypertension arises when the pressure increases in the blood vessels returning to the liver from the gastrointestinal tract via the portal venous system. This occurs due to the presence of scarring in the liver and it can manifest in the development of enlarged veins (varices) in the oesophagus or stomach and the collection of fluid (ascites) in the abdomen. More advanced cirrhosis also affects the liver's synthesis of blood clotting factors and this can be measured using the international normalised ratio (INR). Patients are classified as Child Pugh A if the total score is 5-6 points, Child Pugh B for 7-9 points and Child Pugh C for 10-15 points. Increasing Child Pugh score is associated with increased cirrhosis-related mortality and morbidity.

Measure	**1 Point**	**2 Points**	**3 Points**
Total bilirubin, µmol/L	<34	34–50	>50
Serum albumin, g/L	>35	28–35	<28
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild to Moderate	Severe or Refractory
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

Table 2. Child Pugh scoring system for cirrhosis severity

The BCLC classification divides patients into 5 prognostic stages (0, A, B, C, D), and these serve as guide to recommended treatment allocation (Figure 2). Cancer stage is determined by the number and size of tumours ('nodules') in the liver, the spread of cancer beyond the liver into lymph nodes or other tissues and tumour growth into the main blood vessels ('portal invasion'). The BCLC system also represents a prognostic score and it has been widely used to stratify participants when comparing HCC treatments in clinical trials.

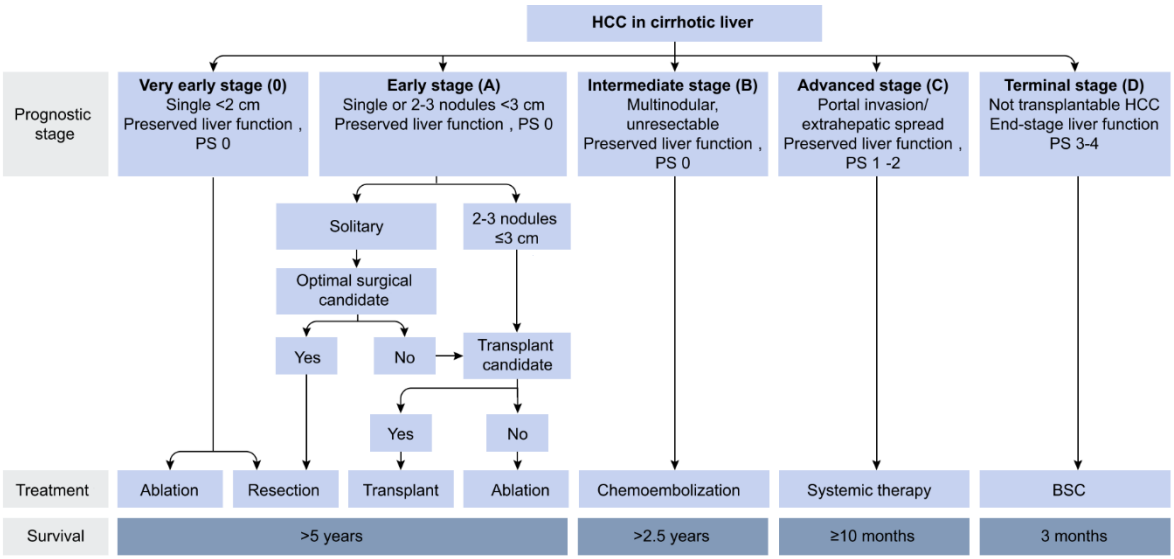

Figure 2. BCLC staging system with survival estimates: PS = performance status (EASL, 2018)

2.1.4 Treatment

The eligibility for different HCC treatments based on the BCLC classification takes into consideration several patient- and cancer-related factors. The HCC treatments that offer the best chance of a cure are the most invasive. Provision of these treatments may be limited by poor liver function due to underlying cirrhosis, or late presentation of advanced cancer in patients not known to have cirrhosis. The development of cirrhosis-related complications (such as portal hypertension) also directly affects the suitability of certain treatments (EASL, 2018).

2.1.4.1 Liver Resection

Liver resection is a surgical procedure, involving the excision of the HCC and surrounding liver tissue (hepatectomy). The presence of portal hypertension leads to the development of enlarged veins (varices) in the abdomen, which increases the risk of bleeding during surgery. Surgery also puts a large physiological stress on the liver; declining liver function in advanced cirrhosis increases the risk of liver failure post-operatively. Similarly, the resection of larger tumours causes greater disruption of underlying liver function. This can lead to features of liver failure (or decompensation), such as the development of ascites.

The assessment of an 'optimal surgical candidate' (Figure 2) for liver resection in the presence of cirrhosis is outlined in the EASL Guidelines and involves consideration of underlying liver function, the presence of portal hypertension, and the extent of hepatectomy (EASL, 2018). This is summarised in Figure 3, using an algorithm adapted from Citterio and colleagues to

assess the risk of liver decompensation after resection (Citterio et al., 2016). The Model for End-Stage Liver Disease (MELD) score is used to assess liver function in cirrhosis, using values for serum bilirubin, creatinine and INR (Malinchoc et al., 2000). The extent of hepatectomy is defined by the number of liver segments resected.

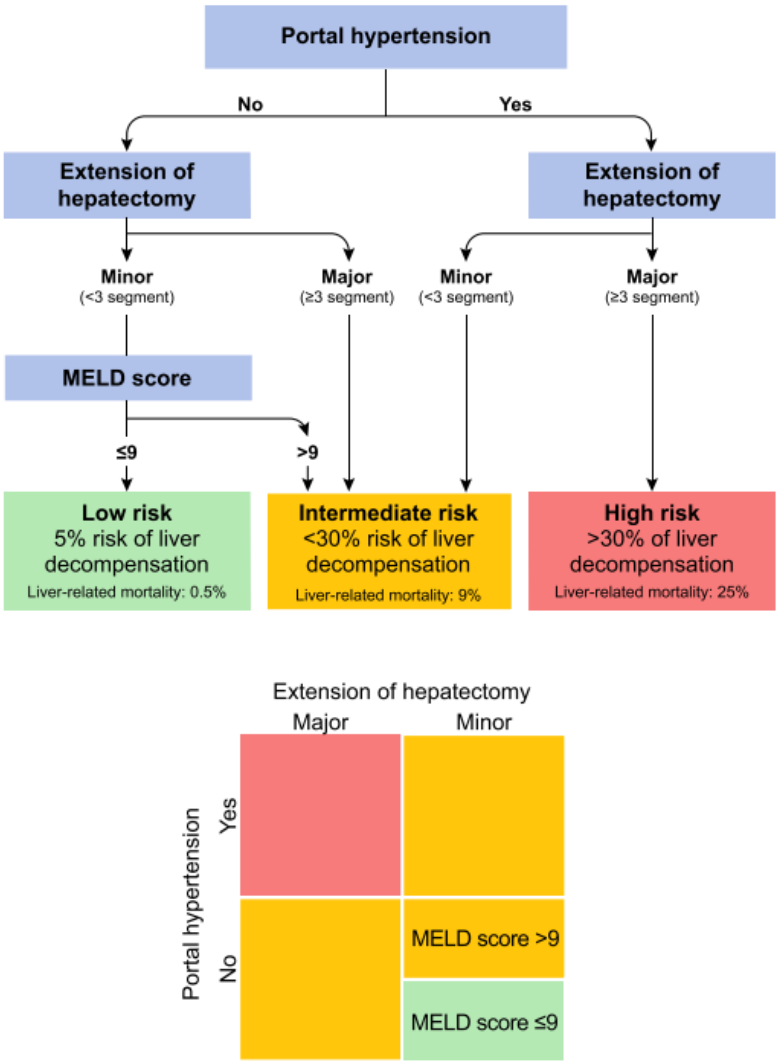

Figure 3. Assessment of the risk of liver decompensation after resection for HCC in cirrhosis, according to the presence of portal hypertension, the extent of the resection and MELD score (EASL, 2018).

Removal of an HCC with resection is considered curative. However, it requires physiological fitness and the increased risk of surgery associated with co-morbid conditions may preclude it as a treatment option for some patients. Following resection, not only is there a risk of cancer recurrence at the site of previous surgery, but also cirrhosis in the background liver presents a risk of new HCCs developing.

2.1.4.2 Liver Transplantation

Liver transplantation involves the removal of the whole liver (which may contain HCC) and replacement with a donor liver. Like resection, transplantation is recommended when the HCC is confined to the liver. However, since transplantation also cures the underlying cirrhosis, patients with more severe liver disease and portal hypertension may be eligible for this curative treatment. In the UK, there is a requirement for abstinence from alcohol for those with alcohol-related liver disease to be eligible for liver transplantation. This may limit transplant as a treatment option in the short term for those patients with advanced cirrhosis and HCC.

There are additional restrictions on the size and number of tumours and many health systems employ the Milan criteria, which require a single tumour ≤ 5 cm in size or ≤ 3 tumours each ≤ 3 cm in size, and no macrovascular invasion (Mazzaferro et al., 1996, Mazzaferro et al., 2009). Patients meeting these criteria have a significant survival advantage and less chance of cancer recurrence after liver transplantation.

Unlike resection, additional considerations in patient selection for transplantation include the availability and allocation of donor organs, which remains a scare resource. In most international health systems, prioritisation for liver transplantation is based on cirrhosis severity based on the MELD score, which reflects expected liver-related mortality. In recent years, the UK has adopted a similar cirrhosis severity score developed specifically for transplantation (the UKELD score (Barber et al., 2011). Since 2018, a transplant-benefit score, based on expected net life years gained from transplant has been adopted (Gimson, 2020).

2.1.4.3 Ablation

Tumour ablation involves several techniques that cause local destruction of liver cancer tissue using directed microwave or radio-frequency radiation, or thermal techniques. This causes a localised inflammatory reaction and the underlying liver function must be robust enough to withstand this. Ablation is considered the first-line therapy for very early HCCs. The technique is not suitable for larger tumours as it may precipitate liver decompensation and since the procedure also requires a general anaesthetic, it requires a degree of physiological reserve. Ablation is considered potentially curative, but like resection, there is a risk of new HCCs developing in the remaining liver (Doyle et al., 2019).

2.1.4.4 Trans-arterial chemoembolisation

Trans-arterial chemoembolisation (TACE) involves the insertion of tiny beads containing chemotherapy (most commonly doxorubicin) via the blood vessels supplying the liver, using guidewires under x-ray guidance (Llovet et al., 2002). The beads are deposited locally to block the blood vessels supplying the tumour and the procedure can be performed under local anaesthetic. This treatment can be used for larger tumours, which are unsuitable for ablation. In patients with declining performance status or advanced cirrhosis, the risks of TACE may outweigh the benefits. Like ablation and resection, the remaining liver must be robust enough for TACE and it can lead to liver decompensation.

Although not considered a curative treatment, it can slow the growth and progression of HCC. It may also be used to treat patients awaiting liver transplantation, in order to limit the growth of tumours to ensure they remain within the Milan criteria (Bruix et al., 2016).

2.1.4.5 Systemic Therapies

Sorafenib is an oral chemotherapy agent, which was the first drug to demonstrate a survival benefit in HCC (Llovet et al., 2008b). It is a multi-tyrosine kinase inhibitor and it can be used to slow the progression of HCC and may be used in metastatic disease. Preserved liver function is a prerequisite for treatment and advanced cirrhosis is a contraindication (EASL, 2018). Cirrhosis can affect the metabolism of chemotherapy drugs and increase the toxicity. Sorafenib may slow the progression of HCC and improve overall survival, but it is not a curative therapy.

Since 2017, new systemic therapies have emerged, including new tyrosine kinase inhibitors (eg. lenvatinib and regorafinib), monoclonal antibodies (eg. ramucirumab and bevacizumab), and immune checkpoint inhibitors (eg. pembrolizumab, nivolumab and atezolizumab) (Kudo, 2020). These newer therapies are better tolerated than sorafenib, and combination immunotherapy with atezolizumab plus bevacizumab increases overall survival compared with sorafenib (Finn et al., 2020). Atezolizumab selectively targets programmed-death ligand 1 (PD-L1), which reduces T-call suppression by the tumour. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF), which inhibits angiogenesis and tumour growth. These newer treatments were not available when the 2018 EASL guidelines were published.

2.1.4.6 Stereotactic Ablative Radiotherapy

Stereotactic ablative radiotherapy (SABR) is another HCC treatment that has emerged in recent years. This involves the precise delivery of high doses of radiotherapy and offers an alternative treatment modality when more invasive treatments are not possible, such as tumour involvement of a major blood vessel. The technique is associated with low levels of radiation-induced liver injury, given the targeted delivery (Shanker et al., 2021). SABR was also not widely available when the latest EASL guidelines were published.

2.2 Estimating Survival in Hepatocellular Carcinoma

2.2.1 International Guidelines

The EASL guidelines (EASL, 2018) provide broad estimates for survival within each BCLC stage following recommended treatment (Figure 2). Within each BCLC stage and treatment modality, there is a significant range in expected survival reflected by the heterogeneity of the patients. Very early (BCLC Stage 0) HCCs have the best prognosis, with 5-year survival greater than 70% after radiofrequency ablation (RFA) (Livraghi et al., 2008). A meta-analysis showed that 3-year survival for patients with single HCCs <3cm treated with RFA was 76% (Cucchetti et al., 2013). The EASL guidelines suggest that 5-year survival for BCLC Stage A HCCs is between 50-70% for transplant, resection and ablation, but acknowledge that these estimates are based on studies in highly selected candidates.

The previous EASL guidelines (EASL, 2012), suggested an estimated overall survival of 20 months for patients with BCLC Stage B treated with TACE, based on two clinical trials (Llovet et al., 2002, Lo et al., 2002). In the latest guidelines (EASL, 2018), a median survival of 40 months is reported based on studies involving well-selected candidates (Takayasu et al., 2012, Burrel et al., 2012). Reported survival following Sorafenib is based on the original clinical trials, demonstrating an overall survival of 10.7 months (Llovet et al., 2008a).

These estimates are based on outcomes in clinical trials but real-world survival estimates for different treatments are more limited (Sapisochin and Bruix, 2017, Vitale et al., 2017, Uhlig et al., 2018). Generalising clinical trial survival outcomes to estimate an individual's survival following cancer treatment can be challenging and real-world patient selection is likely to be more variable. However, in HCC, this is even more complicated due to the influence of liver-related mortality in the presence of advanced cirrhosis.

2.2.2 Competing Risk of Liver-related Mortality

Individuals who develop HCC in the setting of advanced cirrhosis are at risk of both cancer- and liver-related mortality. Even after potentially curative treatment for HCC, individuals with advanced cirrhosis may die as a result of liver failure (Cabibbo et al., 2017). In population-based studies, assessment of cirrhosis severity using the Child Pugh score is problematic due to the potentially subjective assessment of hepatic encephalopathy and ascites. The Albumin-Bilirubin (ALBI) grade (based on serum albumin and a logarithm of bilirubin concentrations)

provides an objective assessment of functional liver reserve in patients with HCC. Cirrhosis severity is categorised into three grades, ALBI 1, ALBI 2 and ALBI 3. This has been shown to predict overall survival following liver resection (Johnson et al., 2015) and subsequently radiofrequency ablation (Chen et al., 2019).

Survival analysis in HCC needs to account for liver-related deaths. One approach is to consider a multi-state disease model for cirrhosis (Jepsen et al., 2015). In this review, Jepsen discusses several different disease models which can be used to describe the clinical course of cirrhosis. A simple two-state disease model ('dead' or 'alive') can be used for standard survival analysis, but to analyse cause-specific mortality, additional disease states are needed (eg. 'death from cirrhosis' or 'death from HCC'). This approach facilitates 'competing risk' analysis and requires the use of different survival models in order to study clinical outcomes. The key difference in this approach is that when an individual experiences one outcome (eg. 'death from cirrhosis'), they are no longer at risk of experiencing the competing outcome (eg. 'death from HCC').

Another model proposed by Jepsen includes a disease state transition from 'compensated' to 'decompensated' cirrhosis. This represents disease progression and the development of liver failure (Figure *4*). Differentiating between compensated and decompensated cirrhosis is helpful when studying HCC because this is a key determinant of treatment eligibility. It can be challenging in clinical practice to differentiate between liver- and cancer-related mortality, but this model includes death with or without prior decompensation, which is an approximation for liver-related death.

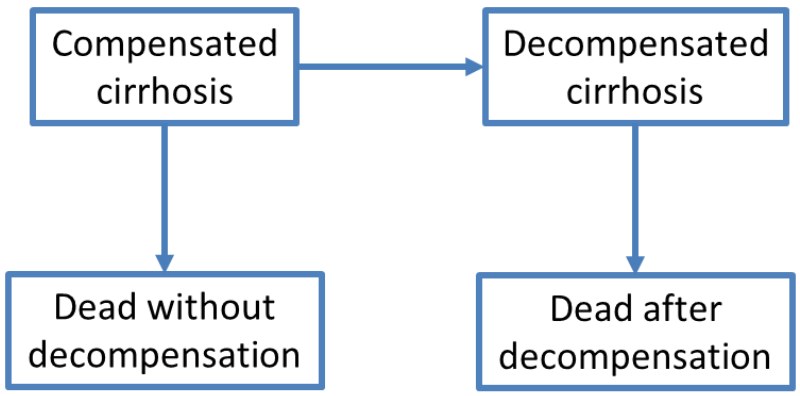

Figure 4. Multi-state disease model for cirrhosis.(Jepsen et al., 2015)

Decompensated cirrhosis is characterised by the development of hepatic encephalopathy, ascites and bleeding from varices. These clinical features represent advanced cirrhosis and liver failure. Not only does hepatic decompensation represent a life-threatening complication of cirrhosis, it precludes most HCC treatments apart from liver transplantation.

Patients with cirrhosis and HCC are at 'competing' risks of different clinical outcomes based on this multi-state disease model. The cumulative risk (or cumulative incidence) is the probability of experiencing an outcome event within a specified time period. Statistical methods including the Aalen-Johansen estimator can be used to calculate the cumulative incidence function and competing risk (Aalen and Johansen, 1978, Andersen and Keiding, 2002). Cause-specific cumulative incidence can also be modelled using parametric survival models (Lambert et al., 2017).

2.2.3 Using National Cancer Registries to Investigate Clinical Outcomes

Population-based cancer registry data has been used to describe cancer incidence and mortality in different cancers, in addition to regional variation in clinical outcomes (Coleman et al., 2011). In HCC, registry data has been used to assess regional variation in clinical outcomes and treatment allocation in France (Goutté et al., 2017).

In England, the National Cancer Registration and Analysis Service (NCRAS) dataset contains reliable information about all patients diagnosed with cancer, including HCC. This dataset contains patient-level information, including demographic details and details about tumour characteristics (Henson et al., 2020). However, the registry does not contain information about the presence of underlying cirrhosis. Also, blood tests are not included in the dataset, so cirrhosis severity cannot be calculated using the MELD score, Child Pugh score or ALBI score.

Individual patient data in the NCRAS dataset can be linked to Hospital Episode Statistics (HES) data. This contains inpatient diagnosis and procedure codes within the ICD10 (International Classification of Diseases, tenth revision) and OPCS4 (Office of Population, Censuses and Surveys' Classification, fourth revision) coding systems. Whenever a patient is admitted to an NHS hospital in England, diagnosis and treatment codes are generated in the HES dataset. These linked datasets have been used extensively in population-based cancer outcomes research (Downing et al., 2017, Tataru et al., 2018). The HES database can be used to adjust for baseline factors in survival analyses, including medical co-morbidities and levels of deprivation. Cirrhosis-related diagnosis and treatment codes present in the inpatient record can be analysed in order to characterise underlying cirrhosis in these patients. The NCRAS and HES datasets were previously collated and maintained within Public Health England (PHE) until 2021, when the responsibility for their management was transferred to NHS Digital.

2.3 Characterising Liver Disease in Electronic Health Records

2.3.1 Identification of Cirrhosis

In clinical practice, cirrhosis is determined histologically by liver biopsy, or radiologically via CT or MRI scanning, ultrasound and transient elastography. Many patients are diagnosed clinically after exhibiting characteristic signs, which often relate to portal hypertensive complications such as the development of ascites and oesophageal varices. These conditions relate to more advanced cirrhosis and they commonly result in inpatient care, leading to the recording of diagnostic codes in the electronic health record (EHR), such as HES in England.

Previous international studies have described methods to use EHRs to identify cirrhosis and different definitions of cirrhosis have been used (Ratib et al., 2017). Some investigators (Jepsen et al., 2010, Kramer et al., 2008) used cirrhosis diagnosis codes only, whereas others also included codes relating to varices (Nehra et al., 2013, Lapointe-Shaw et al., 2018). In England, Ratib and colleagues used a combination of the inpatient HES database and General Practice (GP) records to identify cirrhosis and its complications (Ratib et al., 2014a), including procedure codes for the treatment of oesophageal varices from endoscopy reports (which are recorded as inpatient admissions in HES).

Utilising GP records enabled the estimation of the prevalence of cirrhosis in the general UK population (Ratib et al., 2014a). Limiting analysis to inpatient records is appropriate when studying HCC because the prevalence of cirrhosis is much higher than in the general population and there is an increased likelihood that cirrhosis diagnosis codes are captured by inpatient EHRs.

2.3.2 Classification of Cirrhosis Severity

In the absence of blood tests for the calculation of Child Pugh or Model for End Stage Liver Disease (MELD) scores, cirrhosis severity can be classified using the Baveno consensus (de Franchis, 2005). This stratifies cirrhosis severity based on the presence of portal hypertensive complications (varices and ascites). In a previous analysis (D'Amico et al., 2006), pooled data from two natural history studies in cirrhosis were used to identify four clinical states in cirrhosis, represented by the Baveno stages. For each state, the annual mortality rate was calculated and there was a significant increase in mortality with increasing Baveno stage (Figure 5).

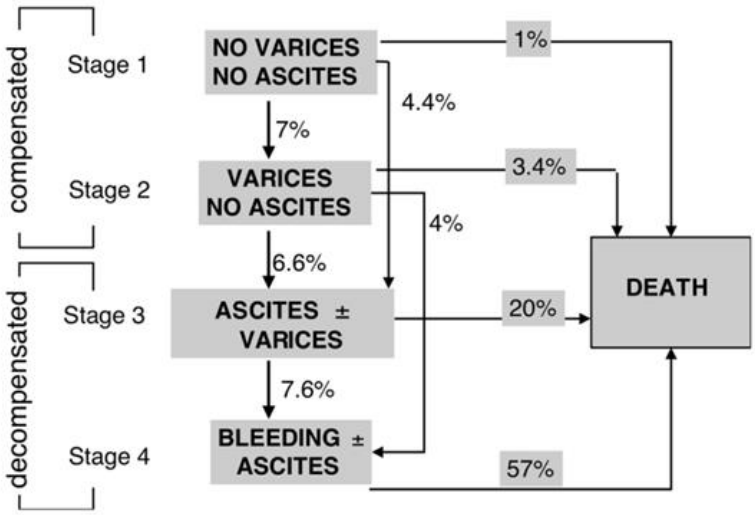

Figure 5. Transition probabilities between cirrhosis stages with annual mortality rate and stage transition rates (D'Amico et al., 2006)

The Baveno classification has been used to grade cirrhosis severity in population-based studies (Ratib et al., 2014a). Ascites and varices represent complications of advanced cirrhosis and they often result in hospital admission. These events are captured in the inpatient HES and can be used to estimate cirrhosis severity.

3 Aims and Objectives

This project utilises inpatient electronic records and national cancer registration data in order to assess clinical outcomes in HCC in England at a population level. The following research questions will be addressed in the analyses:

1. Can routinely collected administrative data in electronic health records be used to identify the presence, severity and aetiology of underling cirrhosis in patients with HCC?

2. Which baseline factors determine treatment allocation and overall survival in HCC?

3. What is the overall survival and rate of cause-specific mortality following non-curative HCC treatments?

4. How do baseline factors influence overall survival and cause-specific mortality following potentially curative non-transplant HCC treatments, including liver resection and ablation?

5. What is the nature of regional variation in baseline factors and treatment allocation in HCC in England?

4 General Methods

This project exploits routinely collected data held in linked national health records to assess clinical outcomes in HCC in England at a population level. The NCRAS dataset contains patient-level information, which includes age, sex, ethnicity and cancer stage. In addition to population-based health research, the NCRAS dataset is used in public health, performance evaluation and commissioning. This includes assessment of cancer survival statistics and service evaluation across the NHS.

The data collected by NCRAS comes from multiple sources, including cancer multidisciplinary team meetings, pathology reports, treatment records and hospital Patient Administration Records (Henson et al., 2020). Specialist cancer registration officers in NCRAS review the extracted data from several sources. Automated and manual data quality controls are undertaken throughout the registration process to ensure completeness, validity and comparability. These data are tested against Office for National Statistics data regarding cancer incidence and survival, and serious errors have been recorded in less than 0.1% of cancer registrations (ONS, 2016).

In order to assess clinical outcomes in HCC, additional baseline factors need to be considered, including the presence and severity of cirrhosis at HCC diagnosis, and the aetiology of underlying liver disease and medical co-morbidities. These factors are not routinely collected in the NCRAS dataset, so further analysis was required in order to derive these data from linked inpatient Hospital Episode Statistics (HES) records. When patients are admitted to hospital, diagnosis and treatment codes are generated during their inpatient episode. NHS trusts employ clinical coders to review case notes after hospital admission episodes; diagnosis and procedure codes are recorded and submitted to the national HES database. These administrative codes are used to reimburse hospitals for the care delivered, but they are also used for commissioning, service evaluation and research. Algorithms based on these codes were developed in order to determine the presence, severity and aetiology of cirrhosis from their inpatient electronic health records.

Firstly, algorithms were developed to characterise cirrhosis and validated by comparison with case note review. The *Validation Study* addressed Objective 1 and involved optimisation of algorithms at a single NHS centre, which was then externally validated using another cohort at a different NHS centre. Secondly, these algorithms were applied to the national linked

NCRAS and HES datasets, in order to assess the impact of cirrhosis in patients diagnosed with HCC. The *National Study* addressed Objectives 2-5.

4.1 Ethical Approval

The retrospective *Validation Study* comprised an assessment of the accuracy of clinical coding of inpatient episodes for service evaluation and therefore did not require formal ethical approval. Permission was granted from the Caldicott Guardian for sharing of routinely collected anonymised data between NHS sites. The *National Study* involving PHE data was approved by the NCRAS project review panel and ethical approval was obtained from the North West – Liverpool Central Research Ethics Committee (Project ID 225039).

4.2 Data Usage Statement

This work involves patient-level information collected by the NHS that has either been provided by, or derived from, patients as part of their care and support. The national data are collated, maintained, and quality assured by NCRAS, which was part of Public Health England (PHE) for the duration of the study. Access to the data was facilitated by the PHE Office for Data Release. The management of NCRAS is now overseen by NHS Digital.

5 Validation Study - Patients and Methods

This study involved the development and optimisation of a set of algorithms, based on inpatient HES records, to determine the presence and severity of cirrhosis in patients diagnosed with HCC. In addition, algorithms were developed to determine the aetiology of the underlying liver disease, and to estimate the cause-specific mortality following a diagnosis of HCC. This section outlines the methods employed to test different versions of the algorithms in a validation cohort, using case note review as the gold standard.

5.1 Identification of Cohort

All patients with a new diagnosis of HCC between 1st January 2007 and 31st December 2016 and resident in the secondary care catchment area of Leeds Teaching Hospitals NHS Trust (LTHT) were identified. This 10-year time interval was chosen to provide a large cohort for robust analysis and because there were no significant changes to HCC treatments over this period. Since LTHT is a tertiary centre for HCC referrals, many patients were resident elsewhere and were admitted to LTHT only for their HCC diagnosis and treatment. Therefore, inpatient admissions related to cirrhosis may not be captured by their LTHT inpatient record, so these individuals were not included. Only patients registered in a Clinical Commissioning Group (CCG) local to LTHT were included.

The HCC cohort was identified from the records from the weekly hepatobiliary cancer multidisciplinary team (MDT) meeting at LTHT. Live minutes are taken at this meeting and the reporting of all cases to the national cancer registry within NCRAS is mandatory. A confirmed diagnosis of HCC had usually been made radiologically, using the EASL non-invasive criteria (EASL, 2012). In some cases, a confirmatory targeted liver biopsy had been performed.

5.2 Linkage to Local Electronic Health Records

The local HES records for patients in the HCC cohort were searched to identify all inpatient episodes containing ICD10 diagnosis and OPCS4 treatment codes related to cirrhosis up to death or the censor date in October 2017. The time interval from the HCC diagnosis date to the start date of the episode containing the relevant codes was also recorded. Additionally, ICD10 codes relating to specific liver disease aetiologies were identified, as well as coexisting

medical conditions in order to calculate the Charlson comorbidity index (Charlson et al., 1987). This index has been used extensively in both clinical trials and population studies in order to stratify individuals based on the severity of co-existent medical conditions. It includes a range of pathologies, which are graded according to the annual mortality risk.

Episodes occurring up to five years before HCC diagnosis were included. Since the EHR relies on inpatient codes, if a patient had not had a cirrhosis-related hospital admission prior to the HCC diagnosis, they may not be identified as having cirrhosis. Additional episodes occurring after HCC diagnosis were subsequently included in order to improve the sensitivity of the algorithm, by maximising the number of available inpatient codes. This method assumes that if an individual has subsequent inpatient cirrhosis codes, it is likely that they had cirrhosis at the time of HCC diagnosis given the established risk of the development of HCC in cirrhosis. Similarly, it is expected that by including additional codes, more information about cirrhosis aetiology and other medical comorbidities could be obtained.

5.3 Algorithm Development

5.3.1 Identification of Cirrhosis

Different versions of an Identification Algorithm to determine the presence of cirrhosis from the EHRs were tested. The algorithm developed by Ratib and colleagues (Ratib et al., 2014b) utilised both ICD10 codes for cirrhosis and varices, as well as OPCS4 codes for the treatment of varices. Version 1 of the algorithm was based on this. Patients were identified as having cirrhosis if they had inpatient episodes containing the diagnosis and treatment codes for varices outlined in Table 3. Initially, only codes from episodes occurring before the HCC diagnosis date were included in the detection of cirrhosis. Subsequently, the time interval of included codes was increased incrementally from 0 to 3 years after HCC diagnosis in order to assess the effect on the accuracy of the algorithm.

Cirrhosis Diagnoses (ICD10):	**Codes**
Cirrhosis	K70.3, K71.7, K72.1, K74.4, K74.5, K74.6, K76.6, K72.1, K72.9
Alcoholic hepatic failure	K70.4
Alcoholic liver disease	K70.9
Ascites	R18.X
Varices	I85.9, I86.4, I98.2
Bleeding varices	I85.0, I98.3
Cirrhosis Treatments (OPCS4):	
Treatment of ascites	T46.1, T46.2, J06.1, J06.2
Treatment of varices	G10.4, G10.8, G10.9, G14.4, G17.4, G43.4, G43.7, J06.1, J06.2
Gastrointestinal Haemorrhage (ICD10):	
Gastrointestinal haemorrhage	K92.0, K92.1, K92.2

Table 3. Treatment and procedure codes included in the algorithm to determine cirrhosis status and cirrhosis severity.

In Version 2 of the algorithm, a broader definition of cirrhosis was used, as previously proposed by Leon and colleagues (Leon and McCambridge, 2006). This included codes for “alcoholic liver disease” (ALD, K70.9) and “alcoholic hepatic failure” (AHF, K70.4). Version 3 of the algorithm also included codes for ascites and paracentesis. This assessed the accuracy of including ascites as a cirrhosis-defining condition in the presence of HCC. Previously, investigators have excluded ascites in the definition of cirrhosis because this may be due to malignancy in the absence of cirrhosis in a general population (Ratib et al., 2014b, Nehra et al., 2013). In order to account for this, Version 4 only included ascites-related codes occurring before the HCC diagnosis date.

The different versions of the algorithm were tested against the clinical records in order to determine the presence of cirrhosis at the time of HCC diagnosis. Case note review was undertaken between April and August 2018 and data abstracted by experienced hepatology clinical fellows working in the field for at least 2 years. Approximately 10% were double extracted and disagreements were resolved by consensus review. Cirrhosis was identified based on explicit mention of the term “cirrhosis” in the clinical record or MDT minutes, or evidence of portal hypertension on radiological imaging or endoscopy reports. Additionally, patients were classified as having cirrhosis if this was mentioned explicitly on a histopathology report from a liver biopsy or resection specimen, or a consistent reading on transient elastography. The case note review was used as the gold standard for testing different

versions of the algorithm to classify cirrhosis status. For comparison, previously published algorithms (Kramer et al., 2008, Jepsen et al., 2010, Nehra et al., 2013, Ratib et al., 2014b) were also tested in the same cohort.

5.3.2 Classification of Cirrhosis Severity

The Baveno IV consensus (de Franchis, 2005) was used to classify cirrhosis severity. Compensated cirrhosis was defined by Baveno stage 1 (no varices or ascites) and stage 2 (non-bleeding varices). Decompensated cirrhosis was defined as Baveno stages 3 (ascites, with or without varices) and stage 4 (variceal haemorrhage, with or without ascites). For each hospital episode, the Baveno stage and compensation status were calculated using the ICD10 and OPCS4 codes for varices and ascites in Table *3*.

In order to identify variceal haemorrhage, three versions of the Severity Algorithm were tested. Version A of the Severity Algorithm (based on that developed by Goldberg and colleagues (Goldberg et al., 2012)) contains diagnosis codes for variceal bleeding and Version B (based on the algorithm developed by Ratib and colleagues (Ratib et al., 2014b)) also includes procedure codes for variceal treatment. Finally, Severity Algorithm Version C limits the inclusion of variceal treatment codes to those occurring in an inpatient episode with a concurrent ICD10 code for gastrointestinal haemorrhage (K92.0, K92.1, and K92.2). This is to separate variceal haemorrhage and the prophylactic treatment of non-bleeding varices. Cirrhosis severity was determined by the highest Baveno stage occurring in the five years prior to the HCC diagnosis. In order to increase accuracy, the timeframe for additional episodes included in this assessment were increased incrementally up to four months after the HCC diagnosis.

Clinical case notes were reviewed to determine the true Baveno stage at the time of HCC diagnosis. Baveno stage 2 was determined by the presence of non-bleeding varices explicitly mentioned in endoscopy reports or the clinical records. Portal hypertensive gastropathy was excluded. Baveno stage 3 was identified by explicit mention of ascites in the clinical record, requiring paracentesis or diuretic therapy, but a small volume of ascites only identified in radiology report was excluded. Baveno stage 4 was identified by explicit mention of variceal haemorrhage in endoscopy reports or the clinical records. At the same time, blood tests taken at the time of HCC diagnosis were also recorded for calculation of Child Pugh and MELD scores, as well as ALBI grade for comparison.

5.3.3 Identification of Primary Liver Disease Aetiology

The EHR was searched to identify diagnosis codes occurring during inpatient episodes that relate to the aetiology of the underlying liver disease (Table 4). In a similar manner to previous population-based studies (Roberts et al., 2004, Tovikkai et al., 2014), the primary liver disease category was assigned to each patient. In the Aetiology Algorithm Version α, aetiology was assigned in a hierarchical manner to hepatitis C, primary sclerosing cholangitis (PSC), hepatitis B, primary biliary cholangitis (PBC), autoimmune hepatitis, haemochromatosis, alcohol, non-alcoholic fatty liver disease (NAFLD), and 'other' (including unknown aetiology and the absence of underlying liver disease). Since the diagnosis of "fatty liver" (K76.0) is not specific to NAFLD, patients were assigned to this aetiology if no other aetiology codes were present. Given the association of NAFLD with diabetes mellitus (Fleming et al., 2008b), Aetiology Algorithm Version β contained additional diabetes codes (ICD10 E10 and E11) to define NAFLD in otherwise unassigned cirrhotic patients. There is no specific ICD10 code for PSC, only a code for "cholangitis" (K83.0), which may occur even in the absence of liver disease. Since PSC is a relatively rare condition, patients were classified as having PSC only if they had no other liver disease aetiology.

The effect of an incremental increase in length of follow-up from the date of HCC diagnosis until three years after was assessed, as previously. The clinical records were reviewed to identify the true aetiology and comparison made with that determined by the Aetiology Algorithm.

Aetiology Diagnoses (ICD10):	
Hepatitis C	B18.2
Primary Sclerosing Cholangitis	K83.0
Hepatitis B	B18.0, B18.1
Primary Biliary Cholangitis	K74.3
Autoimmune Hepatitis	K73.0, K73.1, K73.2, K73.8, K73.9, K75.4
Haemochromatosis	E83.1
Alcohol	F10, K70
Non-alcoholic Fatty Liver Disease	K76.0

Table 4. Diagnosis codes included in the algorithm for determining the aetiology of the underlying liver disease

5.3.4 Estimation of Cause-specific Mortality

The inpatient records for each patient were analysed from the date of HCC diagnosis until death or censor date in October 2017. Using the optimised Severity Algorithm, each inpatient episode was assigned a Baveno stage. Clinical events related to decompensated cirrhosis were identified by the emergence of an episode labelled as Baveno 3 or 4. The time interval from HCC diagnosis to a decompensation event was recorded.

At 25-day intervals, the number of patients in each disease state represented in the multi-state disease model (Figure *4*) were calculated. This time interval enabled the calculation of a stepwise linear representation of the cumulative incidence function, displaying the proportion of patients in each disease state over time (Jepsen et al., 2015). At the end of five years of follow-up, the proportion of patients who had died with and without prior decompensation was then determined. The identification of clinical events relating to decompensated cirrhosis serves as an approximation for liver-related mortality in a competing risk analysis.

The total number of patients alive and dead at the end of five years was recorded. Among patients who had died, the case notes were reviewed to examine signs of liver failure and decompensated cirrhosis prior to death. The accuracy of this Cause-specific Mortality Algorithm could then be assessed.

5.3.5 Statistical Analysis

Data management and statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, TX). The sensitivity and specificity of the Identification Algorithm and Severity Algorithm to classify cirrhosis and decompensation status were calculated from 2 x 2 contingency tables, using the case note review as the gold standard test. The sensitivity is the proportion of patients with cirrhosis who are correctly identified from the Identification Algorithm; the specificity is proportion of patients without cirrhosis who are correctly identified as not having cirrhosis by the Identification Algorithm. For identification of Baveno stage and underlying aetiology, agreement between the Severity and Aetiology Algorithms and the clinical records were assessed using the kappa statistic. This is used to assess observer agreement for categorical variables and allows for agreement occurring by chance (Landis and Koch, 1977, Cohen, 1960). Agreement is considered ‘moderate’ if K is 0.41-0.60, ‘substantial’ if K is 0.61-0.80 and ‘almost perfect’ if K is 0.81-1.00.

5.4 External Validation

External validation of the algorithms was undertaken using an equivalent cohort of patients diagnosed with HCC between 1st January 2013 and 31st December 2014 and local to Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT). The same local EHR search was undertaken, and the optimised algorithms were tested. An additional case note review was undertaken using the same criteria in order to test the sensitivity and specificity of the Identification, Severity and Aetiology Algorithms. To assess liver disease aetiology, Aetiology Algorithm Version α was validated using the RLBUHT cohort, but since diabetes codes had not been collected, external validation of Aetiology Algorithm Version β was not undertaken.

6 Validation Study - Results and Analysis

This section outlines the results of different versions of the Identification, Severity, Aetiology and Cause-specific Mortality Algorithms when compared to the validation cohort at LTHT. The effect of changing component codes and variables within the algorithms are presented, along with the performance of the optimised version of each algorithm.

6.1 Cohort Description

During the 10-year study period, 289 patients (median age 69, 79% male) were identified with a new diagnosis of HCC from the LTHT MDT records (Table 5). Case note review identified 191 (66%) of these patients as having underlying cirrhosis and 50 (26%) of these had experienced previous decompensated cirrhosis before HCC diagnosis. A further 15 patients had evidence of advanced fibrosis on biopsy or resection specimen, but a clinical or histological diagnosis of cirrhosis had not been made explicitly.

Patient sub-groups with fewer than 10 individuals are suppressed in Table 5 to avoid potential identification of patients. Patients in age groups 50-59 and 60-69 were more likely to have cirrhosis, whereas those aged more than 80 were less likely to have a cirrhosis diagnosis. There was no association between ethnicity and the presence of cirrhosis. Alcohol and hepatitis C were associated with a greater proportion of patients with a cirrhosis diagnosis.

Within the cohort, 249 (86.2%) had an inpatient hospital record at LTHT. Among the remaining 40 patients without an inpatient EHR, 12 (30%) had cirrhosis according to case note review. The median age of patients with underlying cirrhosis was 67 compared with 73 in the non-cirrhotic group ($P < 0.001$). In the external validation cohort at RLBUHT, 50 patients who met the inclusion criteria were assessed (median age 71, 82% male), 31 (62%) of whom had cirrhosis and 11 (35%) had previous decompensation.

		Total N (%)	No Cirrhosis N (%)	Cirrhosis N (%)	P-value
Characteristic:		289	98 (33.9%)	191 (66.1%)	
Age Group	<50	22 (7.6)	10 (10.2)	12 (6.3)	0.26
	50-59	49 (17.0)	10 (10.2)	39 (20.4)	0.04
	60-69	81 (28.0)	18 (18.4)	63 (33.0)	0.03
	70-79	92 (31.8)	31 (31.6)	61 (31.9)	0.95
	80+	45 (15.6)	29 (29.6)	16 (8.4)	<0.001
Sex	Male	228 (78.0)	76 (77.6)	152 (79.6)	0.83
	Female	61 (21.1)	22 (22.4)	39 (20.4)	0.73
Ethnicity	White	252 (87.1)	87 (88.8)	165 (86.4)	0.86
	Black	12 (4.2)	--	--	0.58
	South Asian	12 (4.2)	--	--	0.21
	Chinese	--	--	--	0.15
	Other Ethnic Group	--	--	--	0.70
	Not Stated	--	--	--	0.22
Aetiology	HCV	44 (15.2)	--	>10	<0.001
	HBV	17 (5.9)	--	--	0.69
	PBC	--	--	--	0.06
	AIH	--	--	--	0.21
	Haemochromatosis	19 (6.6)	--	--	0.48
	Alcohol	68 (23.5)	--	>10	<0.001
	NAFLD	43 (14.9)	13 (13.3)	30 (15.7)	0.60
	Other/ unknown	88 (30.4)	67 (68.4)	21 (11.0)	<0.001
MELD	<10			90 (47.1)	
	10-14			73 (38.2)	
	15-19			21 (11.0)	
	20+			7 (3.7)	
Child Pugh	A			131 (68.6)	
	B			44 (23.0)	
	C			16 (8.4)	
Previous Decompensation	Ascites			37 (19.3)	
	Variceal bleed			13 (6.8)	

Table 5. Baseline characteristics of the LTHT cohort. HCV = hepatitis C, HBV = hepatitis B, PBC = primary biliary cholangitis, AIH = autoimmune hepatitis, NAFLD = non-alcoholic fatty liver disease. Groups with small number of patients (<10) were suppressed to avoid identification (marked "–").

6.2 Identification of Cirrhosis

Limiting the inclusion of inpatient episodes to those occurring prior to the HCC diagnosis results in a sensitivity of less than 50% for cirrhosis detection (Table 6). When additional episodes occurring up to three years after HCC diagnosis are included, the sensitivity increases to greater than 80% for all versions of the algorithm, without significant loss of specificity.

The component codes in the different versions of the Identification Algorithm (Versions 1-4) are summarised in the column headings of Table 6. Algorithm Version 1 did not used ascites as a cirrhosis-defining condition and did not include ALD and AHF in the definition of cirrhosis. Including ALD and AHF in the definition (Version 2) increased the sensitivity of cirrhosis detection. Sensitivity was increased further by the inclusion of ascites (Version 3). However, including ascites as a cirrhosis-defining condition reduces the specificity of Version 3, but when this is limited to episodes that occurred before the HCC diagnosis, the specificity improves in Version 4 of the Identification Algorithm.

The performance characteristics of the optimised Identification Algorithm (Version 4, including episodes up to three years post HCC diagnosis) are summarised in Table 7. The sensitivity is 86% (95% confidence interval, CI: 82%-90%) and the specificity is 98% (95% CI: 96%-100%), with a positive predictive value (PPV) of 99% and negative predictive value (NPV) of 79% (95% CI: 74%-83%). When Version 4 of the Identification Algorithm was applied to the RLBUHT cohort with three years of follow-up, the sensitivity was 79% and specificity was 100%. The optimised algorithm performed better than published algorithms for cirrhosis detection when they were applied to the LTHT cohort (Table 8).

	Algorithm Version 1 No Ascites - ALD - AHF				Algorithm Version 2 No Ascites + ALD + AHF				Algorithm Version 3 Ascites + ALD + AHF				Algorithm Version 4 Pre-HCC Ascites + ALD + AHF			
Time post HCC Diagnosis / days	Sens	95% CI	Spec	95% CI	Sens	95% CI	Spec	95% CI	Sens	95% CI	Spec	95% CI	Sens	95% CI	Spec	95% CI
0	0.45	0.39-0.51	1.00	1.00-1.00	0.47	0.41-0.52	1.00	1.00-1.00	0.49	0.43-0.54	1.00	1.00-1.00	0.49	0.43-0.54	1.00	1.00-1.00
30	0.52	0.47-0.58	1.00	1.00-1.00	0.54	0.49-0.60	1.00	1.00-1.00	0.57	0.51-0.63	0.99	0.98-1.00	0.57	0.51-0.63	1.00	1.00-1.00
60	0.60	0.55-0.66	1.00	1.00-1.00	0.64	0.58-0.69	1.00	1.00-1.00	0.66	0.61-0.72	0.98	0.96-1.00	0.66	0.61-0.71	1.00	1.00-1.00
90	0.66	0.61-0.72	1.00	1.00-1.00	0.70	0.65-0.75	1.00	1.00-1.00	0.73	0.68-0.78	0.97	0.95-0.99	0.72	0.67-0.77	1.00	1.00-1.00
120	0.69	0.64-0.74	1.00	1.00-1.00	0.73	0.68-0.78	1.00	1.00-1.00	0.75	0.70-0.80	0.97	0.95-0.99	0.75	0.70-0.80	1.00	1.00-1.00
150	0.72	0.67-0.77	1.00	1.00-1.00	0.76	0.72-0.81	1.00	1.00-1.00	0.79	0.74-0.83	0.96	0.94-0.98	0.78	0.73-0.83	1.00	1.00-1.00
180	0.73	0.68-0.78	0.99	0.98-1.00	0.77	0.73-0.82	0.99	0.98-1.00	0.80	0.75-0.84	0.95	0.92-0.97	0.79	0.74-0.84	0.99	0.98-1.00
365	0.76	0.71-0.81	0.99	0.98-1.00	0.81	0.76-0.85	0.99	0.98-1.00	0.83	0.78-0.87	0.94	0.91-0.97	0.82	0.78-0.87	0.99	0.98-1.00
730	0.80	0.76-0.85	0.98	0.96-1.00	0.84	0.80-0.88	0.98	0.96-1.00	0.87	0.83-0.91	0.95	0.93-0.98	0.85	0.81-0.89	0.98	0.96-1.00
1095	0.81	0.77-0.86	0.98	0.96-1.00	0.85	0.81-0.89	0.98	0.96-1.00	0.88	0.84-0.92	0.92	0.89-0.95	0.86	0.82-0.90	0.98	0.96-1.00
Total Follow-up	0.81	0.77-0.86	0.98	0.96-1.00	0.85	0.81-0.89	0.98	0.96-1.00	0.88	0.84-0.92	0.92	0.89-0.95	0.86	0.82-0.90	0.98	0.96-1.00

Table 6. Performance of different versions of the cirrhosis status algorithm. Sens = sensitivity, Spec = specificity, ALD = Alcoholic Liver Disease, AHF = Alcoholic Hepatic Failure. CI = confidence interval.

		True Status		
		Non-cirrhotic	Cirrhotic	Total
Cirrhosis Algorithm	Negative for Cirrhosis	96	26	122
	Positive for Cirrhosis	2	165	167
	Total	98	191	289

Table 7. 2 x 2 Contingency table for cirrhosis identification by optimised Identification Algorithm Version 4 with three years of follow-up.

Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)
Kramer *et al.*	72	100	100
Jepsen *et al.*	71	100	100
Nehra *et al.*	80	98	99
Ratib *et al.*	80	98	99
Identification Algorithm Version 4	86	98	99

Table 8. Performance of different published algorithms for cirrhosis detection in the LTHT cohort of patients, compared with optimised Identification Algorithm Version 4. PPV = positive predictive value

6.3 Classification of Cirrhosis Severity

The performance of the three versions of the Severity Algorithm for determining Baveno stage are summarised in Table 9. The component codes in the different versions of the Severity Algorithm (Versions A, B and C) are summarised in the column headings. Compared with Version A, the agreement between the Severity Algorithm and the case note review was slightly worse using Version B (which classifies the treatment of varices as Baveno stage 4). The corresponding sensitivity for detecting decompensation (defined by Baveno stage 3 and 4) was increased in Version B, but the specificity was reduced (Table 10). Agreement between the Severity Algorithm and the clinical record was optimised in Version C, when variceal haemorrhage was defined by treatment for varices and a concurrent gastrointestinal bleeding code. Including codes from episodes occurring up to 60 days after HCC diagnosis improved the agreement further.

	Algorithm Version A Variceal bleeding codes		**Algorithm Version B** Variceal bleeding codes or treatment codes		**Algorithm Version C** Variceal bleeding codes or treatment codes + UGIB	
Time after HCC Diagnosis/ days	Correct Baveno Stage (%)	K-statistic	Correct Baveno Stage (%)	K-statistic	Correct Baveno Stage (%)	K-statistic
0	80	0.67	80	0.67	81	0.70
30	82	0.70	81	0.70	83	0.73
60	83	0.71	82	0.71	84	0.74
90	81	0.69	80	0.69	82	0.71
120	81	0.69	80	0.69	82	0.71

Table 9. Performance of different versions of the Severity Algorithm for identifying the correct Baveno stage. UGIB = Upper gastrointestinal bleeding, K = kappa statistic.

	Algorithm Version A Variceal bleeding codes				**Algorithm Version B** Variceal bleeding codes or treatment codes				**Algorithm Version C** Variceal bleeding codes or treatment codes + UGIB			
Time after HCC Diagnosis / days	Sens	95% CI	Spec	95% CI	Sens	95% CI	Spec	95% CI	Sens	95% CI	Spec	95% CI
0	0.74	0.69-0.79	0.98	0.97-1.00	0.78	0.73-0.83	0.96	0.94-0.98	0.76	0.71-0.81	0.98	0.96-1.00
30	0.76	0.71-0.81	0.99	0.97-1.00	0.80	0.75-0.85	0.82	0.78-0.86	0.78	0.73-0.83	0.98	0.96-1.00
60	0.78	0.73-0.83	0.99	0.97-1.00	0.82	0.76-0.86	0.96	0.94-0.98	0.80	0.75-0.85	0.98	0.96-1.00
90	0.78	0.73-0.83	0.98	0.96-1.00	0.82	0.76-0.86	0.95	0.93-0.98	0.80	0.75-0.85	0.97	0.95-0.99
120	0.78	0.73-0.83	0.98	0.96-1.00	0.82	0.76-0.86	0.95	0.93-0.98	0.80	0.75-0.85	0.97	0.95-0.99

Table 10. Performance of different versions of the Severity Algorithm for predicting decompensation. Sens = sensitivity, spec = specificity, UGIB = Upper gastrointestinal bleeding.

The performance characteristics of the component codes are summarised in Table 11 and Table 12; in Severity Algorithm Version B, the sensitivity for detecting bleeding varices is increased, but the PPV and overall agreement with the Baveno stage is reduced due to the misclassification of non-bleeding varices. The sensitivity for detecting ascites is increased when both diagnosis and paracentesis procedure codes are included.

	Algorithm Version A Variceal bleeding codes					**Algorithm Version B** Variceal bleeding codes or treatment codes					**Algorithm Version C** Variceal bleeding codes or treatment codes + UGIB				
Clinical Condition	Sens	95% CI	Spec	95% CI	PPV	Sens	95% CI	Spec	95% CI	PPV (%)	Sens	95% CI	Spec	95% CI	PPV
Varices	0.76	0.71-0.81	1.00	0.99-1.00	92	0.62	0.56-0.67	1.00	0.99-1.00	90	0.76	0.71-0.81	1.00	0.99-1.00	96
Bleeding Varices	0.31	0.25-0.36	1.00	1.00-1.00	80	0.92	0.89-0.95	0.96	0.94-0.99	54	0.62	0.56-0.67	0.99	0.97-1.00	67

Table 11. Performance of different versions of the Severity Algorithm at 60 days post-HCC diagnosis for detecting varices and bleeding varices. Sens = sensitivity, spec = specificity, CI = confidence interval, PPV = positive predictive value, UGIB – upper-gastrointestinal bleed.

	Ascites detection using Algorithm Version C (ICD10 codes and OPCS4 codes)					**Ascites detection using ICD10 code R18.X only**				
Clinical Condition	Sens	95% CI	Spec	95% CI	PPV (%)	Sens	95% CI	Spec	95% CI	PPV (%)
Ascites	0.73	0.68-0.78	0.98	0.96-0.99	73	0.57	0.51-0.62	0.98	0.97-1.00	84

Table 12. Performance of ICD10 code R18.X for detection of ascites compared with the optimised Severity Algorithm Version C that includes additional OPCS4 codes for paracentesis (T46.1 and T46.2). Sens = sensitivity, spec = specificity, CI = confidence interval, PPV = positive predictive value.

Using Severity Algorithm Version C with a 60-day interval, agreement between the clinical record and calculated Baveno stage was 84% in the LTHT cohort, with a kappa coefficient of 0.74 (95% CI: 71%-77%). This represents ‘substantial’ correlation. The sensitivity for detecting prior decompensation was 80% (95% CI: 75%-85%) and specificity was 98% (95% CI: 96%-100%), with a PPV of 89% (95% CI: 85% - 93%) and NPV of 96% (95% CI: 94%-98%). When applied to the RLBUHT cohort, the agreement of Baveno stage with the clinical record was 81% (kappa 0.70). The sensitivity for detecting decompensation was 73% and specificity was 90%.

Using Identification Algorithm Version 4, 167 patients in the LTHT cohort were identified as having cirrhosis. Among these, 45 (27%) had prior decompensation according to Severity Algorithm Version C and 122 (73%) had no previous decompensation. From the case note review of patients with previous decompensation, and using blood test results taken at the time of HCC diagnosis, 13/45 (29%) were Child Pugh A, 19 (42%) were Child Pugh B and 13 (29%) were Child Pugh C. The median MELD score was 13 (interquartile range, IQR 10-17). Among those coded without prior decompensation, 98/122 (80%) were Child Pugh A, 22/122 (18%) were Child Pugh B and 2/122 (2%) were Child Pugh C. The median MELD score was 9 (IQR 7-11). Comparison between the compensation status derived from the Severity Algorithm and the MELD and Child Pugh scores is summarised in Figure 6.

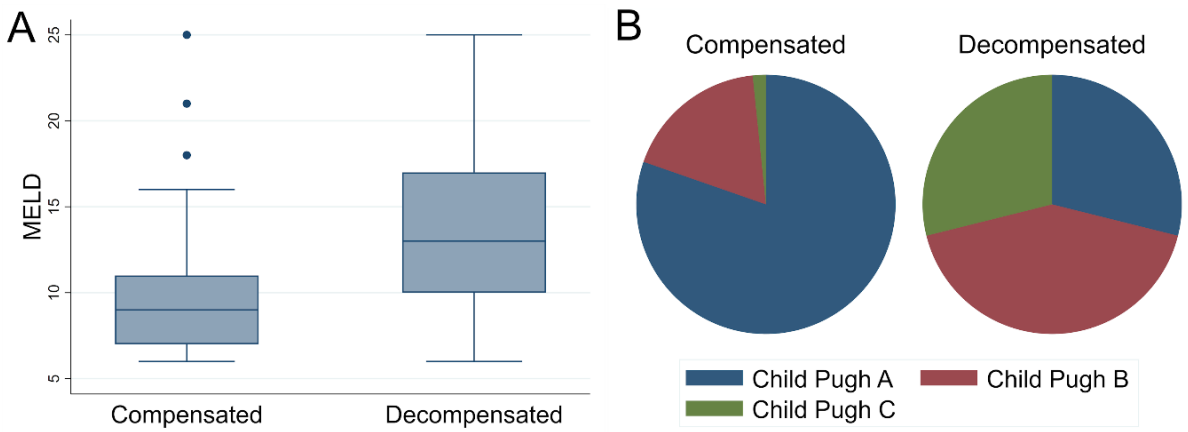

Figure 6. Box-and-whisker plots showing the distribution of MELD scores (A) and pie graphs showing the distribution of Child Pugh class (B) within compensated and decompensated cirrhosis groups determined by Severity Algorithm Version C.

Patients identified with decompensated cirrhosis also had a higher ALBI score at the time of HCC diagnosis compared with those with compensated cirrhosis (Figure 7). Among the patients identified with prior decompensation, 1/45 (2%) were ALBI grade 1, 27/45 (60%) were ABLI grade 2 and 17/45 (38%) were ALBI grade 3. Among those who did not have previous codes relating to decompensation, 45/122 (37%) were ALBI grade 1, 68/122 (56%) were ALBI grade 2 and 9/122 (7%) were ALBI grade 3.

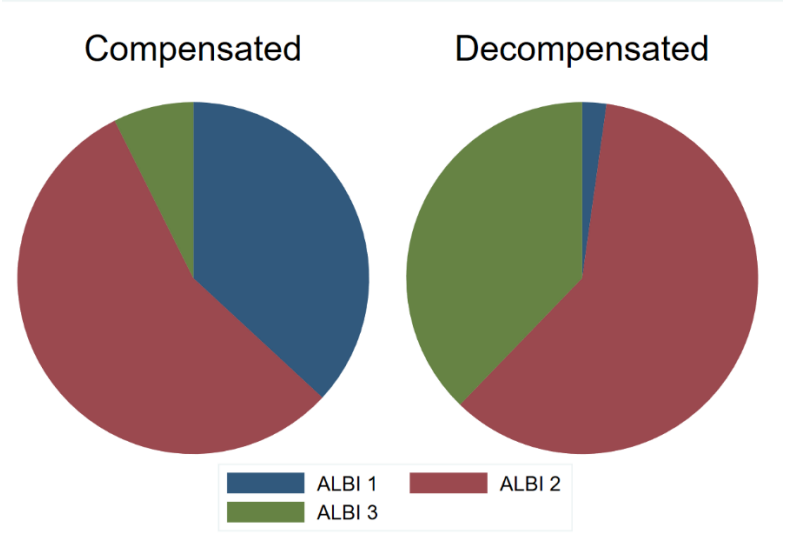

Figure 7. Distribution of ALBI grades within compensated and decompensated cirrhosis groups determined by the Severity Algorithm.

6.4 Identification of Primary Liver Disease Aetiology

In the LTHT cohort, increasing the length of follow-up after HCC diagnosis for the inclusion of episodes containing diagnosis codes increases the diagnostic accuracy of both versions of the Aetiology Algorithm for determining the underlying liver disease (Table 1). The overall agreement between the predicted and true aetiology is increased in Aetiology Algorithm Version β and there is only a slight improvement when codes from greater than one year are included.

	Aetiology Algorithm Version α		**Aetiology Algorithm Version β**	
Time after HCC Diagnosis/ days	Correct Aetiology (%)	K-statistic	Correct Aetiology (%)	K-statistic
0	55	0.40	60	0.47
30	59	0.45	63	0.52
60	63	0.51	66	0.57
90	67	0.57	71	0.62
120	69	0.59	72	0.64
180	70	0.60	73	0.65
365	71	0.63	74	0.67
730	73	0.65	75	0.68
1095	73	0.66	75	0.68

Table 13. Performance of two versions of the Aetiology Algorithm with increasing length of follow-up for inclusion of inpatient episode codes. K = kappa statistic

Aetiology Algorithm Version α with 1 year of follow-up identified the correct aetiology in 71% of patients (95% CI: 66%-76%). The kappa statistic for overall agreement was 0.63 (95% CI: 0.61-0.70). Table 14 shows the agreement between true aetiology and that predicted by Aetiology Algorithm Version α for each. It was lowest for NAFLD cirrhosis; among 43 patients, only 5 (12%) were diagnosed with this aetiology from their inpatient codes.

		Aetiology Predicted by Aetiology Algorithm Version α								Total	Correct Aetiology (%)
		Other	HCV	HBV	PBC	AIH	Haemo	Alcohol	NAFLD		
True Aetiology	Other	77	0	0	0	0	1	8	2	88	88
	HCV	5	37	0	0	0	0	2	0	44	84
	HBV	4	2	10	0	0	0	1	0	17	59
	PBC	0	0	0	7	0	0	0	0	7	100
	AIH	1	0	0	0	1	0	1	0	3	33
	Haemo	3	0	0	0	0	15	1	0	19	79
	Alcohol	11	0	0	0	0	1	54	2	68	79
	NAFLD	34	1	0	0	1	2	0	5	43	12
	Total	135	40	10	7	2	19	67	9	289	71

Table 14. Agreement (shaded cells) between primary liver disease aetiology according to Aetiology Algorithm Version α with one year of follow-up and true aetiology according to clinical records. HCV = hepatitis C, HBV = hepatitis B, PBC = primary biliary cholangitis, AIH = autoimmune hepatitis, Haemo = haemochromatosis, NAFLD = non-alcoholic fatty liver disease.

Aetiology Algorithm Version β identified the correct aetiology in 74% of patients (95% CI: 69%-79%). The kappa statistic for overall agreement was 0.67 (95% CI: 0.65-0.68). There was an improvement in the detection of NAFLD; among 43 patients, 20 (47%) were diagnosed from their inpatient codes (Table 15).

		Aetiology Predicted by Aetiology Algorithm Version β								Total	Correct Aetiology (%)
		Other	HCV	HBV	PBC	AIH	Haemo	Alcohol	NAFLD		
True Aetiology	Other	71	0	0	0	0	1	8	8	88	81
	HCV	5	37	0	0	0	0	2	0	44	84
	HBV	4	2	10	0	0	0	1	0	17	59
	PBC	0	0	0	7	0	0	0	0	7	100
	AIH	1	0	0	0	1	0	1	0	3	33
	Haemo	3	0	0	0	0	15	1	0	19	79
	Alcohol	9	0	0	0	0	1	54	4	68	79
	NAFLD	19	1	0	0	1	2	0	20	43	47
	Total	112	40	10	7	2	19	67	32	289	74

Table 15. Agreement (shaded cells) between primary liver disease aetiology according to Aetiology Algorithm Version β with one year of follow-up and true aetiology according to clinical records. HCV = hepatitis C, HBV = hepatitis B, PBC = primary biliary cholangitis, AIH = autoimmune hepatitis, Haemo = haemochomatosis, NAFLD = non-alcoholic fatty liver disease

When applied to patients identified with cirrhosis only, Aetiology Algorithm Version β with one year of follow-up identifies the correct aetiology in 79% of patients (95% CI: 72%-85%), with a kappa statistic of 0.73 (95% CI: 0.66-0.79). Among 24 patients with NAFLD cirrhosis, the correct aetiology was identified in 19 cases (79%). Among 14 patients with cirrhosis classified as 'other' (including unknown aetiology) according to the clinical records, six of these were identified as having NAFLD based on the presence of diabetes and four had inpatient diagnosis codes related to alcohol in the past.

When applied to the RLBUHT cohort, Aetiology Algorithm Version α with one year of follow-up identified the correct aetiology in 68% of patients (95% CI: 54%-80%), with a kappa of 0.60 (95% CI: 0.53-0.67). Among patients identified with cirrhosis, Aetiology Algorithm Version α with one year of follow-up identified the correct aetiology in 81% of patients (95% CI: 62%-91%), with a kappa of 0.60 (95% CI: 0.53-0.67).

6.5 Estimation of Cause-specific Mortality

Using the Identification Algorithm Version 4, 167 patients were identified as having cirrhosis and 45 of these (27%) had previous decompensation at the time of HCC diagnosis (using Severity Algorithm Version C). Changes in the proportion of patients in each disease state (specified as either alive or dead, with or without prior decompensation) over time is represented graphically in Figure 8. This represents the cumulative incidence function, namely the probability of an individual experiencing one of the outcomes within this period of follow-up.

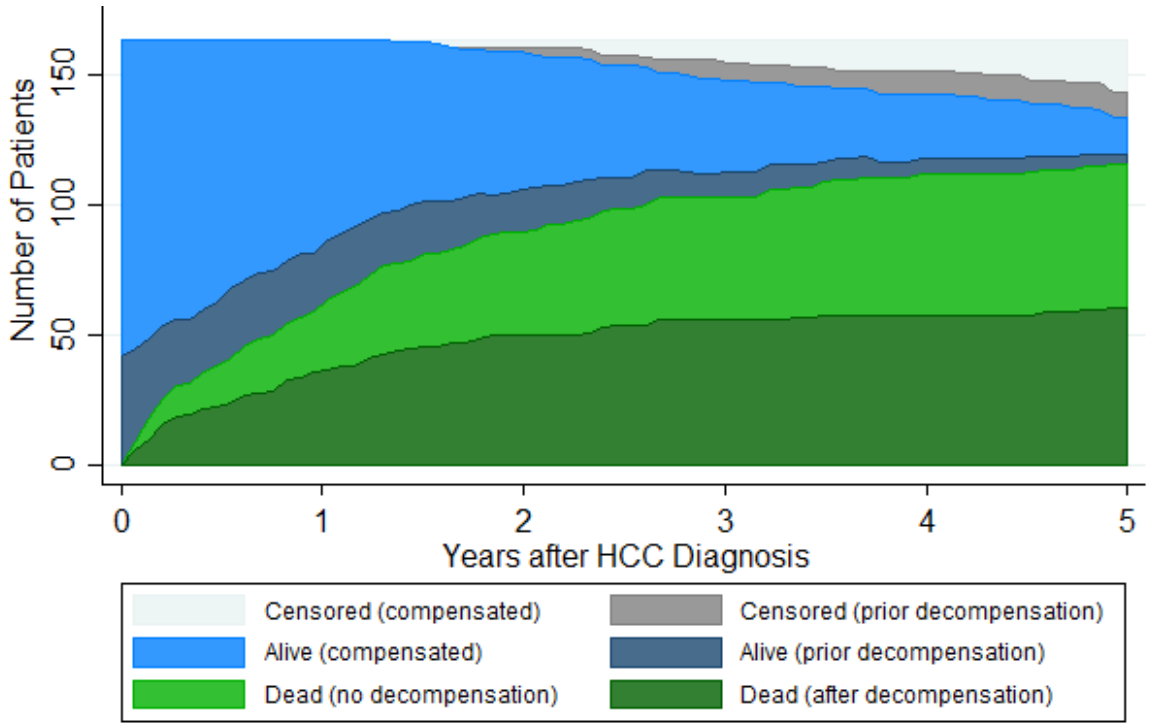

Figure 8. Representation of the cumulative incidence function demonstrating cirrhosis state occupancy following HCC diagnosis

At 5 years post-HCC diagnosis, 116 patients (71%) had died, 18 patients were alive, and 30 cases had been censored due to end of follow-up. Among the patients who had died, 55 (47%) had no decompensation events prior to death and, according to the model, these cases are classified as cancer-related mortality. From case note review, five of these patients had signs of liver failure at death. The remaining 61 patients (53%) had an inpatient admission related to decompensated cirrhosis prior to death (liver-related mortality) and from the case note review, 45 of these had clinical signs of liver failure at death.

The presence of clinical signs of liver failure prior to death in the case notes was used as an approximation of liver-related mortality in this model. Using case note review as the gold standard to define the 'true status', the performance characteristics of the Cause-specific Mortality Algorithm are summarised in Table 16. The sensitivity for identifying a liver-related death is 90% (95% CI: 85%-95%) and the specificity is 76% (95% CI: 68%-84%), with a PPV of 74% and NPV of 91%.

		True Status		
		Liver Failure before Death	No Liver Failure before Death	Total
Cause-specific Mortality Algorithm	Liver-related	45	16	61
	Cancer-related	5	50	55
	Total	50	66	116

Table 16. 2x2 contingency table for the identification of liver failure prior to death using the Cause-specific Mortality Algorithm

6.6 Summary of the Optimised Algorithm Performance

These algorithms have been developed to identify and characterise cirrhosis for use in the linked NCRAS-HES dataset. The performance characteristics of the final algorithms are summarised in Table 17, which demonstrates the validity of their use in the *National Study.*

	Sensitivity	Specificity	PPV	NPV
Identification of Cirrhosis (Identification Algorithm Version 4)	86%	98%	99%	79%
Identification of Decompensation (Severity Algorithm Version C)	80%	98%	89%	96%
Identification of liver-related mortality (Cause-specific Mortality Algorithm)	90%	76%	74%	91%

Table 17. Summary of the performance characteristics of the optimised algorithms for detecting the presence and severity of cirrhosis from inpatient electronic health records in patients with HCC. PPV – positive predictive value, NPV – negative predictive value

6.7 Discussion of Results

This Validation Study has demonstrated the reliability of an algorithm to identify and assess the severity of cirrhosis in patients diagnosed with HCC from inpatient HES records. It has also demonstrated the utility of this method to identify underlying liver disease aetiology and to estimate cause-specific mortality by identifying the presence of decompensated cirrhosis.

6.7.1 Identification of Cirrhosis

A broad definition of cirrhosis improved the sensitivity of cirrhosis detection without significant loss of specificity. Similarly, performance was improved by an incremental increase in the 'time window' after HCC diagnosis, during which time more inpatient diagnosis codes were included. The case note review validated the assumption that the presence of cirrhosis codes in the EHR after the HCC diagnosis date suggests that cirrhosis was present at the time of HCC diagnosis. Since this method relies on inpatient EHRs, patients require a hospital admission for cirrhosis-related codes to be generated.

Identification Algorithm Version 4 used the presence of ascites as a cirrhosis-defining diagnosis only if this occurred before the HCC diagnosis date. This version showed superior cirrhosis detection compared with published algorithms in the HCC validation cohort, without loss of specificity (Table 8). It is assumed that if ascites occurred before an HCC diagnosis then it is more likely to be related to decompensated cirrhosis, whereas in the presence of HCC this could represent malignant ascites.

A limitation of this algorithm is the uncertainty over the patients who do not have an inpatient EHR. In this validation study, there were 40/289 (13.8%) such patients in whom additional analysis about underlying liver disease was not possible. By limiting to inpatient episodes, the algorithm did not identify 12/191 (6.3%) of patients known to have cirrhosis from their case notes. Patients who survive longer after their HCC diagnosis may be more likely to be identified with cirrhosis from the algorithm if cirrhosis-related codes are generated in the future – this may introduce a 'survivor bias' in the identification of cirrhosis (van Walraven et al., 2004).

6.7.2 Classification of Cirrhosis Severity

Severity Algorithm Version C has been shown to assess cirrhosis severity accurately using the Baveno classification. This simple model relies on distinct clinical events, such as the presence of oesophageal varices and ascites. Since these events are clinically significant, the expectation is that they are accurately coded within the EHR. Since day-case endoscopy is included in the inpatient EHR, it is expected that a high proportion of patients with varices will be accurately captured by the algorithm. The accuracy of the algorithm was improved by distinguishing between prophylactic banding of oesophageal varices and variceal haemorrhage.

The Baveno classification has been shown to predict overall survival in cirrhosis (D'Amico et al., 2006). This study also demonstrates the correlation with cirrhosis severity based on MELD and Child Pugh scores. Differences occur because these scores use contemporary blood results, whereas the Baveno score relies on historical complications of cirrhosis. However, for assessing underlying liver disease severity, the Baveno classification provides as assessment of the significance of underlying portal hypertension, which is critically important when determining HCC treatment allocation. It also correlates with the ALBI grade, which has been validated for use in HCC for estimating underlying cirrhosis severity (Johnson et al., 2015).

6.7.3 Identification of Primary Liver Disease Aetiology

The accuracy of the identification of liver disease aetiology is dependent on the detail of the clinical coding in the EHR. The Aetiology Algorithm was optimised by including additional episodes following the HCC diagnosis date. However, the accuracy varied according to the underlying diagnosis, especially in the presence of non-alcoholic fatty liver disease (NAFLD). At the time of this study, there was no specific diagnosis code within ICD10 for this condition apart from ‘fatty liver’, which may also be associated with other aetiologies. The accuracy of the algorithm was improved when cirrhosis in the presence of diabetes (but no other identified risk factors) was classified as NAFLD.

Using a hierarchy of aetiologies simplifies the analysis, but in reality, it is likely that patients have additional co-factors (such as alcohol). This validation study did not include any patients with PSC and small numbers for hepatitis B, haemochromatosis, AIH and PBC. The accuracy of these diagnoses from this validation is therefore limited. Since there is no specific ICD10 code for PSC (it can only be identified as K83.0 ‘cholangitis’), this diagnosis was removed

from future analyses in the *National Study*. If a patient had a previous diagnosis of cholangitis due to gallstones, this would be misinterpreted as underlying PSC. There was a large proportion of patients with unknown (or 'other') aetiology. This method does not distinguish between an unclassified underlying liver aetiology and the development of HCC in a normal liver.

6.7.4 Estimation of Cause-specific Mortality

The competing risk of liver- and cancer-related mortality has been estimated using the presence and absence of decompensated cirrhosis in the multi-state disease model. Even in clinical practice, it can be challenging to determine cause-specific mortality. This simplified model utilises the presence of hepatic decompensation prior to death to approximate liver-related mortality. Cancer-related mortality is approximated by the absence of liver decompensation.

The case note review shows comparable rates of decompensation prior to death in those patients identified by the Cause-specific Mortality Algorithm. The occurrence of liver decompensation is a clinically important outcome for patients who may experience distressing symptoms that frequently necessitate inpatient admission. Decompensation is also a key determinant in the assessment of fitness for further HCC treatments. Although this model is only an approximation of cause-specific mortality, it provides a clinically relevant description of outcomes and a framework for interpreting competing risk in HCC.

7 National Study - Patients and Methods

This study involves the identification and analysis of a national cohort of patients diagnosed with HCC in England over a 10-year period. This cohort was derived from the linked NCRAS and HES datasets and patient characteristics were described using the algorithms developed in the *Validation Study.* This section describes the methods used to address Objectives 2-5, to understand the clinical outcomes for patients who received different treatments for HCC across different regions in England.

7.1 Description of NCRAS Dataset

7.1.1 Identification of National HCC Cohort

7.1.1.1 Public Health England Data Request

This project was undertaken in partnership with HCC-UK and NCRAS, which received funding from the British Association for the Study of the Liver (BASL). Dr Anya Burton, the PHE analyst who prepared the HCC cohort, was funded by BASL. The case definition for HCC within the dataset was agreed by consensus opinion within the HCC-UK/ NCRAS/ BASL partnership. The project proposal was approved by the NCRAS review panel (see Appendix), which authorised the use of PHE data for these analyses.

An application was made to the Office for Data Release (ODR) at Public Health England to obtain an extract comprising all incident cases of HCC within the NCRAS dataset between 1st January 2007 and 31st December 2016. HCC was defined by ICD10 code C22.0 (liver cell carcinoma) and the morphology code M8170 (hepatocellular carcinoma). Exclusion criteria included patients under the age of 20, those lost to follow-up and unknown vital status.

The linked NCRAS and HES datasets contain demographic information and tumour characteristics, as well as diagnosis and procedure codes from inpatient hospital episodes. A bespoke extract of the linked HES dataset was obtained, containing inpatient hospital episodes from 5 years before HCC diagnosis until death or censor date in March 2018. Surgical and loco-regional HCC treatments require an inpatient admission; therefore procedure codes are generated in HES and are captured in this extract. Additionally, outpatient treatment with oral chemotherapy agent Sorafenib is captured in the Systemic Anti-

Cancer Therapy Data Set (SACT). The data items contained within the extract are summarised in Table 18.

Data Item	Description
Pseudo-anonymised Patient ID	Anonymised identifier for each patient
Age at Diagnosis	Age at HCC diagnosis (in 5-year age bands)
Sex	Sex
Ethnic group	Ethnic group
Vital status	Alive/ dead status at censoring date in March 2018
Survival Interval	Interval (in days) from HCC diagnosis date until death or end of follow-up
Year of diagnosis	Year of HCC diagnosis
Geographical area	Geographical location of patient residence, including Cancer Alliance region and Sustainability and Transformation Partnership (STP)
Index of Multiple Deprivation (IMD)	Income domain of IMD quintile
Cancer stage	Registered TNM stage at diagnosis from the registry
Episode ID	Inpatient hospital episode identifier
Diagnosis Code and Interval to Episode ID	ICD10 codes relating to cirrhosis or medical co-morbidities for characterising patients with HCC. The time interval (in days) is from HCC diagnosis date until the start of the inpatient episode containing that code [this is a negative number if episode occurred before HCC diagnosis date]
Procedure Code and Interval	OPCS4 codes relating to cirrhosis complications and HCC treatments. The time interval (in days) is from HCC diagnosis date until the procedure date [this is a negative number if episode occurred before HCC diagnosis date]
Sorafenib therapy and Interval	Time interval (in days) from HCC diagnosis date until the start of Sorafenib treatment
Site of Treatment	NHS Trust in which treatment procedure took place
Death Certification	ICD10 codes in the registered cause of death, as well as specified ‘underlying cause of death’

Table 18. Summary of the data items requested from PHE for the HCC cohort

The data was obtained in 'long' format from PHE; each row contained the patient pseudo-identifier, along with an ICD 10 diagnosis code (or OPCS4 procedure code), with the associated hospital episode identifier. The additional data items in Table 18 were included as columns for each individual. These data were curated by Dr Robert Driver in order to obtain the baseline characteristics and facilitate the subsequent analyses.

7.1.1.2 Information Security

The cohort identification and data linkage was undertaken within PHE. Each participant was assigned an anonymous identifier and further steps were taken to minimise disclosure risk. This included the avoidance of dates of birth or death – instead age was given in 5-year age bands. Similarly, specific dates of inpatient admissions and treatment dates were not included; instead, the time interval from HCC diagnosis date was provided.

The data was transferred securely and held within a Virtual Research Environment (VRE) in the ISO27001 compliant Integrated Research Campus in the Leeds Institute for Data Analytics. All analysis was undertaken within the VRE and the results verified by a third party prior to release, in order to ensure that there was no risk of disclosure of patient-identifiable data. Groups containing small numbers were suppressed to minimise disclosure risk.

7.1.2 Identification of Baseline Characteristics from Linked Dataset

The bespoke data extract was analysed further in order to determine the baseline characteristics of the HCC cohort. The following methods were used to describe the baseline factors:

7.1.2.1 Age and Sex

In order to minimise disclosure risk, 5-year age bands at date of HCC diagnosis were used instead of date of birth. The frequency and distribution of ages at HCC diagnosis for males and females were described using histograms.

7.1.2.2 Ethnicity

Ethnic group is assigned to each inpatient episode in the HES dataset. Patients self-assign ethnicity, but there are limitations due to missing data and the recording of multiple ethnicities

for individual patients. Different strategies to account for this have been described (Downing et al., 2011). In this cohort, the most common known ethnic group was assigned to each patient. In the event of ties, the most recent ethnic group was used.

7.1.2.3 Cancer Stage

The cancer registry records the 'best' cancer stage at diagnosis, derived from the TNM stage (Brierley et al., 2017). The cancer stage group is graded from I to IV and relates to both the size of the primary tumour and the presence of nodal and metastatic disease (Table 19). An 'unknown' cancer stage was recorded for those individuals with missing data about cancer stage.

Stage Group	T Stage	N Stage	M Stage
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Table 19. Cancer stage group based on TNM classification used in 'best' cancer stage at diagnosis.

7.1.2.4 Index of Multiple Deprivation

Using the income domain of the index of multiple deprivation (IMD), each patient was assigned a quintile based on their geographical location of residence (Ministry of Housing Communities and Local Government, 2015) ; Quintile 1 was the least deprived group and Quintile 5 the most deprived.

7.1.2.5 Medical Comorbidities

Coexisting medical conditions present at the time of HCC diagnosis were assessed using ICD10 diagnosis codes from the inpatient HES record. The Charlson comorbidity index (Charlson et al., 1987) was determined using the presence of specific ICD10 codes found in inpatient episodes in the preceding five years before HCC diagnosis (Thygesen et al., 2011).

For the purpose of this project, the Charlson index was modified to reflect the cohort population. Assessment of the presence of underlying liver disease and its severity are included in the Baveno classification algorithm, so liver disease was removed from the co-morbidity calculation. Similarly, since all patients have HCC, only contributions from metastatic disease or another coexisting cancer present at HCC diagnosis are included in the calculation of the Charlson index. The diagnosis codes included in the calculation are detailed in Table 20.

Comorbidity Diagnosis	**ICD10 codes**
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Peptic Ulcer disease	K22.1; K25-K28
Diabetes mellitus	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Diabetes mellitus with chronic complications	E10.2-E10.8
Hemiplegia	G81; G82
Moderate/severe renal disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Leukaemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Metastatic solid tumor	C76-C80
AIDS-defining illness	B21-B24

Table 20. Diagnosis codes included in the calculation of the Charlson co-morbidity index.

7.1.2.6 Underlying Liver Disease

The optimised algorithms from the validation study were applied to the national cohort. The presence of cirrhosis was determined using Identification Algorithm Version 4, using HES episodes from 5 years before and 3 years after HCC diagnosis. The Baveno stage at HCC diagnosis and derived decompensation status were assessed using Severity Algorithm Version C, using HES episodes from 5 years before and 3 months after HCC diagnosis.
The aetiology of underlying liver disease was established using Aetiology Algorithm β, using HES episodes from 5 years before and one year after HCC diagnosis. The aetiologies were ascribed in the same hierarchy described previously to determine the primary liver disease. The presence of alcohol component codes in patients identified with all other aetiologies was also analysed to identify alcohol as a co-factor in other primary liver diseases.

7.1.2.7 Statistical Analysis

The associations between baseline factors were investigated by cross-tabulation and significance testing was undertaken using Pearson's χ^2 test (Pearson, 1900). The significance of associations between covariates was assessed using Pearson residuals; namely the individual χ^2 contribution of each cell in the cross-tabulation (Goodman and Kruskal, 1954).

7.1.3 Identification of HCC Treatments from the Linked Datasets

Procedure codes relating to HCC treatments were included in the inpatient HES extract, with the associated time interval from HCC diagnosis (Table 21). Ablative therapies encompassed radiofrequency ablation, microwave ablation, percutaneous ethanol injection (PEI) and electroporation. The additional data extract from the SACT data set was used to identify patients who received Sorafenib and the time interval from the HCC diagnosis date. The inclusion of these treatments is limited since SACT only contains records from 2014.

HCC Treatments (OPCS4)	OPCS4 Codes
Liver transplant	J01.1, J01.2, J01.3, J01.5, J01.8, J01.9
Liver resection	J02.1, J02.2, J02.3, J02.4, J02.6, J02.7, J02.8, J02.9, J03.1, J03.5, J03.8, J03.9
Ablation	J08.3, J08.8, J08.8, J08.9, J03.2, J03.3, J03.4, J12.4, J12.5, J12.7, J12.8, Y13.7, J12.6, J12.8, Y12.3
Trans-arterial chemoembolisation (TACE)	J10.1, J10.3, J10.8, J10.9

Table 21. Procedure codes used to identify HCC treatments.

7.2 Assessment of Treatment Allocation

In order to investigate the association of baseline factors and geographical location with primary HCC treatment allocation, the most definitive treatment was identified for every patient. Each individual's primary treatment allocation was categorised in a hierarchical manner from liver transplant, liver resection, ablation, trans-arterial chemoembolisation (TACE), Sorafenib and best supportive care.

7.2.1 Baseline Predictors of Treatment Allocation

Univariable analysis of HCC treatment allocation was undertaken using cross-tabulation of baseline characteristics with primary treatment modality. Significant associations with baseline factors were identified using Pearson residuals.

Multivariable analysis of treatment allocation was undertaken using multinomial logistic regression (MLR). MLR is an extension of binary logistic regression when the categorical outcome (in this case the primary treatment) has multiple levels (Chan, 2005). This method enables the comparison of co-factors within each categorical baseline variable, using a maximum likelihood model to fit to the treatment allocation. Each co-factor is compared with the referent co-factor within each variable (usually the largest co-factor) to assess the association with each outcome group (UCLA, 2020b).

The outcome of the MLR is presented as a relative risk ratio (RRR); it indicates how the probability of the outcome falling in the comparison group compared with the referent group changes as the categorical variable changes. For example, when comparing hepatitis C with alcohol-related liver disease, the RRR can estimate the likelihood that patients with hepatitis C receive a liver transplant compared with receiving best supportive care (as the reference category), given the other variables in the model remain constant. A RRR > 1 would indicate that patients with hepatitis C are more likely to receive a liver transplant than best supportive care compared with those with alcohol-related liver disease. These analyses were undertaken in Stata using the `mlogit` command, specifying each of the baseline factors as categorical variables.

7.3 Assessment of Clinical Outcomes

7.3.1 Overall Survival

Overall survival in the total cohort was calculated using the time interval from HCC diagnosis to death or censor date. Kaplan-Meier (KM) statistics were used to estimate the overall survival (Kaplan and Meier, 1958), and groups compared using the log-rank test. The KM method estimates the survival probability from observed survival times – it is a step function that changes at the time of each event (death). The KM survival curve is a plot of the survival probability over time – the median survival estimate is given as the time after which 50% of the participants have died. The log-rank test is used to compare two or more survival curves – it compares the observed number of events (deaths) in each group to the expected number if the survival curves were the same. The log-rank test was used to compare all of the categorical predictor variables in these analyses.

The KM method is useful for univariable analyses, but when considering multiple prognostic factors for overall survival, the Cox proportional hazards model was used (Cox, 1972). This model involves the calculation of a 'hazard function', which represents the risk of death at a particular time. The predictor variables (or 'covariates') are included in the regression model and for each, the 'hazard ratio' (HR) is derived which compares the risk associated with that variable to the control group. A HR >1 is associated with an increased hazard and hence a reduced survival time. The proportional hazards assumption requires that the HR remains constant over time (Rulli et al., 2018). This was tested graphically using a plot of the log cumulative hazard, according to established methodology (Williamson et al., 2002).

Using the time intervals to HCC treatment relative to the HCC diagnosis date, the overall survival following HCC treatment was calculated. In order to investigate procedure-related mortality, the 90-day mortality after individual HCC treatments was calculated. Considering this binary outcome, logistic regression was used to determine predictive factors for 90-day mortality.

7.3.2 Competing Risk

The competing risk of liver- and cancer-related mortality following HCC treatment was investigated using a multistate model of cirrhosis. Liver-related mortality was approximated by death following decompensation post-treatment and cancer-related mortality was approximated by the absence of such decompensation (Figure 9). In this multistate disease model, patients were considered to be in one of three disease states: alive, dead without decompensation ('cancer-related mortality'), or dead after decompensation ('liver-related mortality'). Using Severity Algorithm Version C, decompensation was identified in all inpatient episodes occurring after HCC treatment by the presence of ascites or variceal haemorrhage.

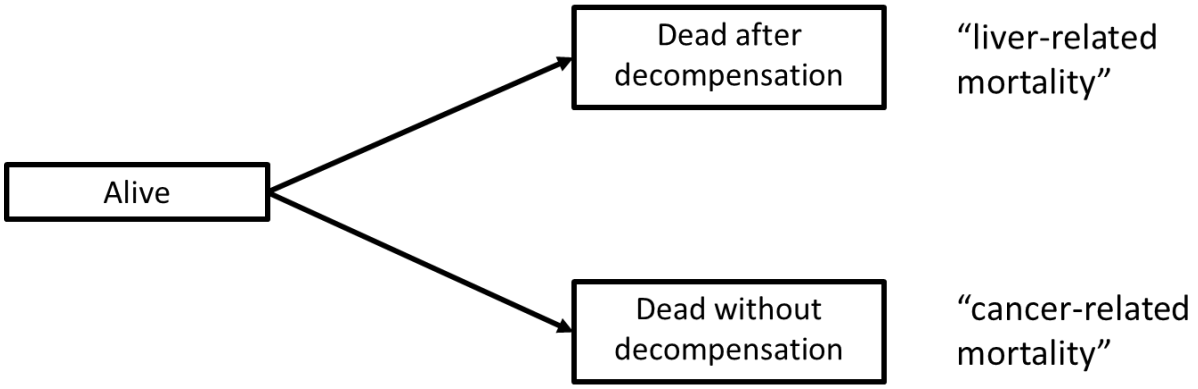

Figure 9. Multistate model of cirrhosis for patients receiving HCC treatment

The clinical outcomes for patients who received a liver transplant are more complex than other therapies and are not suited to this simplified model. Post-transplant survival is influenced by multiple additional factors, such as post-transplant surgical complications and the effects of immunosuppression and immune-mediated rejection. This simplified multistate model of cirrhosis is not applicable because the patient no longer has cirrhosis – therefore liver-related mortality is not accurately modelled by portal hypertensive complications.

Analysis of the outcomes for patients who received a liver transplant were therefore limited to overall survival, rather than cause-specific mortality. Within the HCC-UK/ NCRAS/ BASL partnership, another research group analysed post-transplant outcomes using the more detailed UK Transplant database.

7.3.2.1 Descriptive Representation of Competing Risk

Utilising the same methodology as the *Validation Study*, the number of patients in each disease state represented in the multi-state disease model were calculated at 25-day intervals following HCC treatment. A graphical representation of the cumulative incidence function was be calculated, describing the proportion of patients in each disease state over time. This approximates the cause-specific mortality.

These state occupancy graphs were calculated for each HCC treatment. Patients were stratified according to liver disease severity in order to describe the impact on liver- and cancer-related mortality.

7.3.2.2 Cumulative Incidence Function

When considering survival outcomes in a conventional two-state disease model (dead or alive), the risk of death over time can be estimated by the number of deaths occurring at time intervals after a diagnosis or treatment. This 'cumulative risk' of death can be computed as 1 minus the log of the KM survival probability. However, in a multistate system, this approximation does not work because individuals experiencing one outcome (eg. liver-related mortality) will no longer be at risk of experiencing the alternative outcome. (eg. cancer-related mortality). In the Kaplan-Meier method they would be incorrectly censored (Jepsen et al., 2015).

In multistate systems, it is necessary to compute the 'state occupancy probability' and this is most commonly achieved computationally using the Aalen-Johansen estimator (Aalen and Johansen, 1978, Andersen and Keiding, 2002). This generates the cause-specific 'cumulative incidence function' (CIF), which gives the probability of a particular outcome over time (eg. the liver-related mortality), accounting for the competing risk of a different outcome (eg. cancer-related mortality).

The CIFs for the two clinical outcomes in the proposed disease model (Figure 9) were calculated by considering the presence or absence of inpatient episodes with decompensated cirrhosis after HCC treatment. The change in CIFs over time for the two outcomes was plotted. Different CIFs for baseline cirrhosis severity (Baveno stage) were plotted in order to assess the impact on cause-specific mortality.

An alternative method for modelling the cause-specific CIF is to use a flexible parametric survival model (Lambert et al., 2017). In this method, the follow-up period is split into discrete intervals and a polynomial function is then fitted to the observed survival function. This model produces a smoothed estimate of the cause-specific CIF. It has the advantage that multiple covariates can be compared simultaneously and time-dependent covariates can be modelled. This method was also used to model the competing risk following HCC treatment and comparison made with the Aalen-Johansen estimator.

7.3.2.3 Fine and Gray Regression

Using the multistate disease model, prognostic factors for the two outcomes were determined using a Fine and Gray regression (Fine and Gray, 1999). This is the multistate equivalent of a Cox regression and it enables analysis of the effect of predictive factors on the risk of competing events (Jepsen et al., 2015). It estimates the 'subdistribution hazard ratio' (SHR) for a predictive factor. Although the SHR does not translate directly into a clinically meaningful value, if the SHR is >1, the relative risk of that outcome is also >1. Therefore, Fine and Gray regression can determine whether a predictive factor has an effect on the risk of an outcome, but it does not quantify this effect. Analogous to the Cox model, the SHRs are adjusted for other baseline factors in multivariable analysis.

When considering the competing risks of liver- and cancer-related mortality following HCC treatment, the Fine and Gray model was used to compare the impact of liver disease severity (using the Baveno stage). Multivariable analysis was possible using this model, with adjustment for other baseline factors.

7.4 Assessment of Regional Variation

7.4.1 Baseline Characteristics

Based on their address of residence, each patient in the cohort was assigned to one of 19 Cancer Alliance (CA) regions in England. For each CA, the proportion of patients in each baseline factor category were calculated. This proportion was compared to distribution of baseline factors across the whole country, and significance assessed by the χ^2 test. In this manner, an assessment of the distribution of baseline factors in different regions could be assessed, with the impact of this on treatment allocation.

7.4.2 Treatment Allocation

For each CA, the proportion of patients who received TACE, ablation, resection or transplant for HCC treatment were calculated as a crude rate. Utilising the Stata command `funnelcompar`, funnel plots were used to display the variation in treatment rates across CAs using the Spiegelhalter approach (Spiegelhalter, 2005). Control limits related to the total number of HCC cases per CA were constructed and those outside 99.8% were considered outliers.

In order to adjust for the variation in baseline factors across the different CAs, a mixed-effects logistic regression was employed, using the Stata command `melogit` UCLA (2020a). This is used to model a particular binary outcome (receiving a specific curative treatment or not) when data are 'clustered' (groups defined by CA). The odds of a receiving a specific treatment were modelled as a linear combination of the predictor variables (baseline characteristics) for each patient. The 'expected' treatment rate for each CA could then be estimated, based on the distribution of baseline characteristics for patients within each region. The ratio of observed to expected treatment rate was then plotted on funnel plots, using control limits of 99.8% to identify outliers.

8 National Study - Results and Analysis: Factors Determining HCC Treatment Allocation

This section describes the baseline characteristics of the HCC cohort and investigates the factors which determine treatment allocation and overall survival in HCC (Objective 2).

8.1 Baseline Characteristics

The HCC cohort comprised 19,436 patients diagnosed with HCC in England from 2007-2016 and among these 18,424 (94.8%) had at least one inpatient episode within the HES dataset. Within the cohort, 78.0% were male and 77.9% self-identified as White, but in 11.6% of cases, ethnicity data was missing or not stated. The median 5-year age band at diagnosis among males was 65-69 and among females, it was 70-74 (Figure 10). The baseline characteristics of the national cohort are summarised in Table 22.

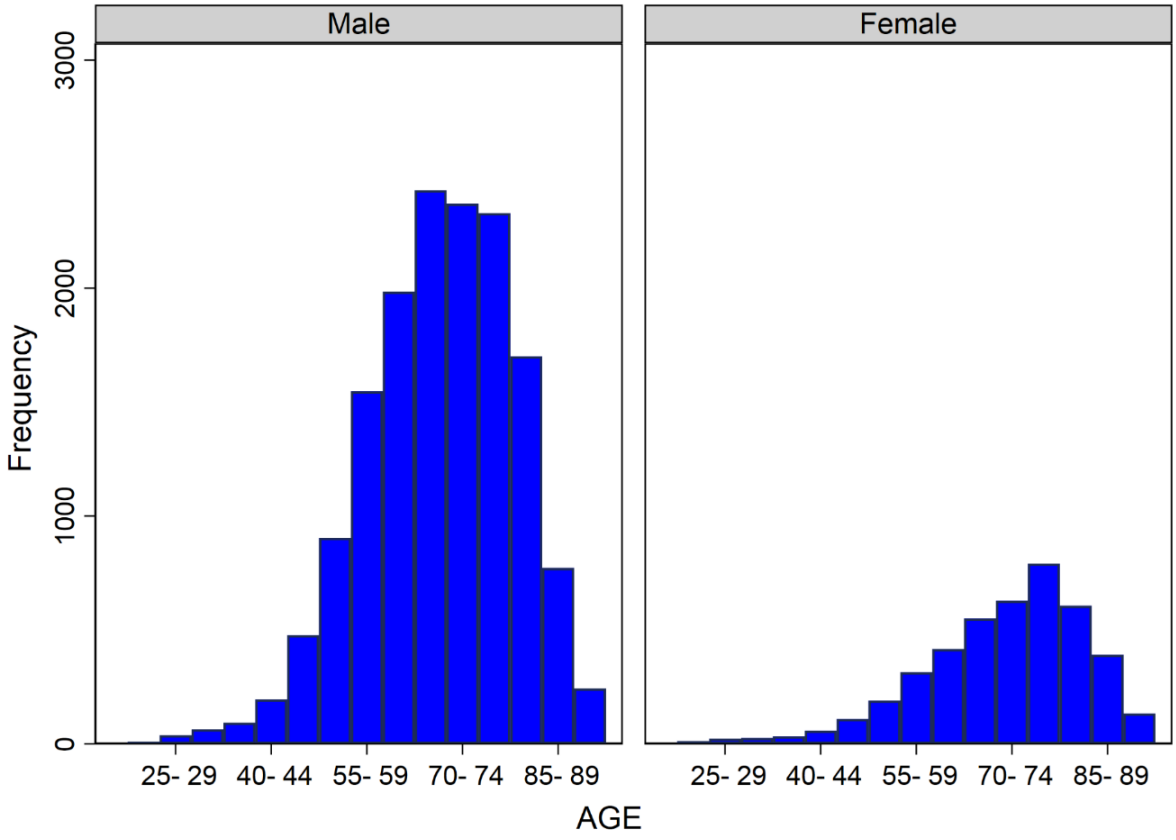

Figure 10. Distribution of age at HCC diagnosis in 5-year bands with sex

Characteristic		N (%)
Total		19436
Sex	Male	15155 (78.0)
	Female	4281 (22.0)
Age	<50	1137 (5.8)
	50-59	2955 (15.2)
	60-69	5380 (27.7)
	70-79	6119 (31.5)
	80+	3845 (19.8)
Ethnicity	Not Stated	2250 (11.6)
	White	15132 (77.9)
	Black/ Black British	447 (2.3)
	Asian/ South Asian British	847 (4.4)
	Other Ethnic Group	556 (2.9)
	Chinese	204 (1.0)
Aetiology	Other	8169 (42.0)
	HCV	2616 (13.5)
	HBV	700 (3.6)
	Haemochromatosis	566 (2.9)
	PBC	386 (2.0)
	AIH	201 (1.0)
	Alcohol	3967 (20.4)
	NAFLD	2831 (14.6)
Cirrhosis	No Cirrhosis Codes	8093 (41.6)
	Compensated Cirrhosis (no varices)	4930 (25.4)
	Cirrhosis with varices	2107 (10.8)
	Decompensated Cirrhosis	4306 (22.1)
Cancer Stage	Missing	14583 (75.0)
	Stage I	865 (4.4)
	Stage II	982 (5.1)
	Stage III	937 (4.8)
	Stage IV	2069 (10.6)
Charlson Index	0	5630 (29.0)
	1	4227 (21.8)
	2	2840 (14.6)
	3+	6739 (34.7)
IMD	1 (least deprived)	2985 (15.4)
	2	3570 (18.4)
	3	3839 (19.8)
	4	4140 (21.3)
	5 (most deprived)	4902 (25.2)

Table 22. Baseline characteristics of total HCC cohort.

8.1.1 Underlying Liver Disease

The number of patients identified with underlying cirrhosis from their HES record was 11,343/ 19436 (58.3%). Assuming that algorithm version 4 detects 86% of cases (based on the sensitivity in the *Validation Study*), the estimated prevalence of cirrhosis in the total population is 67.9%.

The number of patients registered with a diagnosis of HCC has increased over time (from 1,284 in 2007 to 2,655 in 2016) and the proportion of patients with an inpatient cirrhosis code increased from 51.9% in 2007 to 61.6% in 2015 (χ^2 = 62.7, P<0.001), as shown in Figure 11.

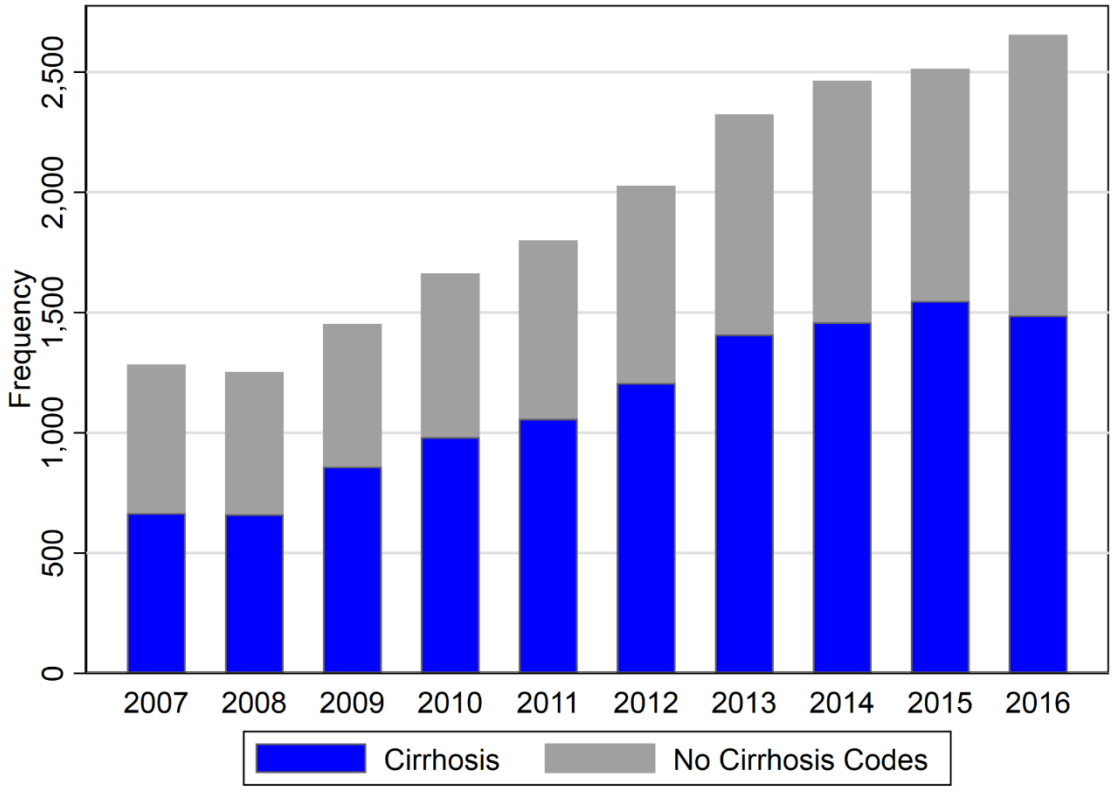

Figure 11. Number of patients registered with a new diagnosis of HCC over time, with the proportion with an inpatient cirrhosis code

A comparison of the baseline factors in those patients identified with cirrhosis and those without is summarised in Table 23. Patients who had inpatient cirrhosis codes were younger and more commonly male, and more commonly from a more socially deprived location. Those without cirrhosis codes had a more advanced cancer stage recorded and were more likely to have more significant medical co-morbidities (Charlson index of 3 or more), such as cardiovascular disease that may preclude invasive surgical treatments.

Characteristic		Total (%)	Cirrhosis (%)	No Cirrhosis (%)	P-value
Sex	Male	15155 (78.0)	9011 (79.4)	6144 (75.9)	<0.001
	Female	4281 (22.0)	2332 (20.6)	1949 (24.1)	
Age	<50	1137 (5.8)	673 (5.9)	464 (5.7)	<0.001
	50-59	2955 (15.2)	2302 (20.3)	653 (8.1)	
	60-69	5380 (27.7)	3820 (33.7)	1560 (19.3)	
	70-79	6119 (31.5)	3307 (29.1)	2812 (34.8)	
	80+	3845 (19.8)	1241 (10.9)	2604 (32.2)	
Ethnicity	Not Stated	2250 (11.6)	706 (6.2)	1544 (19.1)	<0.001
	White	15132 (77.9)	9295 (81.9)	5837 (72.1)	
	Black/ Black British	447 (2.3)	261 (2.3)	186 (2.3)	
	Asian/ South Asian British	847 (4.4)	581 (5.1)	266 (3.3)	
	Other Ethnic Group	556 (2.9)	376 (3.3)	180 (2.2)	
	Chinese	204 (1.0)	124 (1.1)	80 (1.0)	
Aetiology	Other	8169 (42.0)	1423 (12.6)	6746 (83.4)	<0.001
	HCV	2616 (13.5)	2314 (20.4)	302 (3.7)	
	HBV	700 (3.6)	493 (4.3)	207 (2.6)	
	Haemochromatosis	566 (2.9)	376 (3.3)	190 (2.3)	
	PBC	386 (2.0)	319 (2.8)	67 (0.8)	
	AIH	201 (1.0)	168 (1.5)	33 (0.4)	
	Alcohol	3967 (20.4)	3670 (32.3)	297 (3.7)	
	NAFLD	2831 (14.6)	2580 (22.8)	251 (3.1)	
Cancer Stage	Missing	14583 (75.0)	8709 (76.8)	5874 (72.6)	<0.001
	Stage I	865 (4.4)	588 (5.2)	277 (3.4)	
	Stage II	982 (5.1)	683 (6.0)	299 (3.7)	
	Stage III	937 (4.8)	487 (4.3)	450 (5.6)	
	Stage IV	2069 (10.6)	876 (7.7)	1193 (14.7)	
Charlson Index	0	5630 (29.0)	3264 (28.8)	2366 (29.2)	<0.001
	1	4227 (21.8)	2770 (24.4)	1457 (18.0)	
	2	2840 (14.6)	1813 (16.0)	1027 (12.7)	
	3+	6739 (34.7)	3496 (30.8)	3243 (40.1)	
IMD	1 (least deprived)	2985 (15.4)	1630 (14.4)	1355 (16.7)	<0.001
	2	3570 (18.4)	2026 (17.9)	1544 (19.1)	
	3	3839 (19.8)	2224 (19.6)	1615 (20.0)	
	4	4140 (21.3)	2446 (21.6)	1694 (20.9)	
	5 (most deprived)	4902 (25.2)	3017 (26.6)	1885 (23.3)	

Table 23. Baseline characteristics of the HCC cohort, tabulated by the presence of cirrhosis.

Decompensated cirrhosis was present prior to the HCC diagnosis in 4,306/ 19,436 (22.1%) of all patients and 4,306/ 11,343 (38.0%) of those patients with inpatient cirrhosis codes. There is an association between age and liver disease severity at the time of HCC diagnosis (χ^2 = 2,007, P <0.001), as shown in Table 24. Patients who are older than 80 are significantly more likely to have no cirrhosis codes in their HES record (χ^2 contribution 628). Similarly, patients aged 50-59 and aged 60-69 are more likely to have cirrhosis codes (χ^2 contribution 271 and 207 respectively). Those aged 50-59 were the most likely to have prior decompensated cirrhosis at the time of HCC diagnosis (χ^2 contribution 118).

		Age Group n (%)					
		<50	50-59	60-69	70-79	80+	Total
Liver Disease Severity	No Cirrhosis Codes	464 (5.7)	653 (8.1)	1,560 (19.3)	2,812 (34.8)	2,604 (32.2)	8,093
	Cirrhosis (Baveno 1)	291 (5.9)	923 (18.7)	1,568 (31.8)	1,554 (31.5)	594 (12.1)	4,930
	Cirrhosis (Baveno 2)	116 (5.5)	446 (21.2)	761 (36.1)	627 (29.8)	157 (7.5)	2,107
	Cirrhosis (Baveno 3&4)	266 (6.2)	933 (21.7)	1,491 (34.6)	1,126 (26.2)	490 (11.4)	4,306
	Total	1,137 (5.9)	2,955 (15.2)	5,380 (27.7)	6,119 (31.5)	3,845 (19.8)	19,436

Table 24. Cross tabulation of age with liver disease severity at diagnosis.

There is a strong association between aetiology and liver disease severity (χ^2 = 10,359, P <0.001), as summarised in Table 25. Among patients with previous decompensation, 1,696/ 4,306 (39.4%) had alcohol-related liver cirrhosis (χ^2 contribution= 759). Likewise, among those with alcohol-related liver disease, 1,696/ 3,967 (42.8%) had previous decompensation. Hepatitis B and haemochromatosis had the highest proportion of patients (68.4% and 71.2% respectively) with no reported cirrhosis or Baveno stage 1 cirrhosis.

The analysis was repeated considering alcohol as an aetiological co-factor among the primary liver disease groups (Table 26). This was achieved using the presence of alcohol-related inpatient codes in patients with other underlying aetiologies. This was most prevalent in those with hepatitis C; alcohol codes were present in 987/ 2,616 (37.7%) of all patients with hepatitis C. Among all patients with hepatitis C and previous decompensation, 426/762 (55.9%) had alcohol as an additional co-factor.

		Aetiology n (%)								
		Other	HCV	HBV	PBC	AIH	Haemo	Alcohol	NAFLD	Total
Liver Disease Severity	No Cirrhosis Codes	6,746 (83.3)	302 (3.7)	207 (2.6)	67 (0.8)	33 (0.4)	190 (2.4)	297 (3.7)	251 (3.1)	8,093
	Cirrhosis (Baveno 1)	712 (14.4)	1,031 (20.9)	272 (5.5)	92 (1.9)	66 (1.3)	213 (4.3)	1,343 (27.2)	1,201 (24.4)	4,930
	Cirrhosis (Baveno 2)	188 (8.9)	521 (24.7)	75 (3.6)	92 (4.4)	43 (2.0)	76 (3.6)	631 (30.0)	481 (22.8)	2,107
	Cirrhosis (Baveno 3&4)	523 (12.2)	762 (17.7)	146 (3.4)	135 (3.1)	59 (1.4)	87 (2.0)	1,696 (39.4)	898 (20.9)	4,306
	Total	8,169 (42.0	2,616 (13.5)	700 (3.6)	386 (2.0)	201 (1.0)	566 (2.9)	3,967 (20.4)	2,831 (14.6)	19,436

Table 25. Cross tabulation of liver disease aetiology with liver disease severity.

		Aetiology n (%)					
		HCV	HBV	PBC	AIH	Haemo	Total
Liver Disease Severity	No Cirrhosis Codes	34 (64.2)	*	*	*	--	53
	Cirrhosis (Baveno 1)	345 (78.2)	21 (4.8)	*	*	57 (12.9)	441
	Cirrhosis (Baveno 2)	182 (77.1)	*	*	*	25 (10.6)	236
	Cirrhosis (Baveno 3&4)	426 (78.0)	39 (7.1)	27 (5.0)	*	44 (8.1)	546
	Total	987	74	45	29	141	1,276

*Table 26. Cross tabulation of liver disease aetiology with liver disease severity in patients who had additional diagnosis codes related to alcohol. * = small numbers (<20 individuals) suppressed to prevent disclosure*

There is an association between liver disease aetiology and ethnicity (χ^2 = 4,668, P <0.001), as shown by cross-tabulation in Table 27. Hepatitis B is more common among Black (χ^2 contribution = 1064) and Chinese populations (χ^2 contribution= 1272). Hepatitis C is more common in Asian populations (χ^2 contribution = 230).

		Aetiology n (%)								
		Other	HCV	HBV	PBC	AIH	Haemo	Alcohol	NAFLD	Total
Ethnicity	Not Stated	1,573 (69.9)	148 (6.6)	64 (2.8)	*	*	34 (1.5)	238 (10.6)	167 (7.4)	2,250
	White	6,010 (39.7)	1,875 (12.4)	189 (1.3)	354 (2.3)	179 (1.2)	526 (3.5)	3,560 (23.5)	2,439 (16.1)	15,132
	Black	126 (28.2)	134 (30.0)	147 (32.9)	*	*	*	*	*	447
	Asian	251 (29.6)	276 (32.6)	101 (11.9)	*	*	*	80 (9.5)	125 (14.8)	847
	Other	157 (28.2)	153 (27.5)	95 (17.0)	*	*	*	65 (11.7)	71 (12.8)	556
	Chinese	52 (25.5)	30 (14.7)	104 (50.1)	*	*	*	*	*	204
	Total	8,169 (42.0)	2,616	700	566	386	201	3,967	2,831	19,436

*Table 27. Cross tabulation of liver disease aetiology with ethnicity. * = small numbers (<20 individuals) suppressed to prevent disclosure*

There was also an association between sex and aetiology (χ^2 = 4,668, P <0.001). PBC was more common in females (χ^2 contribution= 466), as was AIH (χ^2 contribution= 182). Alcohol-related liver disease was less common in females (χ^2 contribution= 200).

8.1.2 Cancer Stage

Data for cancer stage was missing in 75% of cases. Reporting has increased over time (Figure 12) and in 2016, 55.3% of patients had a recorded cancer stage in the registry. Cancer stage was associated with cirrhosis severity (χ^2 = 332, P <0.001), as shown in Table 28. Among the total 4,853 patients with a recorded cancer stage, 2,219 (45.7%) had no cirrhosis codes, 1,714 (35.3%) had compensated cirrhosis, and 920 (20.0%) had previous decompensation. Those patients with stage IV disease were less likely to have inpatient cirrhosis codes (χ^2 contribution = 65).

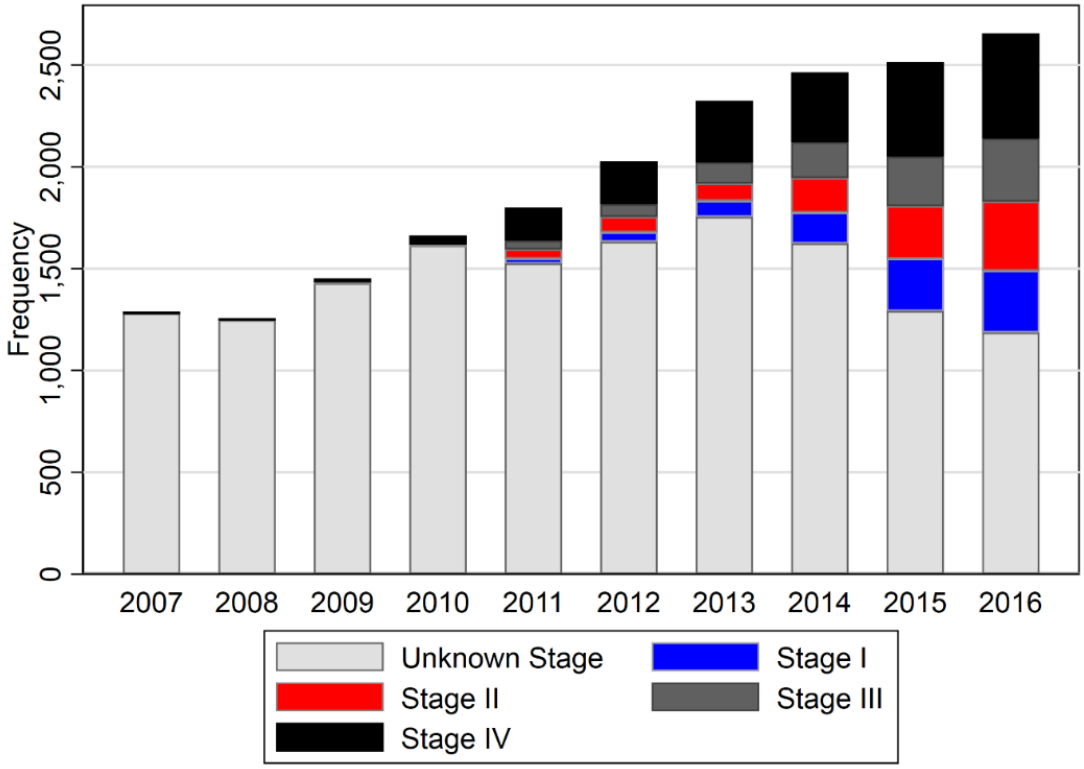

Figure 12. Number of cases with a recorded cancer stage in the registry over the period of study

		Cancer Stage, n (%)				
		Stage I	Stage II	Stage III	Stage IV	Total
Liver Disease Severity	No Cirrhosis Codes	277 (12.5)	299 (13.5)	450 (20.3)	1,193 (53.8)	2,219
	Cirrhosis (Baveno 1)	280 (22.9)	319 (26.1)	248 (20.3)	375 (30.7)	1,222
	Cirrhosis (Baveno 2)	127 (25.8)	163 (33.1)	77 (15.7)	125 (25.4)	492
	Cirrhosis (Baveno 3&4)	181 (19.7)	201 (21.9)	162 (17.6)	376 (40.8)	920
	Total	865 (17.8)	982 (20.2)	937 (19.3)	2,069 (42.6)	4,853

Table 28. Distribution of cirrhosis severity among patients with known cancer stage at diagnosis

8.2 Treatment Allocation

The total number of patients who received each HCC treatment modality is summarised in Table 29. Most patients (61.8%) did not undergo specific cancer treatment and received best supportive care only.

HCC Treatment Modality	**N= 19,436**
Best Supportive Care (N, %)	12,013 (61.8)
Sorafenib (N, %)	743 (3.8)*
TACE (N, %)	2,816 (14.5)
Ablation (N, %)	1,416 (7.3)
Resection (N, %)	1,495 (7.7)
Transplant (N, %)	953 (4.9)

*Table 29. Frequency of primary HCC treatment modality in the cohort. *Sorafenib records only included from 2014.*

Univariable analysis (Table 30) shows the number of patients receiving primary HCC treatment stratified by baseline characteristics; highly significant associations (P<0.001) are identified by the Pearson residuals. The outcome of the multinomial logistic regression is displayed in Table 31. These analyses determine the baseline factors associated with each treatment modality and a summary of these findings are presented in the following sections.

Characteristic		Primary Treatment Modality						
		BSC n (%)	**Sorafenib** n (%)	**TACE** n (%)	**Ablation** n (%)	**Resection** n (%)	**Transplant** n (%)	**Total**
Sex	Male	9,247 (61.0)	625 (4.1)	2,300 (15.2)	1,109 (7.3)	1,117 (7.4)	757 (5)	15,1555
	Female	2,766 (64.6)	118 (2.8)	516 (12.1)	307 (7.2)	378 (8.8)	196 (4.6)	4,281
Age Group	<50	570 (50.1)	43 (3.8)	143 (12.6)	71 (6.2)	186 (16.4)*	124 (10.9)*	1,137
	50-59	1,455 (49.2)	134 (4.5)	448 (15.1)	258 (8.7)	241 (8.1)	419 (14.2)*	2,955
	60-69	2,967 (55.2)	246 (4.6)	862 (16.0)	460 (8.6)	448 (8.3)	397 (7.4)	5,380
	70-79	3,795 (62.0)	242 (4.0)	1,057 (17.3)	507 (8.3)	506 (8.3)	---	6,119
	80+	3,226 (83.0)*	78 (2.0)	306 (8.0)	120 (3.1)	114 (3.0)	---	3,845
Ethnicity	Not stated	1,773 (78.8)*	99 (4.4)	178 (7.9)*	61 (2.7)*	93 (4.1)*	26 (2.0)	2,250
	White	9,161 (60.5)	555 (3.7)	2,310 (15.3)	1,161 (7.7)	1,184 (7.8)	761 (5.0)	15,132
	Black	219 (49.0)	---	82 (18.3)	50 (11.2)*	58 (13.0)*	---	447
	South Asian	479 (56.6)	38 (4.5)	120 (14.2)	72 (8.5)	66 (7.8)	72 (8.5)*	847
	Other Group	305 (54.9)	21 (3.8)	88 (15.8)	45 (8.1)	54 (9.7)	43 (7.7)	556
	Chinese	76 (37.3)	---	38 (18.6)*	27 (13.2)	40 (19.6)*	---	204
Aetiology	HCV	1,105 (42.2)	87 (3.3)	502 (19.2)*	325 (12.4)*	169 (6.5)	428 (16.4)*	2,616
	HBV	263 (37.6)	35 (5.0)	149 (21.3)	77 (11.0)	118 (16.9)*	58 (8.3)	700
	Haemo	248 (43.8)	24 (4.2)	102 (18.0)	68 (12.0)	93 (16.4)*	31 (5.5)	566
	PBC	180 (46.7)	---	87 (22.5)	55 (14.3)	---	41 (10.6)	386
	AIH	114 (56.7)	---	36 (17.9)	20 (10.0)	---	---	201
	Alcohol	2,403 (60.6)	102 (2.6)	674 (17.0)	404 (10.2)*	134 (3.4)*	250 (6.3)	3,967
	NAFLD	1,646 (58.1)	101 (3.6)	514 (18.2)	279 (9.9)	201 (7.1)	90 (3.2)	2,831
	Other/ unknown	6,054 (74.1)*	382 (4.7)	752 (9.2)	188 (2.3)*	751 (9.2)	42 (0.5)*	8,169
Liver Disease Severity	No Cirrhosis	5,801 (71.7)*	384 (4.7)	795 (9.8)*	188 (2.3)*	911 (11.3)*	---	8,093
	Baveno 1	2,259 (45.8)	190 (3.9)	1,140 (23.1)*	632 (12.8)*	453 (9.2)	256 (5.2)	4,930
	Baveno 2	898 (42.6)	90 (4.3)	482 (22.9)*	325 (15.4)*	56 (2.7)*	256 (12.2)*	2,107
	Baveno 3 & 4	3,055 (71.0)*	79 (1.8)	399 (9.3)	271 (6.3)	75 (1.7)*	427 (9.9)*	4,306
CharIson Index	0	3,087 (54.8)	234 (4.2)	875 (15.5)	449 (8.0)	587 (10.4)	398 (7.1)	5,630
	1	2,255 (53.4)	153 (3.6)	765 (18.1)	383 (9.1)	385 (9.1)	286 (6.8)	4,227
	2	1,660 (58.5)	108 (3.8)	472 (16.6)	279 (9.8)	191 (6.7)	130 (4.6)	2,840
	3 +	5,011 (74.4)*	248 (3.7)	704 (10.5)*	305 (4.5)*	332 (4.9)*	139 (2.1)*	6,739
Cancer Stage	Stage I	229 (26.5)	25 (2.9)	157 (18.2)	164 (19.0)*	208 (24.1)*	82 (9.5)	865
	Stage II	334 (34.0)	39 (4.0)	210 (21.4)	107 (10.9)	189 (19.3)*	103 (10.5)*	982
	Stage III	554 (59.1)	113 (12.1)*	159 (17.0)	---	85 (9.1)	---	937
	Stage IV	1,635 (79.0)*	233 (11.3)*	118 (5.7)*	25 (1.2)*	49 (2.4)*	---	2,069
IMD	1	1,763 (59.1)	120 (4.0)	457 (15.3)	224 (7.5)	284 (9.5)	137 (4.6)	2,985
	2	2,177 (61.0)	146 (4.1)	523 (14.7)	250 (7.0)	284 (8.0)	190 (5.3)	3,570
	3	2,354 (61.3)	151 (3.9)	571 (14.9)	280 (7.3)	310 (8.1)	173 (4.5)	3,839
	4	2,651 (64.0)	145 (3.5)	595 (14.4)	261 (6.3)	284 (6.9)	204 (4.9)	4,140
	5	3,068 (62.6)	181 (3.7)	670 (13.7)	401 (8.2)	333 (6.8)	249 (5.1)	4,902

*Table 30. Cross-tabulation of HCC treatment allocation with baseline factors. *= highly significant Pearson residual (P <0.001)*

		Sorafenib RRR	TACE RRR	Ablation RRR	Resection RRR	Transplant RRR
Sex	Male	Ref	Ref	Ref	Ref	Ref
	Female	**0.67 (0.55-0.83)**	**0.79 (0.70-0.88)**	0.99 (0.86-1.16)	**1.15 (1.00-1.32)**	**1.22 (1.00-1.48)**
Age Group	<50	0.82 (0.57-1.17)	0.81 (0.65-1.01)	0.76 (0.57-1.01)	**1.70 (1.35-2.14)**	**1.59 (1.23-2.05)**
	50-59	1.11 (0.88-1.41)	0.92 (0.80-1.06)	0.92 (0.77-1.11)	1.11 (0.92-1.34)	**1.55 (1.30-1.84)**
	60-69	Ref	Ref	Ref	Ref	Ref
	70-79	**0.70 (0.58-0.85)**	1.10 (0.98-1.22)	1.12 (0.97-1.30)	**0.73 (0.62-0.84)**	**0.03 (0.02-0.06)**
	80+	**0.26 (0.20-0.34)**	**0.44 (0.38-0.51)**	**0.45 (0.36-0.57)**	**0.15 (0.12-0.19)**	**0.01 (0.00-0.04)**
Ethnicity	White	Ref	Ref	Ref	Ref	Ref
	Not Stated	**0.66 (0.52-0.84)**	**0.40 (0.34-0.48)**	**0.36 (0.27-0.47)**	**0.20 (0.16-0.26)**	**0.51 (0.37-0.71)**
	Black	0.94 (0.54-1.64)	1.03 (0.77-1.38)	1.28 (0.90-1.84)	0.80 (0.55-1.14)	0.78 (0.47-1.30)
	South Asian	1.21 (0.84-1.73)	0.83 (0.66-1.03)	0.93 (0.71-1.24)	0.90 (0.67-1.21)	1.33 (0.98-1.80)
	Other Group	0.93 (0.58-1.49)	0.89 (0.68-1.15)	0.87 (0.62-1.23)	0.94 (0.67-1.31)	1.08 (0.74-1.56)
	Chinese	1.87 (0.98-3.58)	1.27 (0.82-1.97)	2.02 (1.21-3.36)	1.59 (0.99-2.54)	1.03 (0.49-2.17)
Aetiology	Alcohol	Ref	Ref	Ref	Ref	Ref
	Other	**1.72 (1.30-2.28)**	**0.67 (0.58-0.78)**	**0.43 (0.35-0.54)**	**1.68 (1.34-2.12)**	**0.54 (0.38-0.78)**
	HCV	**1.55 (1.13-2.12)**	**1.49 (1.28-1.74)**	**1.55 (1.29-1.87)**	**1.69 (1.31-2.19)**	**2.56 (2.11-3.11)**
	HBV	**2.41 (1.51-3.85)**	**2.06 (1.59-2.66)**	**1.74 (1.25-2.43)**	**3.74 (2.65-5.28)**	**2.22 (1.53-3.22)**
	HAEMO	**2.06 (1.28-3.34)**	**1.32 (1.02-1.70)**	**1.75 (1.29-2.37)**	**4.66 (3.37-6.44)**	**2.37 (1.54-3.64)**
	PBC	1.60 (0.72-3.58)	**2.06 (1.54-2.78)**	**1.84 (1.29-2.62)**	1.55 (0.87-2.76)	**4.40 (2.84-6.84)**
	AIH	1.53 (0.60-3.90)	1.21 (0.81-1.83)	1.03 (0.61-1.72)	1.73 (0.90-3.31)	1.79 (0.93-3.44)
	NAFLD	**1.76 (1.31-2.36)**	**1.19 (1.04-1.38)**	1.08 (0.91-1.30)	**2.50 (1.96-3.20)**	1.14 (0.87-1.49)
Liver Disease Severity	No Cirrhosis	Ref	Ref	Ref	Ref	Ref
	Baveno 1	1.11 (0.88-1.40)	**1.80 (1.57-2.06)**	**3.22 (2.62-3.96)**	**0.70 (0.59-0.82)**	**11.94 (6.78-21.01)**
	Baveno 2	**1.38 (1.03-1.85)**	**1.71 (1.45-2.02)**	**3.64 (2.88-4.59)**	**0.20 (0.14-0.27)**	**24.51 (13.83-43.42)**
	Baveno 3&4	**0.38 (0.28-0.51)**	**0.47 (0.40-0.55)**	1.02 (0.81-1.29)	**0.09 (0.07-0.12)**	**14.11 (8.04-24.78)**
Charlson Index	0	Ref	Ref	Ref	Ref	Ref
	1	0.91 (0.73-1.14)	1.03 (0.91-1.17)	0.96 (0.82-1.13)	0.89 (0.76-1.04)	0.98 (0.82-1.18)
	2	1.00 (0.78-1.30)	0.94 (0.82-1.08)	1.05 (0.87-1.25)	**0.67 (0.55-0.81)**	**0.75 (0.60-0.95)**
	3+	**0.60 (0.48-0.74)**	**0.54 (0.48-0.61)**	**0.48 (0.41-0.57)**	**0.38 (0.32-0.44)**	**0.42 (0.33-0.52)**
Cancer Stage	Stage I	Ref	Ref	Ref	Ref	Ref
	Stage II	0.99 (0.58-1.69)	0.87 (0.66-1.15)	**0.42 (0.31-0.57)**	**0.59 (0.44-0.78)**	0.95 (0.65-1.38)
	Stage III	**1.74 (1.09-2.77)**	**0.44 (0.33-0.59)**	**0.06 (0.04-0.10)**	**0.14 (0.10-0.19)**	**0.05 (0.02-0.11)**
	Stage IV	1.34 (0.86-2.09)	**0.14 (0.11-0.19)**	**0.03 (0.02-0.05)**	**0.03 (0.02-0.04)**	**0.04 (0.02-0.07)**
Index of Multiple Deprivation	1	Ref	Ref	Ref	Ref	Ref
	2	0.95 (0.74-1.23)	0.90 (0.77-1.04)	0.86 (0.70-1.05)	**0.78 (0.65-0.95)**	0.99 (0.76-1.28)
	3	0.90 (0.70-1.16)	0.88 (0.76-1.02)	0.85 (0.69-1.03)	**0.77 (0.64-0.93)**	**0.70 (0.54-0.90)**
	4	**0.75 (0.58-0.97)**	**0.78 (0.68-0.91)**	**0.66 (0.54-0.81)**	**0.61 (0.50-0.74)**	**0.60 (0.46-0.77)**
	5	0.78 (0.61-1.00)	**0.74 (0.64-0.85)**	0.84 (0.70-1.02)	**0.59 (0.49-0.71)**	**0.53 (0.42-0.68)**

Table 31. Multinomial logistic regression demonstrating the association of baseline factors with treatment allocation, using best supportive care as the base outcome. RRR = relative risk ratio compared with referent co-factor indicated for each categorical variable. RRR significant at the P<0.05 level are highlighted in bold.

8.2.1 Best Supportive Care

In the univariable analysis (Table 30), there was an association between receiving best supportive care (BSC) and patients being aged over 80. In the MLR (Table 31), where the RRR is < 1, patients are less likely to receive that treatment compared with BSC, when comparing the group in question to the referent group. For patients aged over 80, the RRR is < 1 for all treatments, which suggests that BSC is the most common treatment for patients in this age group compared with those aged 60-69, when adjusted for all other baseline factors.

In univariable analysis, patients receiving BSC were more likely to have 'unknown' liver aetiology. However, in MLR, BSC was less likely for those with 'unknown' liver aetiology compared with alcohol (as the referent group) for both Sorafenib and resection (when adjusted for other baseline factors). This is demonstrated by the RRR > 1 for these subgroups.

Patients with a Charlson index of ≥ 3 were more likely to receive BSC. In total, 5,011/ 6,739 (74.4%) of these patients received BSC. In MLR, the RRR was < 1 for all treatments compared with BSC for patients in this group, compared with those with a Charlson index of zero. Among all patients with previous decompensated cirrhosis, 3,055/ 4,306 (71.0%) received BSC only. Additionally, among patients with a known cancer stage, 79.0% of those with Stage IV disease and 59.1% with Stage III disease also did not receive specific HCC treatment.

8.2.2 Sorafenib

Female patients and those aged over 70 were less likely to receive Sorafenib chemotherapy. Compared with BSC, there was an increased RRR for Sorafenib treatment among patients with 'unknown/ other' liver disease aetiology compared with alcohol. Additionally, those with haemochromatosis, hepatitis B, hepatitis C, and NAFLD had higher rates of Sorafenib treatment than alcohol-related liver disease. Previous decompensation (Baveno stage 3 and 4) and multiple comorbidities (Charlson index 3 or more) were associated with lower rates of Sorafenib treatment (RRR < 1 compared with BSC). Stage III cancers (tumours larger than 5cm or locally invasive, but no distant spread) were the most commonly treated with chemotherapy; the RRR was < 1 for all other treatments compared with BSC for these cancers compared with Stage I cancer.

8.2.3 Trans-arterial Chemoembolisation

TACE was less commonly used to treat female patients and those aged over 80, but it was the most common treatment for patients aged 60-69 and 70-79. There were higher TACE treatment rates among patients with non-alcohol related primary liver disease aetiologies; when adjusted for other baseline factors, the RRR was > 1 for TACE compared with BSC for all known liver disease aetiologies (when compared with alcohol).

There were low treatment rates in patients with no cirrhosis codes, but high rates in those with compensated cirrhosis (Baveno 1 and 2) in univariable analysis. Similarly, the RRR was > 1 for Baveno 1 and 2 compared with the referent no cirrhosis codes group, when comparing TACE to BSC. Previous decompensated cirrhosis and multiple co-morbidities (Charlson index 3 or more) were associated with low rates of TACE. Patients in IMD quintiles 4 and 5 (most deprived) had lower rates of TACE treatment.

8.2.4 Ablation

Ablation was less commonly used to treat patients aged over 80 and there were higher ablation rates among patients with non-alcohol related aetiologies, as demonstrated in both univariable and MLR analyses. Ablation rates were highest among patients with compensated cirrhosis and the presence of multiple co-morbidities (Charlson index 3 or more) was associated with low rates (RRR < 1 compared with BSC). The majority of treated cases were Stage I (smaller tumours less than 2cm and solitary tumours) where cancer stage was recorded.

8.2.5 Resection

Liver resection was more common among those aged under 50 and slightly more common in females. There was a reduction in resection rates with increasing age and this was replicated in MLR; when adjusted for other baseline factors, the RRR was < 1 for resection compared with BSC when comparing age groups 70-79 and >80 to the 60-69 referent age group. The primary liver disease aetiologies with the highest resection rates in univariable analysis were hepatitis B, haemochromatosis and NAFLD. This was replicated with MLR analysis; the RRR was > 1 for these aetiologies (compared with alcohol-related liver disease) when comparing resection to BSC.

Increasing Baveno stage was associated with reduced resection rates and the highest rates were in those with no cirrhosis codes. Resection was most commonly undertaken in patients with Stage I and II disease. Patients in IMD quintile 1 (least deprived) were the most likely to receive treatment with liver resection in multivariable analysis; the RRR was < 1 for all IMD quintiles (compared with IMD quintile 1 as the referent group) when comparing the rate of resection to BSC.

8.2.6 Liver Transplant

Liver transplant was most commonly offered to patients aged under 60 and was very uncommon in those aged over 70. The transplant rate was slightly higher in females. Underlying hepatitis B and C, haemochromatosis and PBC were associated with the highest transplant rates. In MLR, the RRR for these aetiologies was > 1 (compared with alcohol-related liver disease) for transplant compared with BSC, when adjusted for other baseline factors.

Patients with cirrhosis and portal hypertension (Baveno 2) were more likely to receive a liver transplant than the Baveno 1 group, based on the RRR when compared with receiving BSC. Liver transplant was not undertaken for patients with advanced cancer stage. Increasing deprivation, measured by the IMD quintile, was associated with lower rates of liver transplant; the RRR was < 1 for IMD quintiles 3-5 compared with IMD quintile 1 as the referent group when comparing the rate of transplant to BSC.

8.3 Discussion of Results

8.3.1 Baseline Characteristics

The majority of patients (78.0%) were male, which is consistent with a previous population-based study of HCC in France (Goutté et al., 2017), in which 80.1% were male. This finding is seen globally and may be attributable to higher exposure to risk factors including alcohol (El-Serag, 2012), but there is evidence to suggest that high levels of androgenic hormones influence HCC progression (Yu and Chen, 1993). A precise estimate of median age was limited in this study due to the presentation of ages in 5-year age bands. For comparison, 51.3% of patients were aged 70 or over at presentation, which is consistent with the median age of 68.0 years in the French population.

The calculated cirrhosis prevalence of 58.3% is likely to be an under-estimate because the algorithm relies on the presence of cirrhosis codes in the inpatient HES record. Assuming a sensitivity of 86% for cirrhosis detection, the estimated population prevalence of cirrhosis is 67.9%, compared with 73% in the French study. If cirrhosis is not identified, this suggests that HCC developed in a non-cirrhotic liver or cirrhosis codes were not present in the inpatient EHR. If patients present with HCC as the first manifestation of a cirrhosis-related complication, the HES record may not capture a background diagnosis of cirrhosis. The longer that a patient with cirrhosis survives, the more likely they are to have cirrhosis codes in their HES record. This represents survivor bias (van Walraven et al., 2004) and may lead to an under-estimate of the proportion of patients with cirrhosis who do not survive long enough to be identified with cirrhosis from their HES record.

Decompensated cirrhosis was observed in 22.1% of patients prior to HCC diagnosis, and this compares to 27.3% in the French study (Goutté et al., 2017). This is an important observation because preserved liver function is required for all HCC treatments apart from transplantation. Among patients with previous decompensation, alcohol was the most common aetiology and it was a common co-factor among patients with hepatitis C. Older patients and those with more comorbidities are more likely to have no cirrhosis codes; this may be due to HCC being diagnosed in the absence of established cirrhosis, or there may be a survivor bias.

There was no underlying liver disease aetiology identified in 42% of patients. Among those identified with cirrhosis, no aetiology was identified in 12.6% of cases, whereas in those without cirrhosis codes, the proportion with an unspecified aetiology was 83.4%. This may

represent the occurrence of HCC in a normal (non-cirrhotic liver), but it is likely to be influenced by those patients with fewer inpatient HES episodes and so fewer cirrhosis and aetiology codes.

Cancer stage was missing in the majority (75%) of cases, which limits the interpretation in the forthcoming analyses. Stage IV disease was most commonly identified in patients with no cirrhosis codes in their HES record. This may represent the diagnosis of advanced cancer in individuals not known to have cirrhosis, but also there may be survivor bias, since patients with a shorter survival are not identified with cirrhosis from codes in their inpatient record.

One approach to mitigate missing cancer stage data would be to exclude these patients from analyses – however, this would significantly reduce the size of the cohort. Also, this may introduce bias as cancer stage recording improved over time and there was an association with liver disease severity. In Section 10, more detailed analyses of patients who received ablation was possible because cancer stage is more uniform throughout this group (small lesions, confined to the liver). In this manner, missing cancer stage data can be mitigated.

8.3.2 Treatment Allocation

Eligibility for HCC treatment depends on several patient-, liver- and cancer-related factors, as outlined in the BCLC classification. The univariable analysis gives an insight into the proportion of patients who received each treatment and the multinomial logistic regression provides an estimate of the relative influence of each factor.

Most patients (61.8%) diagnosed with HCC received best supportive care only and this can be attributed to a number of factors that meant that they were not eligible for HCC treatment. Most commonly, older patients and those with multiple co-morbidities may be assessed as unfit for surgery, chemotherapy or loco-regional therapy due to a clinical assessment of performance status. Likewise, the presence of advanced cancer or severe liver disease meant that the risks of HCC treatment outweighed the potential benefits. Among those who received best supportive care, 3055/ 6212 (49.2%) had previous decompensation (Baveno 3 and 4) – this highlights the importance of assessing liver disease severity in understanding clinical outcomes in HCC. There were a large number of patients who had unknown cirrhosis status, aetiology and ethnicity. This reflects the scarcity of inpatient HES codes to characterise patients who died soon after the HCC diagnosis.

The absence of cirrhosis codes may occur in patients who present with advanced HCC as the first manifestation of previously undiagnosed cirrhosis. Alternatively, this could represent patients with HCC that has developed in a non-cirrhotic liver. These analyses may also be influenced by survivor bias – patients who received best supportive care had a shorter survival and so are less likely to have inpatient cirrhosis codes.

The association of other baseline factors with HCC treatments is in keeping with the EASL guidelines (EASL, 2018) and reflects patients' fitness and eligibility for invasive therapies. In clinical practice, however, there may be some flexibility as individual circumstances and clinical features are considered when making treatment decisions.

Liver transplant and resection are the most invasive treatments, offering the best chance for cure. However, both require major abdominal surgery - they were more commonly performed in younger patients and those with the fewest comorbidities (Charlson index of 0 or 1). The presence of oesophageal varices (Baveno 2) indicates clinically significant portal hypertension; this is a relative contraindication for liver resection but these patients can be treated with a liver transplant. Cancer stage has a significant impact on the eligibility for surgery; although this information was limited, among those with a known cancer stage only Stage I and II cancers were treated with resection and transplant. Female patients and those with non-alcohol related aetiologies were more likely to receive surgical treatment. This finding may be attributable to these patients presenting at an earlier cancer stage if they are under follow-up for viral hepatitis or haemochromatosis, for example. Cancer progression may be slower in females due to the effect of androgenic hormones (Yu and Chen, 1993) and lead to earlier presentation, but females were also more likely to have non-alcohol related aetiologies.

In the UK, a period of sustained abstinence from alcohol and engagement with substance misuse services for those with alcohol dependence is a pre-requisite for liver transplantation. This may affect the rate of transplant in those with alcohol-related cirrhosis. The finding that patients from the most deprived locations were less likely to receive these treatments may indicate differences in access to healthcare and increased rates of advanced alcohol-related cirrhosis, which may lead to presentation at a later cancer stage and preclusion from transplant.

Ablation and TACE require compensated cirrhosis at the time of treatment. This study demonstrates that 399/ 2816 (14.2%) of patients who received TACE and 271/ 1416 (19.1%) of those who received ablation had previous decompensation (Baveno 3 and 4). These patients were eligible for treatment after an improvement in their liver function. Similarly, 881/

2816 (31.3%) of patients who received TACE and 596/ 1416 (42.1%) of those who received ablation had clinically significant portal hypertension (Baveno 2 or greater). This suggests that in clinical practice, patients with more advanced liver disease may be offered HCC treatment if their liver function improves sufficiently.

Although ablation is considered potentially curative, it is technically possible only for smaller tumours due to the impact on the surrounding liver. Larger tumours can be treated with TACE and this reflects the increase in Stage II cancers treated compared with ablation. Both treatments are less invasive than surgery and more patients with a Charlson index of 2 received these treatments compared to resection and transplant. Ablation requires a general anaesthetic but TACE can be performed under conscious sedation. More patients aged 60-79 were treated with TACE and this may also reflect its suitability for a wider range of patient fitness.

Patients who received Sorafenib were more likely to have Stage III and IV cancer. The cancer staging information is more complete for these patients because they required a histological diagnosis with a liver biopsy before receiving chemotherapy. In order to be eligible for Sorafenib, patients need preserved liver function (hence low rates in the Baveno 3 and 4 group) and they were also younger and had fewer co-morbidities. Patients with an advanced cancer stage may be unable to have loco-regional or surgical treatment and so are more likely to have Sorafenib.

Although there are some associations between ethnicity and treatment allocation in univariable analysis, this is most likely to be explained by the correlation of ethnicity with underlying liver disease aetiology, such as the prevalence of hepatitis B among Black and Chinese populations. There is no correlation between ethnicity and treatment allocation in the MLR analysis.

9 National Study - Results and Analysis: Factors Affecting Survival and Clinical Outcomes

This section describes the predictors of overall survival in all patients diagnosed with HCC. The impact of baseline factors on survival following non-curative HCC treatments are also presented here, along with the rate of decompensation post-treatment and estimates of cause-specific mortality.

9.1 Overall Survival

9.1.1 Baseline Characteristics

Among the 19,436 patients in the cohort, the interval from HCC diagnosis date to death was zero days in 969 individuals. In these patients, the date of registration of HCC was the same as the date of death. The KM model requires non-zero survival times, so the remaining 18,467 patients were included in these survival analyses. The median overall survival for diagnosed with HCC in the cohort was 7.1 months (95% confidence interval, CI 6.8 – 7.3 months). Univariable analysis of the median survival (calculated by the KM model) for the baseline factors is summarised in Table 32.

A sensitivity analysis was undertaken among the group of 969 individuals excluded from these KM survival analyses. Compared with the total cohort, these patients were more commonly aged over 80 (31.6%, Pearson residual $\chi^2 = 56.8$, $P < 0.001$), and more commonly of unknown ethnicity, cancer stage, and aetiology. Among this group, 523 (54.0%, Pearson residual $\chi^2 = 35.4$, $P < 0.001$) had no inpatient cirrhosis codes and 310 (32.0%, Pearson residual $\chi^2 = 42.3$, $P < 0.001$) had previous decompensated cirrhosis.

Characteristic		Median survival / months (95% CI)	Log-rank
Sex	Male	7.2 (6.9-7.5)	χ^2 =0.01, P=0.93
	Female	6.7 (6.2-7.2)	
Age Group	<50	12.6 (10.6-14.7)	χ^2 =951, P<0.001
	50-59	11.4 (10.2-12.8)	
	60-69	8.8 (8.1-9.5)	
	70-79	6.6 (6.2-6.9)	
	80+	4.0 (3.7-4.4)	
Ethnicity	Not stated	3.8 (3.5-4.3)	χ^2 = 74.7, P<0.001
	White	7.4 (7.1-7.7)	
	Black	10.3 (8.2-15.0)	
	South Asian	10.7 (8.8-12.5)	
	Other Ethnic Group	8.8 (7.1-12.1)	
	Chinese	13.6 (9.1-25.1)	
	Mixed	7.3 (3.2-10.5)	
Aetiology	HCV	17.0 (15.5-18.6)	χ^2 = 567, P<0.001
	HBV	14.8 (12.0-17.3)	
	PBC	12.6 (10.3-14.7)	
	AIH	9.0 (7.3-8.5)	
	Haemochromatosis	15.0 (12.2-18.8)	
	Alcohol	7.9 (7.3-8.5)	
	NAFLD	5.7 (5.4-6.1)	
	Other/ unknown	4.3 (4.0-4.5)	
Liver Disease Severity	No Cirrhosis Codes	5.2 (4.9-5.5)	χ^2 = 1371, P<0.001
	Baveno 1	18.2 (17.2-19.3)	
	Baveno 2	14.7 (13.5-15.9)	
	Baveno 3 & 4	2.6 (2.5-2.8)	
Charlson Index	0	11.3 (10.6-12.0)	χ^2 = 1418, P<0.001
	1	10.7 (10.1-11.4)	
	2	8.5 (7.6-9.3)	
	3 +	2.9 (2.8-3.0)	
Cancer Stage	Stage I	44.9 (40.6-50.0)	χ^2 = 1960, P<0.001
	Stage II	27.9 (24.2-30.4)	
	Stage III	6.6 (6.0-7.4)	
	Stage IV	2.6 (2.4-2.8)	
Index of Multiple Deprivation	1	7.3 (6.5-7.8)	χ^2 = 5.0, P=0.29
	2	7.4 (6.8-8.1)	
	3	7.1 (6.6-7.8)	
	4	6.6 (6.1-7.2)	
	5	7.2 (6.6-7.7)	

Table 32. Univariable analysis of median survival for baseline factors. Equality of survivor functions was determined using the log-rank test.

The KM survival curves for groups defined by cirrhosis severity, cancer stage (where known), and Charlson co-morbidity index are shown in Figure 13, Figure 14 and Figure 15.

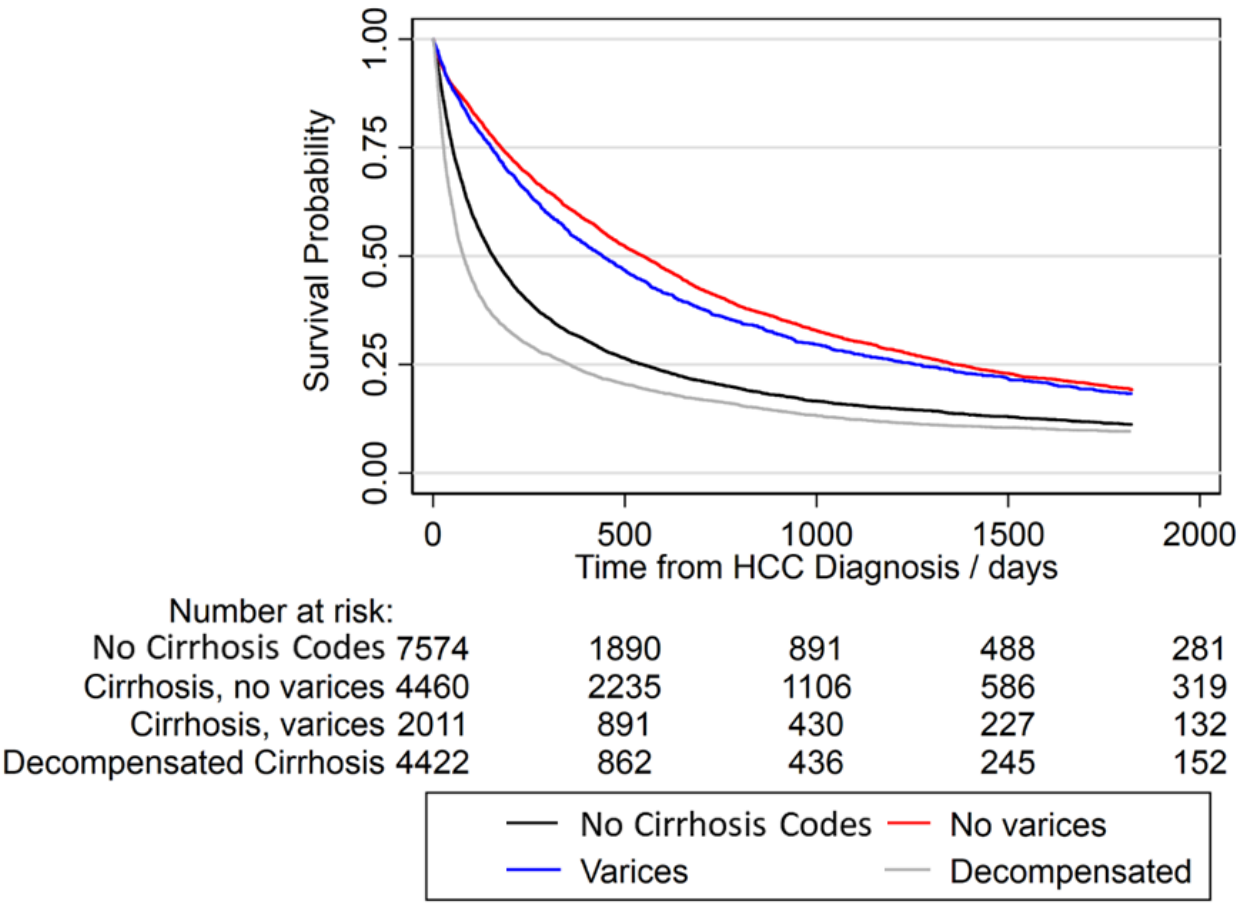

Figure 13. Kaplan Meier survival curve for overall survival from HCC diagnosis date, stratified by cirrhosis severity at HCC diagnosis.

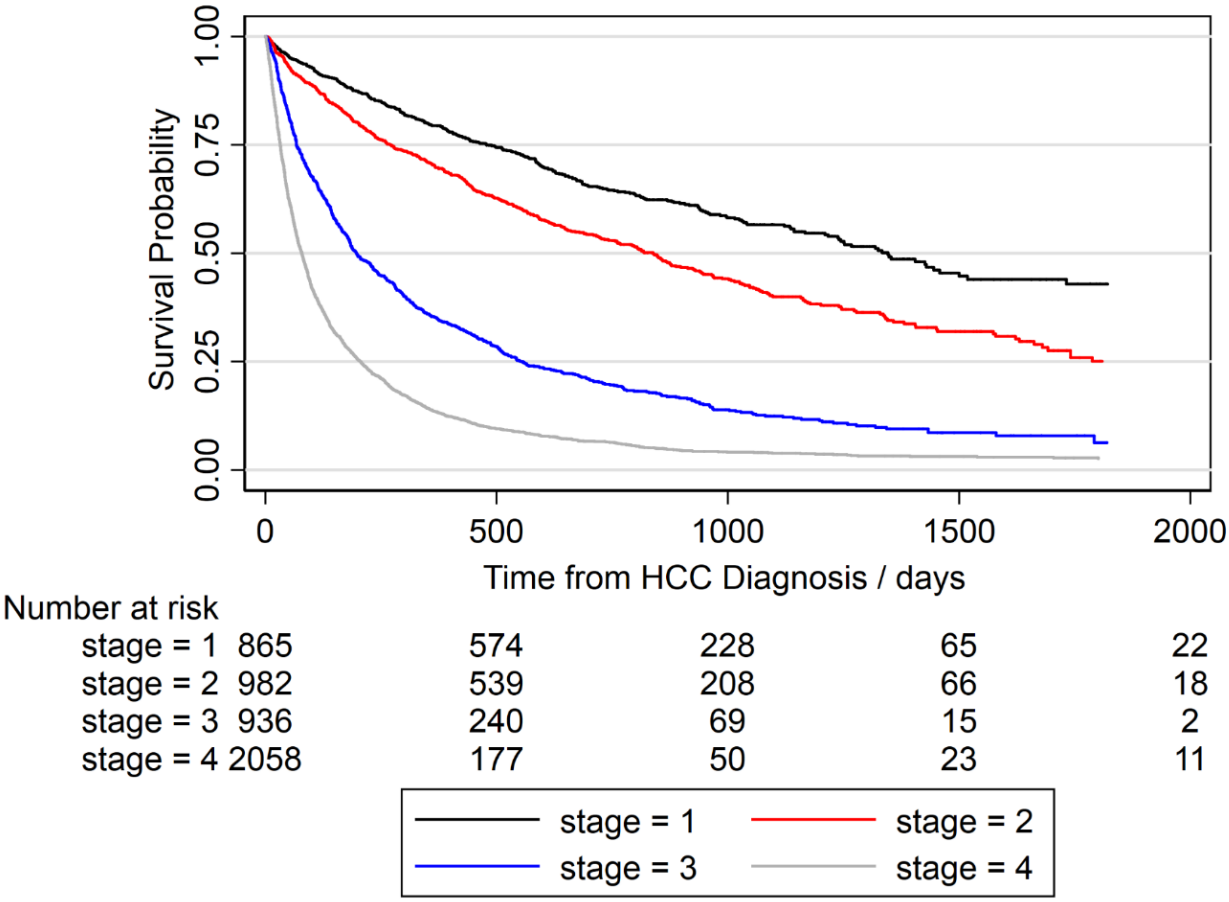

Figure 14. Kaplan Meier survival curve for overall survival from HCC diagnosis date, stratified by cancer stage at HCC diagnosis.

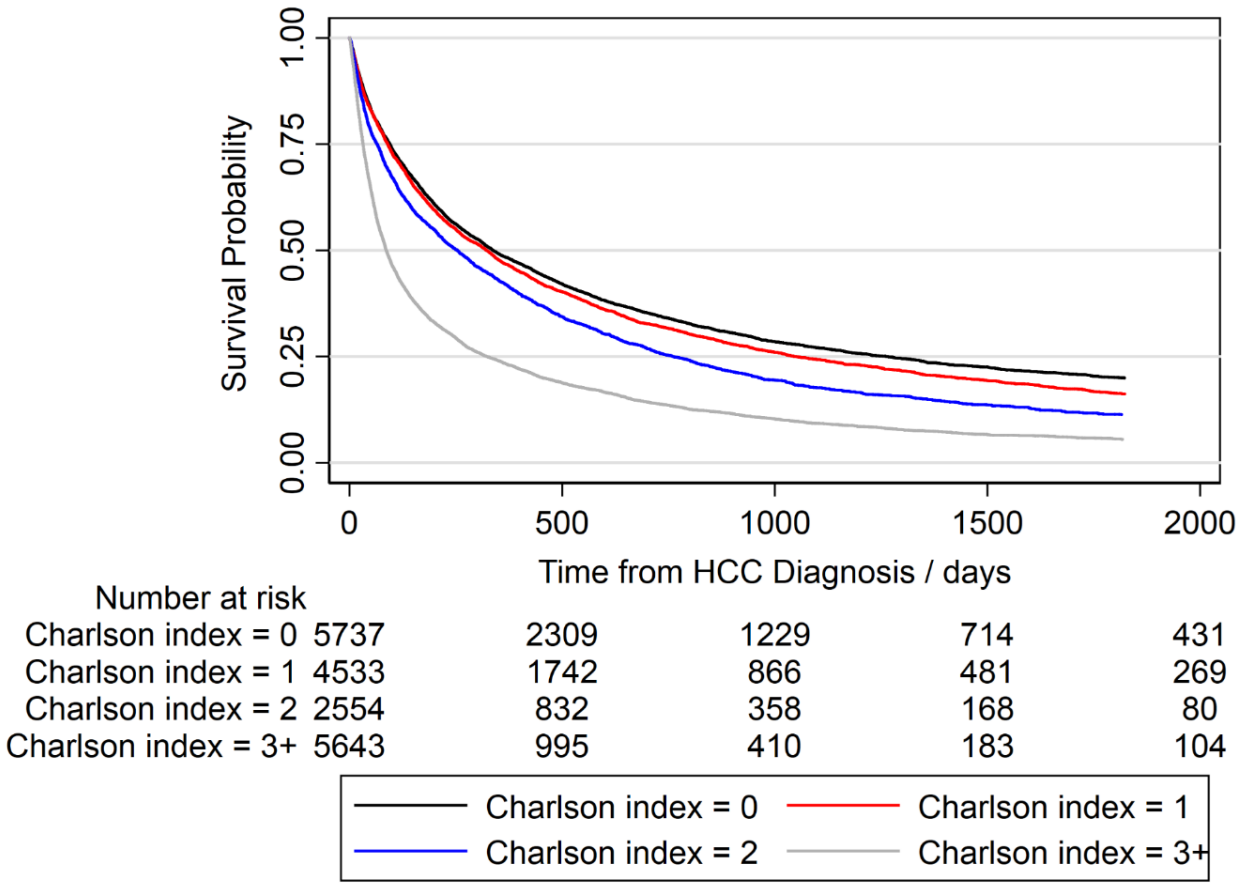

Figure 15. Kaplan Meier survival curve for overall survival from HCC diagnosis date, stratified by Charlson co-morbidity index at HCC diagnosis.

The results of the Cox proportional hazards regression are shown in Table 33. The adjusted hazard ratios (HR) for each covariate are presented relative to the reference variable. Increasing age is associated with overall mortality in multivariable analysis. There is no association between known ethnicity and survival in multivariable analysis; however, HCV and HBV are associated with superior survival and it is noted that these aetiologies were more common among South Asian and Chinese populations (Table 27).

Among patients with inpatient cirrhosis codes, increasing severity is associated with a worse prognosis. Increasing cancer stage and increasing co-morbidities are also associated with reduced overall survival. Increasing social deprivation (measured by income domain) was associated with reduced overall survival.

Characteristic		Hazard ratio (univariable)	Hazard ratio (multivariable)	95% CI	P-value
Sex	Male		ref		
	Female	1.00	0.97	0.93-1.01	0.10
Age Group	<50	0.70*	0.71*	0.65-0.77	<0.001
	50-59	0.83*	0.89*	0.84-0.94	<0.001
	60-69	ref	ref		
	70-79	1.24*	1.22*	1.17-1.28	<0.001
	80+	1.66*	1.50*	1.43-1.58	<0.001
Ethnicity	Not stated	1.36*	1.44*	1.36-1.51	<0.001
	White	ref	ref		
	Black	0.75*	1.09	0.97-1.22	0.16
	South Asian	0.85*	0.97	0.89-1.05	0.48
	Other Ethnic Group	0.84*	1.02	0.92-1.14	0.67
	Chinese	0.64*	0.94	0.79-1.12	0.52
	Mixed	1.01	1.27	0.98-1.65	0.07
Aetiology	HCV	0.64*	0.81*	0.76-0.86	<0.001
	HBV	0.64*	0.83*	0.75-0.92	<0.001
	PBC	0.84*	0.88*	0.78-0.99	<0.001
	AIH	0.94	0.92	0.81-1.04	0.186
	Haemochromatosis	0.70*	0.76*	0.69-0.84	<0.001
	Alcohol	ref	Ref		
	NAFLD	1.12*	0.97	0.92-1.02	0.20
	Other/ unknown	1.3*	1.25*	1.18-1.32	<0.001
Liver Disease Severity	No Cirrhosis	1.70*	1.20*	1.14-1.25	<0.001
	Baveno 1	ref	Ref		
	Baveno 2	1.06	1.11*	1.05-1.18	0.001
	Baveno 3 & 4	2.15*	2.11*	2.01-2.21	<0.001
Charlson Index	0	ref	ref		
	1	1.08*	1.08*	1.03-1.13	0.001
	2	1.28*	1.23*	1.16-1.30	<0.001
	3 +	2.01*	1.69*	1.62-1.77	<0.001
Cancer Stage	Stage I	ref	ref		
	Stage II	1.48*	1.46*	1.27-1.66	<0.001
	Stage III	3.43*	3.11*	2.74-3.52	<0.001
	Stage IV	6.16*	4.86*	4.33-5.45	<0.001
Index of Multiple Deprivation	1	ref	ref		
	2	1.00	1.00	0.95-1.05	0.97
	3	1.01	1.02	0.97-1.08	0.47
	4	1.05	1.08*	1.02-1.14	0.003
	5	1.01	1.09*	1.03-1.15	0.002

*Table 33. Univariable and multivariable analysis of influence of baseline factors on overall survival using Cox proportional hazards model. * = significant at P < 0.05.*

9.1.2 HCC Treatment

The overall survival following HCC treatment is summarised in Table 34, along with the published survival estimates from the EASL Clinical Practice Guidelines (EASL, 2012, EASL, 2018). The KM survival curves from HCC diagnosis, stratified by treatment allocation, are shown in Figure 16.

HCC Treatment Modality	**Number of patients (%)**	**Median Survival/ months (95% CI)**	**1-year survival (%)**	**5-year survival (%)**	**EASL survival / months**
BSC (N, %)	12,013 (61.8)	2.7 (2.6 – 2.8)	14.8	2.1	< 3
Sorafenib (N, %)	743 (3.8)	9.1 (8.3 – 9.8)	38.1	3.0	11
TACE (N, %)	2,816 (14.5)	17.9 (17.1 – 18.8)	64.7	8.1	20
Ablation (N, %)	1,416 (7.3)	36.7 (35.1 – 38.8)	87.3	28.0	36
Resection (N, %)	1,495 (7.7)	65.3 (60.4 – 71.5)	86.5	52.8	-
Transplant (N, %)	953 (4.9)	–	93.7	75.6	-

Table 34. Overall survival stratified by treatment allocation, along with the estimated median survival in the EASL Clinical Practice Guidelines.

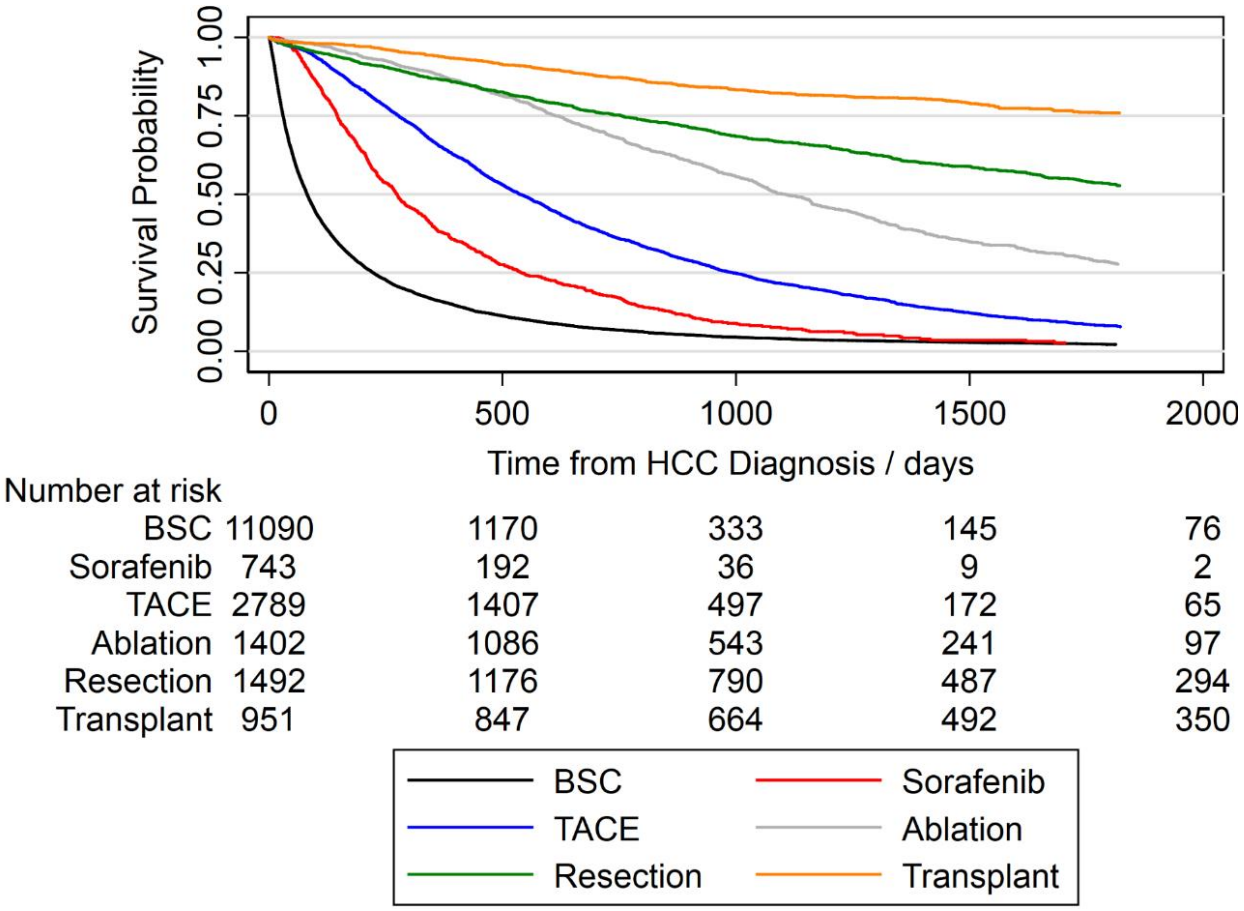

Figure 16. Kaplan Meier survival curve from HCC diagnosis, stratified by primary HCC treatment. BSC – best supportive care, TACE – trans-arterial chemoembolisation.

The clinical outcomes for non-curative HCC treatments (BSC, Sorafenib and TACE) are investigated in Section 9.2, with analysis of the impact of cirrhosis severity on survival and liver decompensation after treatment. Further analysis of clinical outcomes following potentially curative treatment with ablation is undertaken in Section 10. Section 11 includes a comparison of the clinical outcomes following ablation and resection. Given the complexity of analysing clinical outcomes following liver transplantation, further analysis is not presented in this study, as discussed in Section 7.3.2.

9.2 Clinical Outcomes after Non-curative HCC Treatments

In this section, the clinical outcomes are presented for patients who received Sorafenib, TACE and best supportive care. Within each treatment group, the impact of cirrhosis severity on survival and post-treatment decompensation is presented. Cause-specific mortality is estimated using the multi-state model of cirrhosis to approximate liver- and cancer-related mortality.

The baseline characteristics of the patients receiving these treatments are summarised in Table 30. The distribution of liver disease severity among these patients who received non-curative HCC treatment is summarised in Table 35.

	Treatment Modality			**Total**
	BSC	**Sorafenib**	**TACE**	
Cirrhosis Severity	N (%)	N (%)	N (%)	
No cirrhosis codes	5,801 (48.2)	384 (51.7)	795 (28.2)	**6,980**
Baveno 1	2,259 (18.8)	190 (25.6)	1,140 (40.5)	**3,589**
Baveno 2	898 (7.5)	90 (12.1)	482 (17.1)	**1,470**
Baveno 3 & 4	3,055 (25.4)	79 (10.6)	399 (14.2)	**3,533**
Total	**12,013**	**743**	**2,816**	**15,572**

Table 35. Distribution of liver disease severity among patients who received non-curative treatments for HCC.

9.2.1 Best Supportive Care

For patients with cirrhosis who received best supportive care, an estimate of cause specific mortality is described by a graphical representation of the cumulative incidence function (CIF) in Figure 17. The patients are stratified according to Baveno stage at HCC diagnosis. The areas in the graph represent the proportion of patients in each disease state (specified as either alive or dead, with or without an episode of decompensation following HCC diagnosis) over time. Patients with more advanced liver disease at HCC diagnosis are more likely to experience symptoms related to decompensated cirrhosis before death.

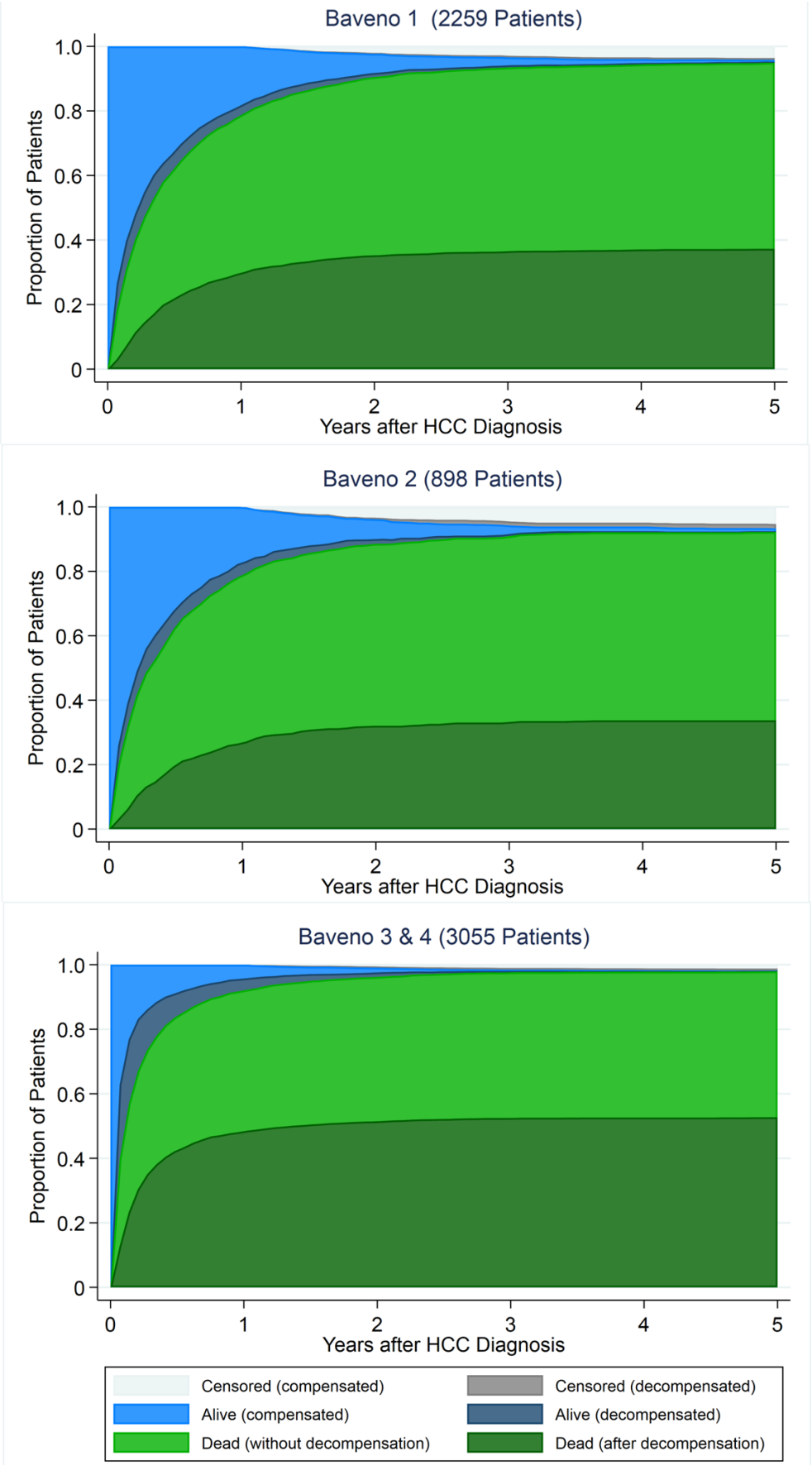

Figure 17. Stacked area graphs representing the cumulative incidence of different disease states following HCC diagnosis for patients with cirrhosis who received best supportive care.

Cancer- and liver-related mortality at 6 months post-HCC diagnosis is summarised in Table 36, along with 6-month all-cause mortality. Cause-specific mortality has been approximated by the presence or absence of decompensated cirrhosis after the HCC diagnosis date. Baveno stage was associated with 6-month all-cause mortality (χ^2 = 2700, P <0.001) and 'liver-related' mortality (χ^2 = 329, P <0.001). However, comparing the Baveno 1 and Baveno 2 groups, there was no difference in all-cause mortality (χ^2 = 1.1, P = 0.74) or liver-related mortality (χ^2 = 1.7, P = 0.92). Considering only those patients with cirrhosis codes, there was no difference in 'cancer-related' mortality between the Baveno groups (χ^2 = 2.4, P = 0.29).

	Total	6-month 'cancer-related' mortality (no decompensation)	6-month 'liver-related' mortality (decompensation)	6-month all-cause mortality
No cirrhosis codes	5,801	4,138 (71.3%)	0	4,138 (71.3%)
Baveno 1	2,259	897 (39.7%)	485 (21.5%)	1,382 (61.2%)
Baveno 2	898	381 (42.4%)	174 (19.3%)	555 (61.8%)
Baveno 3 & 4	3,055	1,264 (41.3%)	1,289 (42.2%)	2,553 (83.6%)

Table 36. Estimates of cause-specific mortality at 6 months post HCC diagnosis for patients who received best supportive care only

The association of cirrhosis severity with early mortality following HCC diagnosis is analysed in Table 37, considering death at 90 days after the registered HCC diagnosis date. For each Baveno stage, the proportion of patients who experienced a hospital admission with decompensated cirrhosis within 90 days of the HCC diagnosis date was calculated. The 90-day 'liver-related' mortality has also been calculated for each Baveno stage by considering the number of these patients who died after decompensation. The Baveno stage was associated with 90 day mortality (χ^2 = 475, P <0.001) and liver-related mortality (χ^2 = 384, P <0.001). Comparing the Baveno 1 and Baveno 2 groups, there was no difference in 90-day mortality (χ^2 = 1.3, P = 0.26) or 90-day liver-related mortality (χ^2 = 0.32, P = 0.57).

	Total	Decompensation within 90 days of HCC Diagnosis	90-day 'liver-related' mortality (decompensation)	90-day mortality rate (all-cause)
No cirrhosis codes	5,801	0	0	3,201 (55.2%)
Baveno 1	2,259	477 (21.1%)	291 (12.9%)	989 (43.8%)
Baveno 2	898	173 (19.3%)	109 (12.1%)	413 (46.0%)
Baveno 3 & 4	3,055	1,448 (47.4%)	1,026 (33.6%)	2,186 (71.6%)

Table 37. Early mortality and decompensation events occurring after 90 days of HCC diagnosis for patients who received best supportive care only.

9.2.2 Sorafenib

All-cause and cause-specific mortality at 12 months after the start of Sorafenib treatment is summarised in Table 38. Patients with clinically significant portal hypertension (Baveno 2, 3 and 4) had a higher mortality rate than those with no cirrhosis codes or Baveno stage 1 cirrhosis ($\chi^2 = 5.1$, $P = 0.02$). The estimated 'liver-related' mortality in these patients with more severe cirrhosis was also higher ($\chi^2 = 77.0$, $P < 0.001$).

	Total	12 month 'cancer-related' mortality (no decompensation)	12 month 'liver-related' mortality (decompensation)	12 month mortality rate (all-cause)
Baveno 1 and no cirrhosis codes	574	343 (59.8%)	50 (8.7 %)	393 (68.4%)
Baveno 2, 3 & 4	169	70 (41.4%)	61 (36.1%)	131 (77.5%)

Table 38. Estimates of cause-specific mortality at 12 months after the start of Sorafenib treatment

The disease state occupancy following treatment with Sorafenib is summarised in Figure 18, representing the incidence of decompensated cirrhosis in patients following Sorafenib treatment. The patients have been stratified according to Baveno stage at HCC diagnosis and this demonstrates the marked increase in decompensation following treatment for those patients with more severe liver disease.

Clinical outcomes within 90 days of the initiation of Sorafenib therapy are summarised in Table 39. Early decompensation was more commonly seen in patients with more advanced cirrhosis ($\chi^2 = 25.8$, $P < 0.001$) and the all-cause 90-day mortality was higher in this group ($\chi^2 = 10.0$, $P = 0.002$). However, the mortality rate in the absence of decompensation was the same for both groups ($\chi^2 = 1.15$, $P = 0.28$).

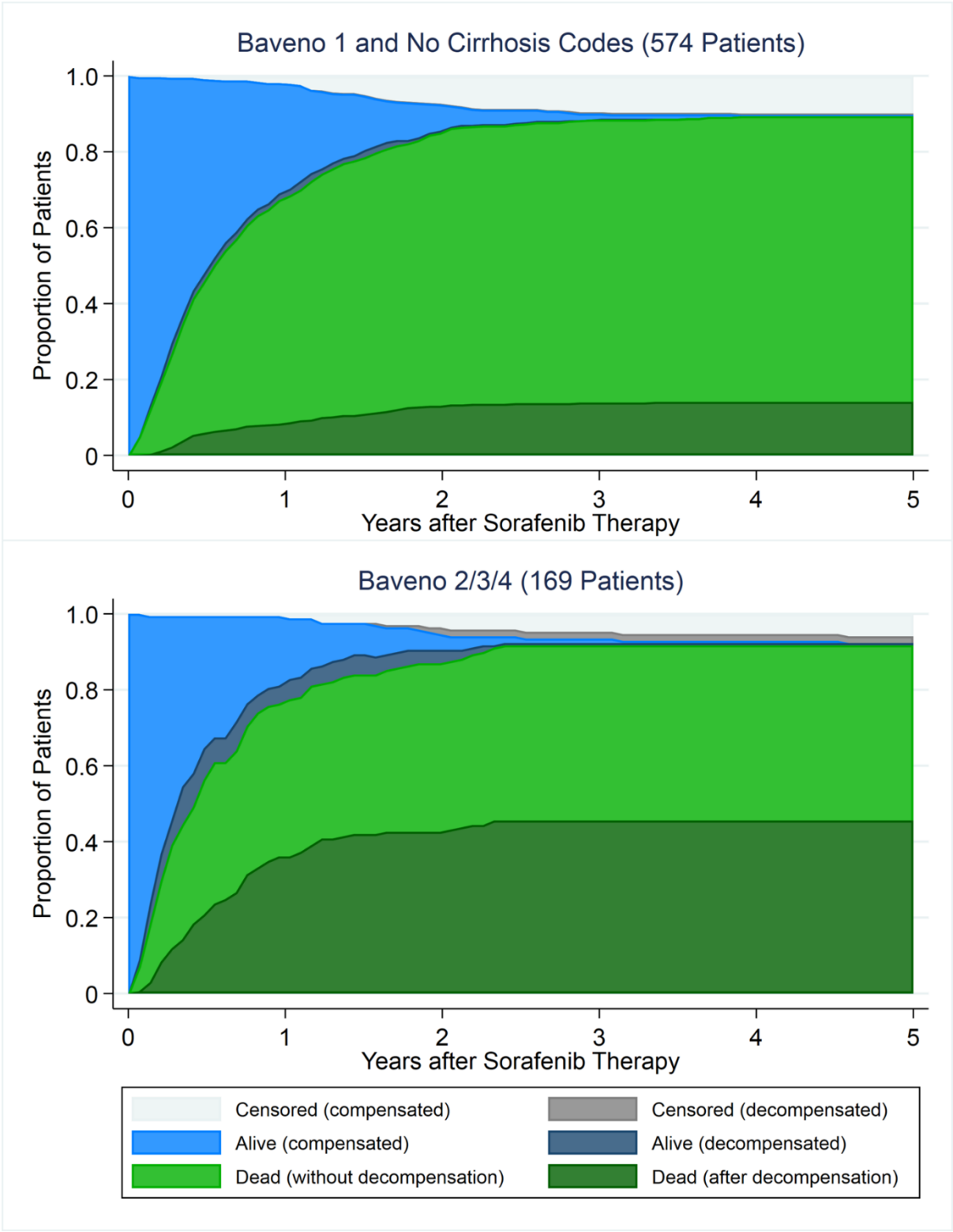

Figure 18. Stacked area graphs representing the cumulative incidence of different disease states following Sorafenib therapy.

	Total	Decompensation within 90 days of first Sorafenib	90-day 'liver-related' mortality (decompensation)	90-day 'cancer-related' mortality (no decompensation)	90-day mortality rate (all-cause)
Baveno 1 and no cirrhosis codes	574	24 (4.2%)	10 (1.7%)	130 (22.6%)	140 (24.4%)
Baveno 2, 3 & 4	169	27 (16%)	17 (10.1%)	45 (26.6%)	62 (36.7%)

Table 39. Early mortality and decompensation events occurring after 90 days of initial Sorafenib treatment.

9.2.3 Trans-arterial Chemoembolisation

All-cause and cause-specific mortality at 12 months after the start of TACE treatment is summarised in Table 40. The patients have been stratified according Baveno stage, with those patients with no cirrhosis codes included with those with Baveno stage 1. Increasing Baveno stage is associated with 12-month mortality ($\chi^2 = 17.7$, $P < 0.001$) and 'liver-related' mortality ($\chi^2 = 141$, $P < 0.001$). There was no difference in 12-month mortality between the Baveno 1 group and the Baveno 2 group ($\chi^2 = 0.41$, $P = 0.52$), but the 'liver-related' mortality was higher in the Baveno 2 group ($\chi^2 = 57.9$, $P < 0.001$).

	Total	12-month 'cancer-related' mortality (no decompensation)	12-month 'liver-related' mortality (decompensation)	12-month mortality rate (all-cause)
Baveno 1 and no cirrhosis codes	1,935	680 (35.1%)	164 (8.5%)	844 (43.6%)
Baveno 2	482	119 (24.7%)	99 (20.5%)	218 (45.2%)
Baveno 3 & 4	399	106 (26.7%)	114 (28.6%)	220 (55.1%)
Total	**2,816**	**905 (32.1%)**	**377 (13.4%)**	**1,282 (45.5%)**

Table 40. Estimates of cause-specific mortality at 12 months after the start of TACE therapy.

The disease state occupancy following treatment with TACE is summarised in Figure 19. Approximately half of the patients with clinically significant portal hypertension (Baveno 2 and above) experienced decompensation before death (approximated as 'liver-related mortality').

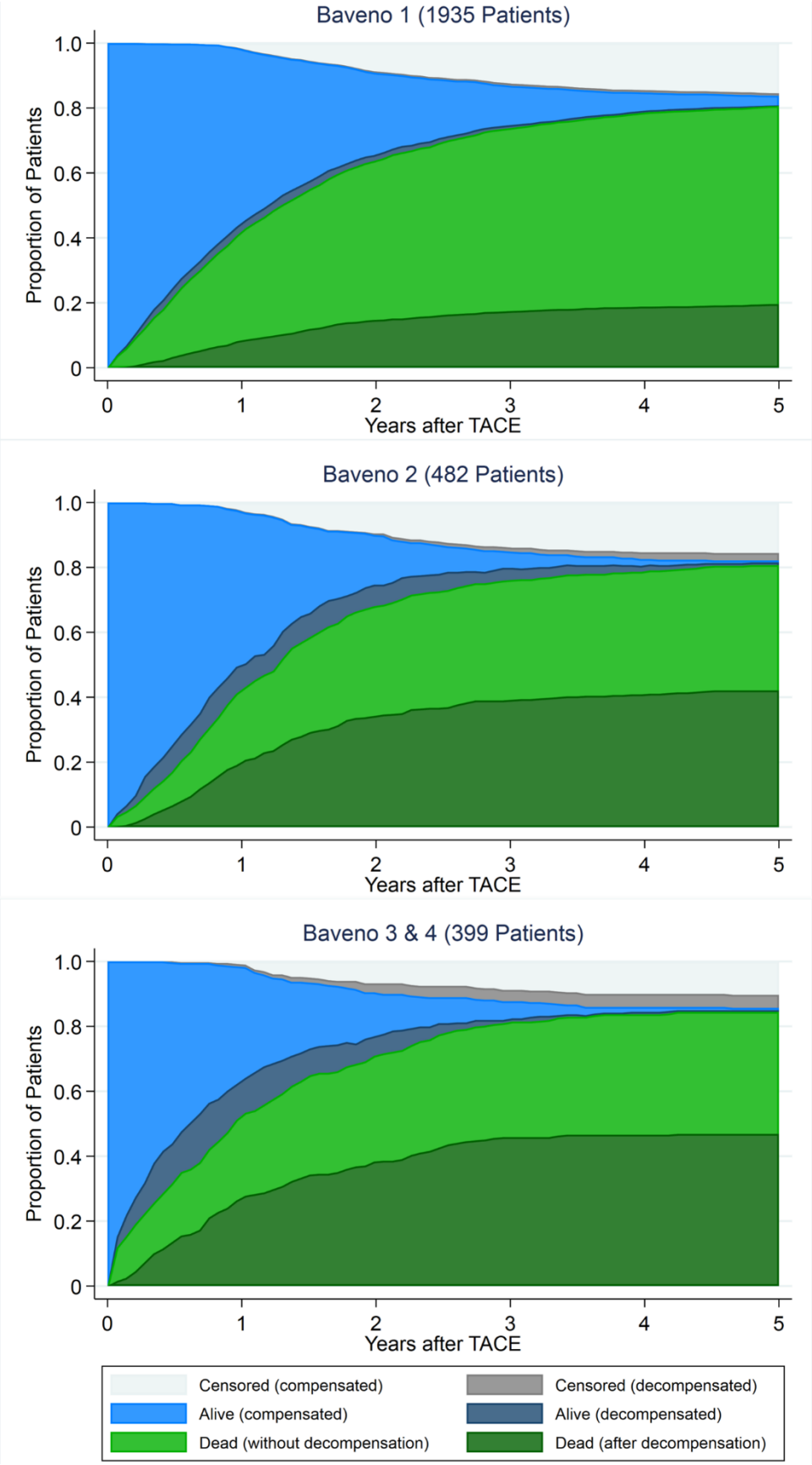

Figure 19. Stacked area graphs representing the cumulative incidence of different disease states following TACE treatment.

Clinical outcomes related to decompensated cirrhosis within 90 days of the first TACE treatment are summarised in Table 41. Early decompensation after TACE was associated with Baveno stage ($\chi^2 = 105$, $P < 0.001$) and this was most strongly associated with the Baveno 3 and 4 group (Pearson residual $\chi^2 = 71.6$, $P < 0.001$). This group was also associated with increased 90-day mortality from all causes ($\chi^2 = 29.4$, $P < 0.001$). The rate of decompensation after TACE was greater in the Baveno 2 group compared with Baveno 1 ($\chi^2 = 24.3$, $P < 0.001$), but the overall 90-day mortality rate was unchanged ($\chi^2 = 2.86$, $P = 0.09$).

	Total	Decompensation within 90 days of first TACE treatment	90-day 'liver-related' mortality (decompensation)	90-day mortality rate (all-cause)
Baveno 1 and no cirrhosis codes	1,935	53 (2.7%)	19 (1.0%)	225 (11.6%)
Baveno 2	482	36 (7.5%)	11 (2.3%)	43 (8.9%)
Baveno 3&4	399	60 (15.4%)	23 (5.8%)	81 (20.3%)
Total	**2,816**	**149 (5.3%)**	**53 (1.9%)**	**349 (12.4%)**

Table 41. Early decompensation and mortality after initiation of TACE therapy.

9.3 Discussion of Results

9.3.1 Baseline Characteristics

Increasing age has an expected influence on overall survival, along with increasing cancer stage (where known) and medical co-morbidities. Not only do these factors present risk factors for poor prognosis, they also impact on the eligibility for potentially curative invasive HCC treatments.

The apparent increased survival in univariable analysis for South Asian, Black and Chinese populations can be explained by the association with hepatitis B and C. These patients may be known to secondary care services due to their known viral hepatitis and so may be more likely to be enrolled with HCC surveillance. This may lead to earlier identification of HCC, amenable to curative treatment.

Increasing cirrhosis severity is associated with worse overall survival. However, the presence of no cirrhosis codes carries a worse prognosis. Again, this may be explained by survivor bias, or the presentation with advanced HCC in patients not known to have cirrhosis.

9.3.2 HCC Treatment

The estimated overall survival for patients undergoing different HCC treatments in England during the study period is comparable with the estimates based on clinical trials published in the EASL Guidelines (EASL, 2012, EASL, 2018). As expected, the 'potentially curative' treatments, including transplant, resection and ablation offer the best overall survival. However, there are significant variations within these groups, and it is the aim of the forthcoming analyses to investigate these further.

9.3.2.1 Best Supportive Care

The outcomes for patients who received best supportive care represent the natural history of HCC and cirrhosis, in the absence of treatment. The graphical representation of the CIF demonstrates that early mortality after HCC diagnosis is highest in patients with advanced liver disease (Baveno 3 and 4). The proportion of patients who died following a hospital admission related to decompensated cirrhosis is greater for those with advanced cirrhosis. In this model, this represents increased liver-related mortality.

Considering clinical outcomes within 90 days of HCC diagnosis, approximately one fifth of patients with previously compensated cirrhosis (Baveno stage 1 or 2) had an inpatient admission with decompensation. Among these, more than 60% died in this period. Nearly half of patients with Baveno stage 3 or 4 experienced further clinical events related to decompensation after their HCC diagnosis and among these, over 70% died within 90 days. These high mortality rates in those patients with the most advanced cirrhosis demonstrate the association of portal hypertensive complications with the development of HCC (Ripoll et al., 2009) . However, it is likely that many of these patients were admitted to hospital due to complications of decompensated liver disease and HCC was diagnosed at the time. These data show an association, but do not provide evidence for a causative link between the development of HCC and the onset of portal hypertensive complications in cirrhosis.

Patients who did not have inpatient cirrhosis codes had a higher 6-month all-cause mortality than those in the Baveno 1 and Baveno 2 groups. As discussed previously, this may reflect a survival bias since some of these patients may have died shortly after their HCC diagnosis and additional diagnosis codes related to cirrhosis were not captured in the HES dataset. However, patients in this group were also older and had more co-morbidities. This highlights a limitation of this simplified model in defining ‘cancer-related’ mortality as ‘non-liver-related’ mortality. In addition, patients with known cirrhosis may be more likely to be diagnosed with HCC earlier, through either routine care or a surveillance programme. This may represent a lead-time bias.

An additional 969 individuals had an overall survival of zero days after HCC diagnosis. It is likely that the cancer diagnosis was registered via the death certificate, so further analyses on these patients was not possible. The sensitivity analysis suggested that there was a higher proportion of patients with no inpatient cirrhosis codes, as well as a high proportion (32.0%) who had previous decompensated cirrhosis. It is likely that these patients presented either with advanced HCC which was not amenable to treatment, or HCC in the background of advanced liver disease which precluded treatment.

9.3.2.2 Sorafenib

Decompensated cirrhosis is a contraindication for Sorafenib treatment. However, a proportion of patients with more advanced liver disease were deemed eligible for treatment. Approximately half of those patients with clinically significant portal hypertension (Baveno 2 and above) experienced decompensation after treatment. This would preclude ongoing

Sorafenib treatment, so is an important consideration for patients and clinicians when deciding on management options.

Chemotherapy agents represent a physiological stress on the liver and decompensation in cirrhosis is a recognised risk with the initiation of Sorafenib. The rate of liver decompensation within 90 days of starting treatment was higher in those patients with significant portal hypertension. The 90-day mortality was higher in this group, and this difference was associated with an increase in liver-related mortality.

In the original clinical trial in Sorafenib (Llovet et al., 2008a), the 12-month mortality was 66% in patients treated with Sorafenib and this is comparable to the 68.4% mortality in the 'no cirrhosis codes and Baveno 1' group. In the trial, 95% of patients were Child Pugh A and the drug was discontinued due to 'liver dysfunction' in 5% of patients. For comparison, the rate of decompensation within 90 days of starting treatment was 4.6% in the 'no cirrhosis and Baveno 1' group, but in those with clinically significant portal hypertension, it was 16%. The 90-day mortality in both Baveno groups (24.4% and 36.7% respectively) was higher than in the trial (16.7%).

These comparisons highlight real-world clinical experience, but caution is needed given the differences in baseline characteristics and the limited detail in the NCRAS dataset. It should also be noted that the trial included patients who had received previous resection (19%), ablation (15%) and TACE (29%), whereas for these analyses, only those patients who received Sorafenib as the primary treatment modality were included.

9.3.2.3 Trans-arterial Chemoembolisation

The overall median survival of 17.9 months was slightly lower than the estimate of 20 months in the EASL Guidelines, which was based on clinical trial data. This may reflect wider inclusion criteria in real-world practice, including patients with more advanced cirrhosis and other co-morbidities. Although the presence of ascites is a contraindication for TACE, patients with prior decompensation are eligible for treatment if the liver function has improved sufficiently at the time of treatment.

Patients with the most severe cirrhosis (Baveno 3 and 4) had a worse overall prognosis and higher rates of decompensation after treatment. Overall survival and 90-day mortality were

similar for those patients who were not known to have significant portal hypertension (Baveno 1 and no cirrhosis codes) and those with compensated cirrhosis and known varices (Baveno 2). However, the rate of decompensation after TACE was higher in the Baveno 2 group and the 'liver-related' mortality was higher according to this model. According to the BCLC classification and EASL guidelines (EASL, 2018), patients are eligible for TACE if they are Child Pugh A with no ascites, but the presence of portal hypertension is not a contraindication. These findings support this selection of patients, who have similar overall survival. However, the higher rate of decompensation after treatment should be considered in clinical practice as this impacts patients' experience as well as fitness for subsequent treatments.

In the original TACE trials, ascites occurred following TACE in 5.2% of cases in one trial (Lo et al., 2002) and TACE was discontinued due to liver dysfunction in 7.5% of cases in another (Llovet et al., 2002). These outcomes are consistent with this study (overall 90-day decompensation rate 5.3%), but this highlights the increased risk of decompensation in the Baveno 3 and 4 group (15.4%). In the same trials, the 12-month mortality was 43% (Lo et al., 2002) and 27.5% (Llovet et al., 2002). In the more recent trials in highly-selected patients (Burrel et al., 2012, Takayasu et al., 2012), the 12-month mortality rate was 11% and 13% respectively. The observed 12-month mortality of 45.5% in this study is consistent with the earlier trials, but it highlights the reduction in survival in the Baveno 3 and 4 group (55.1% mortality at 12 months).

In this simplified model of competing risk, patients in the 'Baveno 1 and no cirrhosis' group had a higher 'cancer related' mortality than the Baveno 2 group. This highlights a limitation in the model, because the absence of portal hypertensive complications are assumed to represent 'cancer-related' mortality. If patients with less severe cirrhosis are offered TACE as primary treatment, it may be assumed that their performance status or cancer stage precluded them from consideration of curative treatment, such as ablation or resection.

More detailed analysis of the outcomes of patients who received TACE is limited by the uncertainty over cancer stage in this study. Without knowing the size and number of tumours being treated with TACE, it is difficult to draw conclusions about the variations in overall survival in this group. It is possible that those patients who had preserved liver function were treated with TACE rather than ablation or resection because of the size of tumours, multi-focal disease, or due to patient factors such as fitness for surgery or anaesthetic.

10 National Study - Results and Analysis: Clinical Outcomes in Ablative Therapies for HCC

In this section, the clinical outcomes for patients receiving ablation for HCC were analysed. The impact of cirrhosis severity on overall survival and cause-specific mortality (defined as the presence or absence of decompensated cirrhosis after treatment) was investigated. Ablation is technically possible only for smaller tumours (BCLC guidelines stipulate less than three tumours of less than 3cm, with disease confined to the liver). Given the limitations of recorded cancer staging in the registry, ablation provides a suitable framework for studying other baseline factors as the cancer stage is assumed more uniform than other treatments.

10.1 Baseline Characteristics

In total, 1,611 patients received ablative therapies and among these, 73 patients had subsequent liver resection and 122 had a liver transplant. The baseline characteristics of the remaining 1,416 patients who received ablation as the primary treatment modality are summarised in Table 42, alongside groups defined by cirrhosis severity. P-values were derived from the Pearson χ^2 test; for each baseline factor, the proportion of patients in each Baveno stage group was compared to the proportions in the whole cohort.

For the purpose of these analyses, patients without any inpatient cirrhosis codes were grouped with cirrhotic patients with Baveno stage 1. Among the 78 patients with Baveno stage 4, only eight had variceal bleeding without ascites so Baveno stages 3 and 4 were combined as ‘decompensated cirrhosis’. Patients with higher Baveno stage were younger, more commonly male, less likely to have multiple co-morbidities, and more likely to have underlying alcohol-related liver disease. During the study, the proportions of each Baveno category receiving ablation remained constant over time and there was no significant change in the baseline characteristics, apart from a greater use of MWA over RFA in the later years (Table 43).

		Total	Baveno 1 n (%)	Baveno 2 n (%)	Baveno 3 & 4 n (%)	χ^2, P Value
		1,416	**820(57.9)**	**325(23.0)**	**271(19.1)**	
Sex	Male	1109	653(58.9)	238(21.4)	218(19.7)	χ^2 = 6.5, P = 0.039
	Female	307	167(54.4)	87(28.3)	53(17.3)	
Age Group	<50	71	36(50.7)	13(18.3)	22(31.0)	χ^2 = 58.4, P <0.001
	50-59	258	131(50.8)	57(22.1)	70(27.1)	
	60-69	460	250(54.4)	113(24.5)	97(21.1)	
	70-79	507	304(60.0)	131(25.8)	72(14.2)	
	80+	120	99(82.5)	11(9.2)	10(8.3)	
	% older than 70	627	403 (64.3)	142(22.7)	82(13.1)	χ^2 = 29.5, P <0.001
Ethnicity	White	1161	662(57.0)	266(22.9)	233(20.1)	χ^2 = 10.4, P = 0.41
	Black	50	33(66)	13(26)	4(8)	
	South Asian	72	41(57.0)	16(22.2)	15(20.8)	
	Other Ethnic Group	45	28(62.2)	11(24.4)	6(13.3)	
	Chinese	27	19(70.4)	7(25.9)	1(3.7)	
	Not Stated	61	37(60.6)	12(19.7)	12(19.7)	
Aetiology	Hepatitis C	325	197(60.6)	68(20.9)	60(18.5)	χ^2 = 151, P <0.001
	Hepatitis B	77	52(67.5)	13(16.9)	12(15.6)	
	Haemochromatosis	68	51(75)	11(16.2)	6(8.8)	
	Primary Biliary Cirrhosis	55	23(41.8)	20(36.4)	12(21.8)	
	Autoimmune Hepatitis	20	6(30)	6(30)	8(40)	
	Alcohol	404	166(41.1)	115(28.4)	123(30.5)	
	NAFLD	279	162(58.1)	79(28.3)	38(13.6)	
	Other	188	163(86.7)	13(6.9)	12(6.4)	
Cancer Stage	1	164	93(56.7)	46(28.1)	25(15.2)	χ^2 = 6.32, P = 0.61
	2	107	60(56.1)	27(25.2)	20(18.7)	
	3	20	10(50)	6(30)	4(20)	
	4	25	14(56)	4(16)	7(28)	
	Unknown	1100	643(58.5)	242(22)	215(19.5)	
Charlson Index	0	449	295(65.7)	89(19.8)	65(14.5)	χ^2 = 23.8, P = 0.001
	1	383	191(49.9)	107(27.9)	85(22.2)	
	2	279	157(56.3)	60(21.5)	62(22.2)	
	3+	305	177(58.0)	69(22.6)	59(19.4)	
IMD Quintile	1	224	131(58.5)	52(23.2)	41(18.3)	χ^2 = 2.86, P = 0.94
	2	250	137(54.8)	58(23.2)	55(22)	
	3	280	169(60.3)	61(21.8)	50(17.9)	
	4	261	153(58.6)	57(21.8)	51(19.6)	
	5	401	230(57.3)	97(24.2)	74(18.5)	
Ablation Technique	RFA	852	494 (58.0)	199 (23.4)	159 (18.7)	χ^2 = 3.70, P = 0.88
	MWA	418	238 (56.9)	97 (23.2)	83 (19.9)	
	Thermal	95	56 (59.0)	22 (23.2)	17 (17.9)	
	Alcohol Injection	21	12 (57.1)	4 (19.0)	5 (23.8)	
	Not specified	30	20 (66.7)	3 (10.0)	7 (23.3)	

Table 42. Baseline characteristics for patients who received ablation.

		Total	2007-2010 n (%)	2011-2013 n (%)	2014-2016 n (%)	χ^2, P Value
		1,416	326 (23)	435 (30.7)	655 (46.3)	
Baveno Stage	Baveno 1	820	189 (23.1)	255 (31.1)	376 (45.9)	χ^2 = 1.76, P = 0.78
	Baveno 2	325	74 (22.8)	105 (32.3)	146 (44.9)	
	Baveno 3 & 4	271	63 (23.3)	75 (27.7)	133 (49.1)	
Ablation Technique	RFA	852	249 (29.2)	303 (35.6)	300 (35.2)	χ^2 = 197, P = 0<0.001
	MWA	418	22 (5.6)	90 (21.5)	306 (73.2)	
	Thermal	95	35 (36.9)	28 (29.5)	32 (33.7)	
	Alcohol Injection	21	7 (33.3)	6 (28.6)	8 (38.1)	
	Not specified	30	13 (43.3)	8 (26.7)	9 (30.0)	

Table 43. Variation in cirrhosis severity and ablation technique over time.

10.2 Overall Survival

For these analyses, the overall survival was taken from the first ablative treatment. The median survival was 31.5 months (95% CI 30.0 – 33.9). Baveno stage was associated with overall survival (log-rank χ^2= 85.6, P <0.001, Figure 20); for Baveno 1, median survival was 38.2 months (95% CI 35.2 – 41.5), for Baveno 2 it was 28.8 months (95% CI 25.4 – 30.7) and for Baveno 3 and 4 it was 19.6 months (95% CI 16.2 – 23.0).

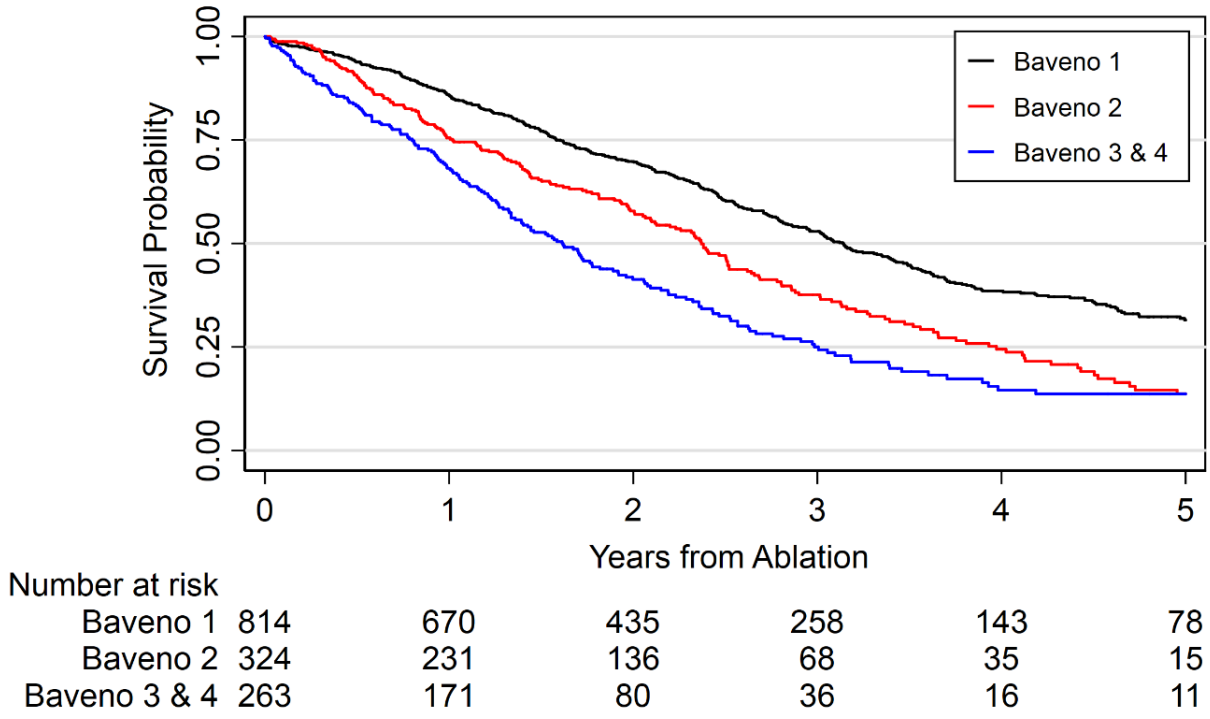

Figure 20. KM survival curves for survival following ablation, stratified by Baveno score.

Using the Cox proportional hazards regression, Baveno stage was shown to predict overall survival, after adjusting for potential confounding baseline factors (Table 44). The adjusted hazard ratio for patients with previous decompensation was 2.36 (95% CI 1.94-2.86) compared with the Baveno 1 group.

		Univariable		Multivariable	
		Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Baveno Stage	1	Ref			
	2	1.57 (1.32-1.85)	<0.001	1.64 (1.37-1.96)	<0.001
	3 & 4	2.18 (1.83-2.59)	<0.001	2.36 (1.94-2.86)	<0.001

Table 44. Univariable and Multivariable analysis of the effect of Baveno stage on overall survival after ablation for HCC using a Cox proportional hazard regression. The multivariable model was adjusted for age, sex, ethnicity, cancer stage, aetiology, Charlson co-morbidity index and IMD quintile.

10.3 90-Day Mortality

In total, 78 patients died within 90 days of the index ablation treatment. Baveno stage was associated with increased 90-day mortality (Table 45), as well as Charlson co-morbidity index. In patients with previous decompensation, the 90-day mortality was 12.2% and the odds ratio compared with the Baveno 1 group was 3.09 (95% CI 1.85-5.14)) using multivariable logistic regression, adjusting for potentially confounding baseline factors.

		90 Day Mortality (%)	Univariable		Multivariable	
			Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Sex	Male	4.87	Ref			
	Female	7.82	1.66 (1.01-2.73)	0.047		
Age Group	<50	1.41	0.24 (0.03-1.79)	0.163		
	50-59	5.81	1.03 (0.54-1.98)	0.929		
	60-69	5.65	Ref			
	70-79	5.52	0.98 (0.56-1.69)	0.930		
	80+	6.67	1.19 (0.53-2.70)	0.674		
Ethnicity	White	5.60	Ref			
	Black	4.00	0.70 (0.17-2.95)	0.630		
	South Asian	6.94	1.26 (0.49-3.23)	0.633		
	Other Ethnic Group	2.22	0.38 (0.05-2.83)	0.347		
	Chinese	3.70	0.65 (0.09-4.85)	0.673		
	Not Stated	6.56	1.18 (0.42-3.36)	0.752		
Aetiology	Alcohol	5.45	Ref			
	Hepatitis C	6.15	1.14 (0.61-2.12)	0.683		
	Hepatitis B	5.19	0.95 (0.32-2.84)	0.929		
	Haemochromatosis	7.35	1.38 (0.50-3.77)	0.533		
	Primary Biliary Cirrhosis	9.09	1.74 (0.63-4.79)	0.287		
	Autoimmune Hepatitis	5.00	0.91 (0.12-7.14)	0.932		
	NAFLD	3.23	0.58 (0.26-1.28)	0.175		
	Other	6.38	1.18 (0.57-2.45)	0.648		
Baveno Stage	1	4.27	Ref		Ref	
	2	3.08	0.71 (0.35-1.46)	0.352	0.79 (0.37-1.69)	0.544
	3 & 4	12.2	3.11 (1.89-5.11)	< 0.001	3.50 (1.99-6.15)	<0.001
Cancer Stage	1	2.44	Ref			
	2	4.67	1.96 (0.51-7.47)	0.324		
	3	0	--			
	4	4.00	1.67 (0.18-15.54)	0.654		
	Unknown	6.18	2.64 (0.95-7.32)	0.063		
Charlson Index	0	3.12	Ref			
	1	4.96	1.62 (0.80-3.28)	0.178		
	2	7.89	2.66 (1.34-5.29)	0.005		
	≥ 3	7.54	2.53 (1.28-5.01)	0.007		
IMD Quintile	1	4.46	Ref			
	2	9.20	2.17 (1.01-4.66)	0.048		
	3	4.64	1.04 (0.45-2.42)	0.924		
	4	4.98	1.12 (0.48-2.61)	0.790		
	5	4.74	1.06 (0.49-2.33)	0.876		

Table 45. Logistic regression of baseline factors predictive of 90-day mortality after ablation for HCC.

10.4 Competing Risk Analysis

An estimate of cause specific mortality following ablation is described by a graphical representation of the cumulative incidence function in Figure 21. The patients have been stratified by Baveno stage. For patients with more severe cirrhosis, a greater proportion experience decompensation after treatment. In the subsequent competing risk analyses, this is categorised as 'liver-related' mortality.

Clinical outcomes within 90 days of the first ablation treatment are summarised in Table 46. The 90-day all-cause mortality is associated with Baveno stage ($\chi^2 = 29.3$, $P < 0.001$). Baveno stage is also associated with the presence of decompensated cirrhosis within 90 days of ablation ($\chi^2 = 29.1$, $P < 0.001$), as well as the approximation of 'liver-related' mortality ($\chi^2 = 6.4$, $P = 0.04$).

	Total	Decompensation within 90 days of first ablation	90-day 'liver-related' mortality (decompensation)	90-day mortality rate (all-cause)
Baveno 1 and no cirrhosis codes	820	8 (1%)	3 (0.4%)	35 (4.3%)
Baveno 2	325	12 (3.7%)	2 (0.6%)	10 (3.1%)
Baveno 3 & 4	270	19 (7.0%)	5 (1.9%)	33 (12.2%)
Total	**1,416**	**39 (2.8%)**	**10 (0.7%)**	**78 (5.5%)**

Table 46. Early decompensation and mortality after first ablation treatment.

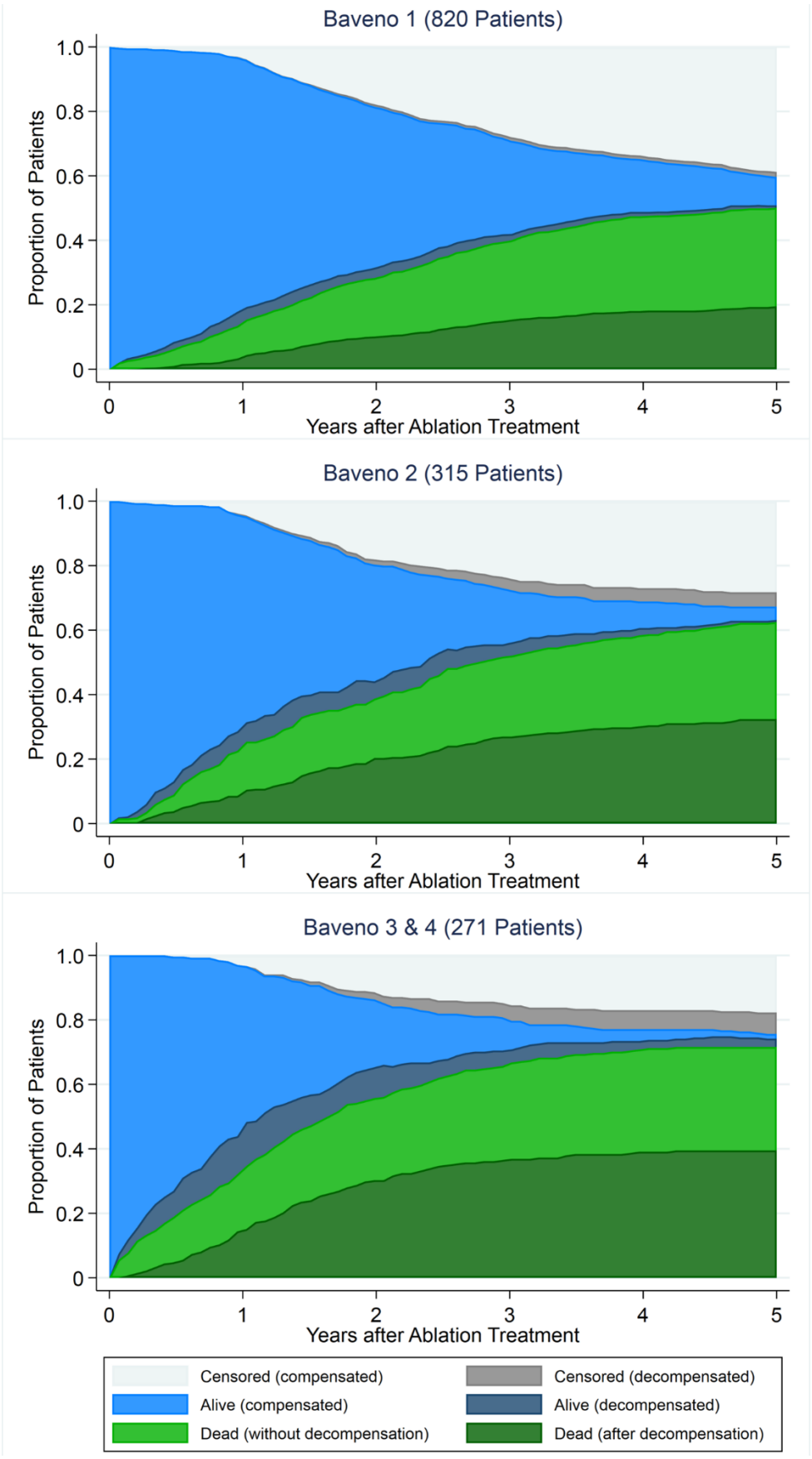

Figure 21. Stacked area graphs representing the cumulative incidence of different disease states following ablation treatment.

The cause-specific cumulative incidence functions for liver- and cancer-related mortality were calculated using both the Aalen-Johansen estimator and Lambert and colleague's flexible parametric model. The CIFs for each outcome, stratified by Baveno stage, are shown in Figure 22. There is a trend in increased liver-related mortality (modelled as decompensated cirrhosis occurring after treatment) with increasing liver disease severity at the time of ablative treatment. There was no difference in cancer-related mortality between the groups using this model.

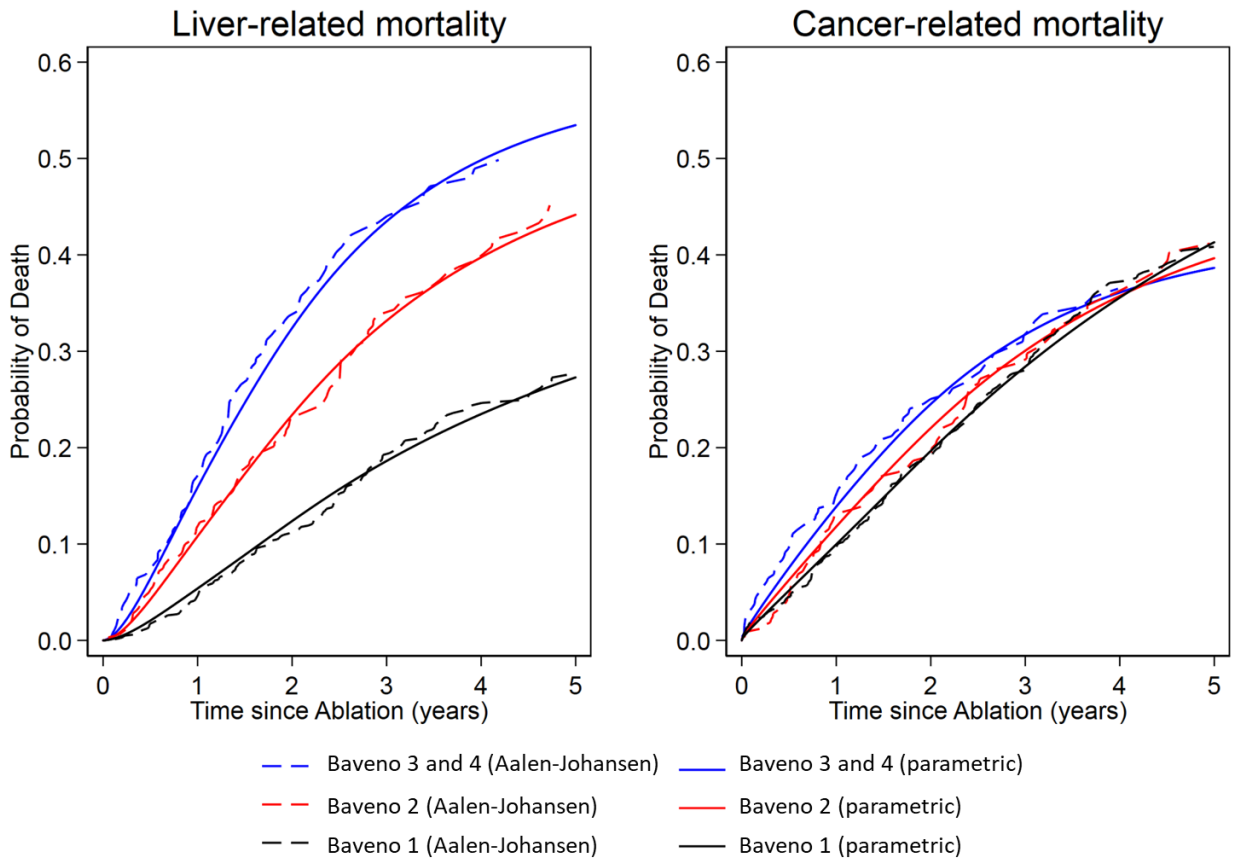

Figure 22. Estimates of the cause-specific cumulative incidence functions for liver- and cancer-related mortality, stratified by Baveno stage category.

Using the Fine and Gray multivariable regression model, the association between Baveno stage and liver- and cancer-related mortality is summarised in Table 47. This analysis is adjusted for potentially confounding baseline variables. Patients with prior decompensation (Baveno 3 & 4) were significantly more likely to experience liver-related mortality than the Baveno 1 group, with a sub-hazard ratio of 2.51 (95% CI 1.91-3.32, P < 0.001), but there was no difference in cancer-related mortality.

		Liver-related mortality		**Cancer-related Mortality**	
		Sub-hazard Ratio (95% CI)	P value	Sub-hazard Ratio (95% CI)	P value
Baveno Stage	1	Ref			
	2	1.68 (1.31-2.17)	<0.001	1.17 (0.90-1.50)	0.235
	3 & 4	2.51 (1.91-3.32)	<0.001	1.17 (0.88-1.56)	0.267

Table 47. Results of the Fine and Gray proportional subhazard model for liver- and cancer-related mortality after ablation for HCC. The potential confounding variables included age, sex, ethnicity, cancer stage, aetiology, Charlson co-morbidity index and IMD quintile

10.5 Discussion of Results

Increasing liver disease severity, measured by the Baveno classification, was the strongest predictor of overall survival and 90-day mortality after ablation for HCC. The median survival was shorter for increasing Baveno stage and this was confirmed in multivariable analysis using the Cox proportional hazards model.

Competing risk analysis demonstrated that this excess mortality relates to an increase in liver-related deaths. The proportion of patients who died after hepatic decompensation increased with increasing Baveno stage. The proportion of patients who died without a preceding decompensation event remained constant. The decrease in overall survival with increasing Baveno stage can be explained by the increase in liver-related mortality, as defined by this model.

Early decompensation within 90 days of ablation therapy was also associated with increasing Baveno stage – this may preclude future HCC treatment and significantly affects patients' experience. However, for those with previously compensated cirrhosis, the overall rate of decompensation was low (1.7%).

11 National Study - Results and Analysis: Comparison of Clinical Outcomes after Liver Resection and Ablation for HCC

In this section, the clinical outcomes for patients who received potentially curative treatment (resection and ablation) for HCC were analysed. Overall survival, and liver- and cancer-related mortality for the two treatments were compared.

11.1 Baseline Characteristics

In total, 1,526 patients underwent liver resection and 31 of these went on to have a subsequent liver transplant. The remaining 1,495 patients who received liver resection as their primary HCC treatment modality were analysed alongside the 1,416 patients in the ablation cohort. The baseline characteristics of this combined cohort of 2,911 patients who received potentially curative treatment are summarised in Table 48.

Compared with resection, ablation was more common among patients with portal hypertension and the proportion receiving ablation increased during the period of study. Patients undergoing resection had fewer co-morbidities and a greater proportion of tumours larger than 2cm (as demonstrated by cancer stage greater than I).

		Total	Ablation n (%)	Resection n (%)	P-value
		2,911	**1416 (49.0)**	**1495 (51.0)**	
Sex	Male	2226	1109 (78.3)	1117 (74.7)	0.022
	Female	685	307 (21.7)	378 (25.3)	0.022
Age Group	<50	257	71 (5.0)	186 (12.4)	<0.001
	50-59	499	258 (18.2)	241 (16.1)	0.133
	60-69	908	460 (32.5)	448 (30.0)	0.143
	70-79	1013	507 (35.8)	506 (33.8)	0.267
	80+	234	120 (8.5)	114 (7.6)	0.400
Ethnicity	White	2345	1161 (82.0)	1184 (79.2)	0.057
	Black	108	50 (3.5)	58 (3.9)	0.619
	South Asian	138	72 (5.1)	66 (4.4)	0.395
	Other Ethnic Group	86	40 (2.8)	46 (3.1)	0.688
	Chinese	67	27 (1.9)	40 (2.7)	0.167
	Mixed Race	13	5 (0.3)	8 (0.5)	0.462
	Not Stated	154	61 (4.3)	93 (6.2)	0.021
Aetiology	Hepatitis C	494	325 (23.0)	169 (11.3)	<0.001
	Hepatitis B	195	77 (5.4)	118 (7.9)	0.008
	Haemochromatosis	161	68 (4.8)	93 (6.2)	0.094
	Primary Biliary Cirrhosis	71	55 (3.9)	16 (1.1)	<0.001
	Autoimmune Hepatitis	33	20 (1.4)	13 (0.9)	0.167
	Alcohol	538	404 (28.5)	134 (9.0)	<0.001
	NAFLD	480	279 (19.7)	201 (13.4)	<0.001
	Other	939	188 (13.3)	751 (50.2)	<0.001
CharIson Index	0	1036	449 (31.7)	587 (39.3)	<0.001
	1	768	383 (27.0)	385 (25.8)	0.428
	2	470	279 (19.7)	191 (12.8)	<0.001
	3+	637	305 (21.5)	332 (22.2)	0.663
IMD Quintile	1	508	224 (15.8)	284 (19.0)	0.024
	2	534	250 (17.7)	284 (19.0)	0.350
	3	590	280 (19.8)	310 (20.7)	0.519
	4	545	261 (18.4)	284 (19.0)	0.696
	5	734	401 (28.3)	333 (22.3)	<0.001
Cancer Stage	1	372	164 (11.6)	208 (13.9)	0.060
	2	296	107 (7.6)	189 (12.6)	<0.001
	3	105	20 (1.4)	85 (5.7)	<0.001
	4	74	25 (1.8)	49 (3.3)	0.010
	Unknown	2064	1100 (77.7)	964 (64.5)	<0.001
Baveno Stage	1	2184	820 (57.9)	1364 (91.2)	<0.001
	2	381	325 (23.0)	56 (3.8)	<0.001
	3 & 4	346	271 (19.1)	75 (5.0)	<0.001
Year of Diagnosis	2007-2010	772	326 (23.0)	446 (29.8)	<0.001
	2011-2013	898	435 (30.7)	463 (31.0)	0.884
	2014-2017	1241	655 (46.3)	586 (39.2)	<0.001

Table 48. Baseline characteristics of patients who underwent resection and ablation for HCC.

11.2 Overall Survival and 90-Day Mortality

Overall survival was significantly longer following resection than ablation (Figure 23, log-rank χ^2 = 140.3, P < 0.001). Among patients who underwent resection, the median survival was 63.8 months (95% CI 58.0 – 71.0) and among those who received ablation, the median survival was 31.5 months (95% CI 30.0 – 33.9). There was no difference in short-term mortality; 90-day mortality following resection was 6.0% and following ablation it was 5.5% (χ^2 0.27, P = 0.61).

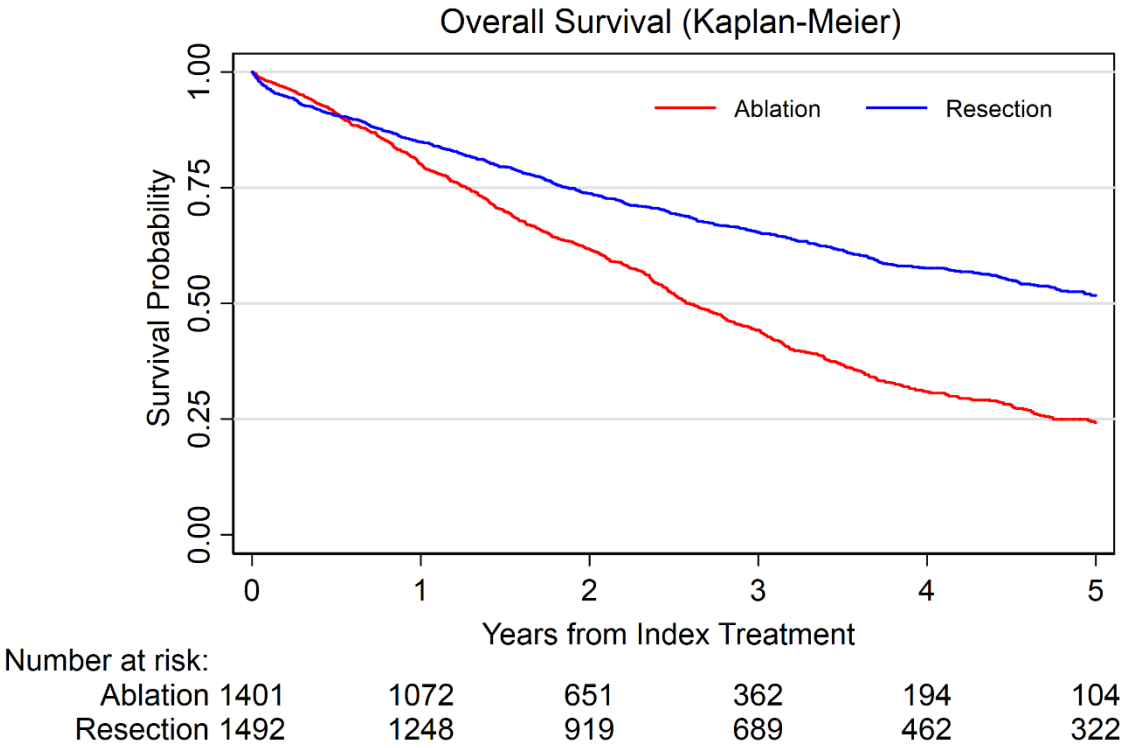

Figure 23. KM estimates of overall survival for patients who underwent resection and ablation.

11.2.1 Sensitivity Analysis

Within the cohort, patients were classified as 'Baveno 1' if they had no inpatient records relating to portal hypertensive complications; this group may contain patients with and without underlying cirrhosis. There were 820 patients classified as Baveno stage 1 who received ablation. Among these, 188 individuals did not have inpatient ICD10 codes for cirrhosis and 632 individuals did have cirrhosis codes. There was no difference in overall survival between these groups (log-rank χ^2 1.44, P = 0.23) (Figure 24). Similarly, there were 1,364 patients classified as Baveno stage 1 who received resection, and no difference in overall survival

between the 911 individuals who did not have inpatient cirrhosis codes and the 453 individuals who did (log-rank χ^2 0.63, P = 0.43) (Figure 25).

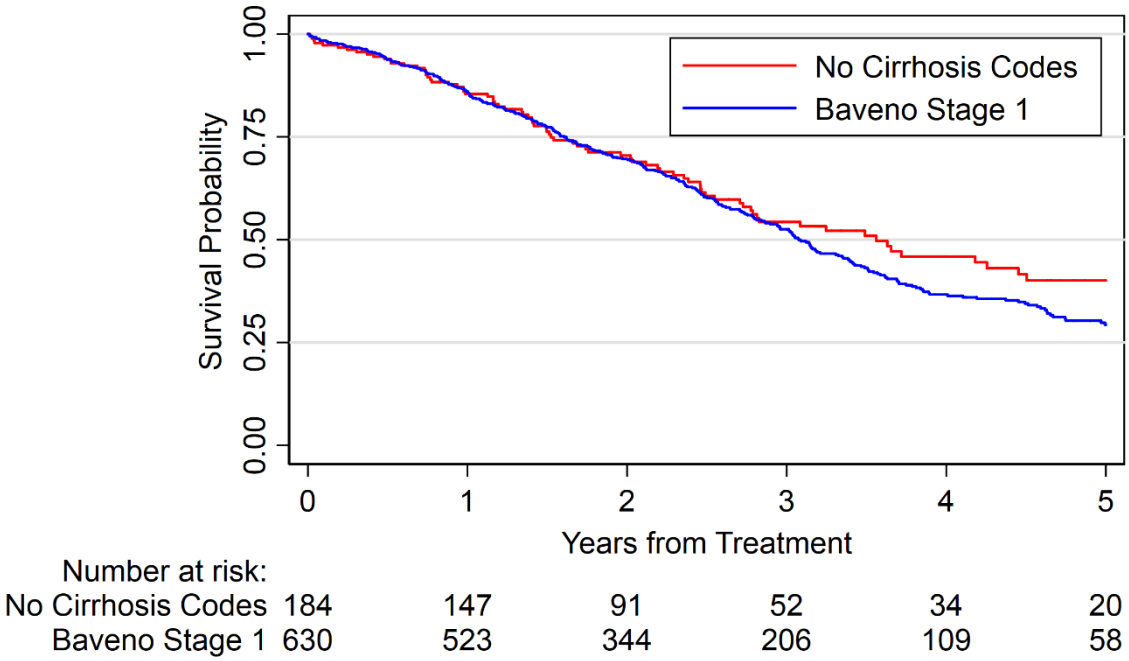

Figure 24. KM survival curve for patients who received ablation and were classified as Baveno stage 1, stratified by the presence and absence of inpatient codes related to cirrhosis.

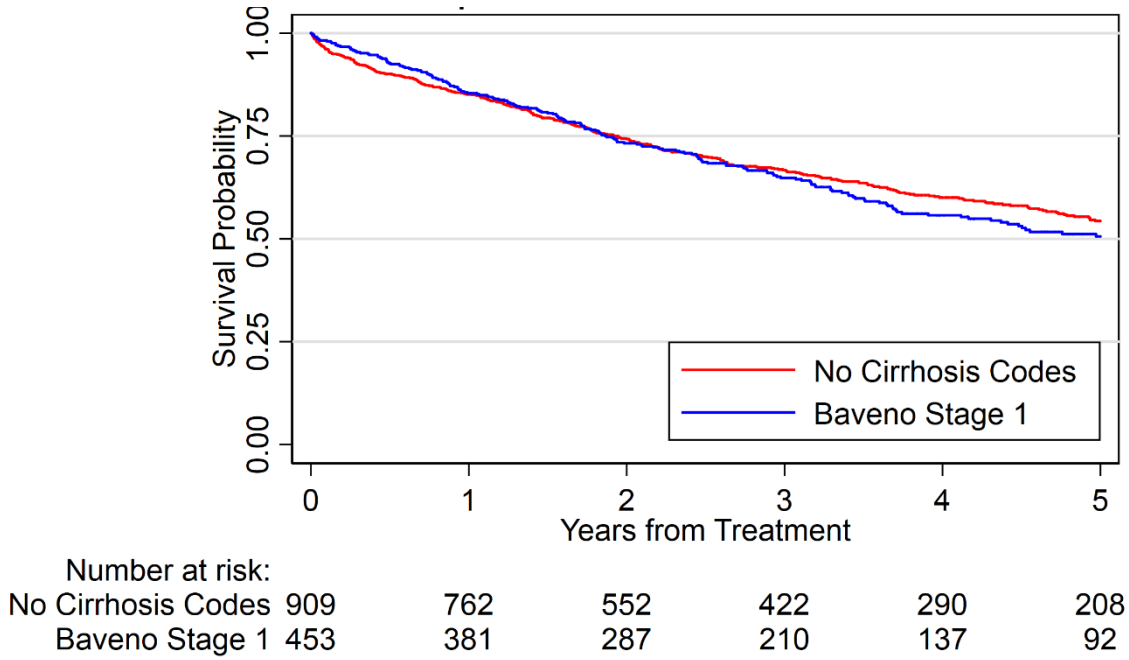

Figure 25. KM survival curve for patients who received resection and were classified as Baveno stage 1, stratified by the presence and absence of inpatient codes related to cirrhosis.

11.3 Competing Risks Analysis

Graphical representations of the cause-specific mortality for patients who received ablation and resection as primary treatment modality are presented in Figure 26.

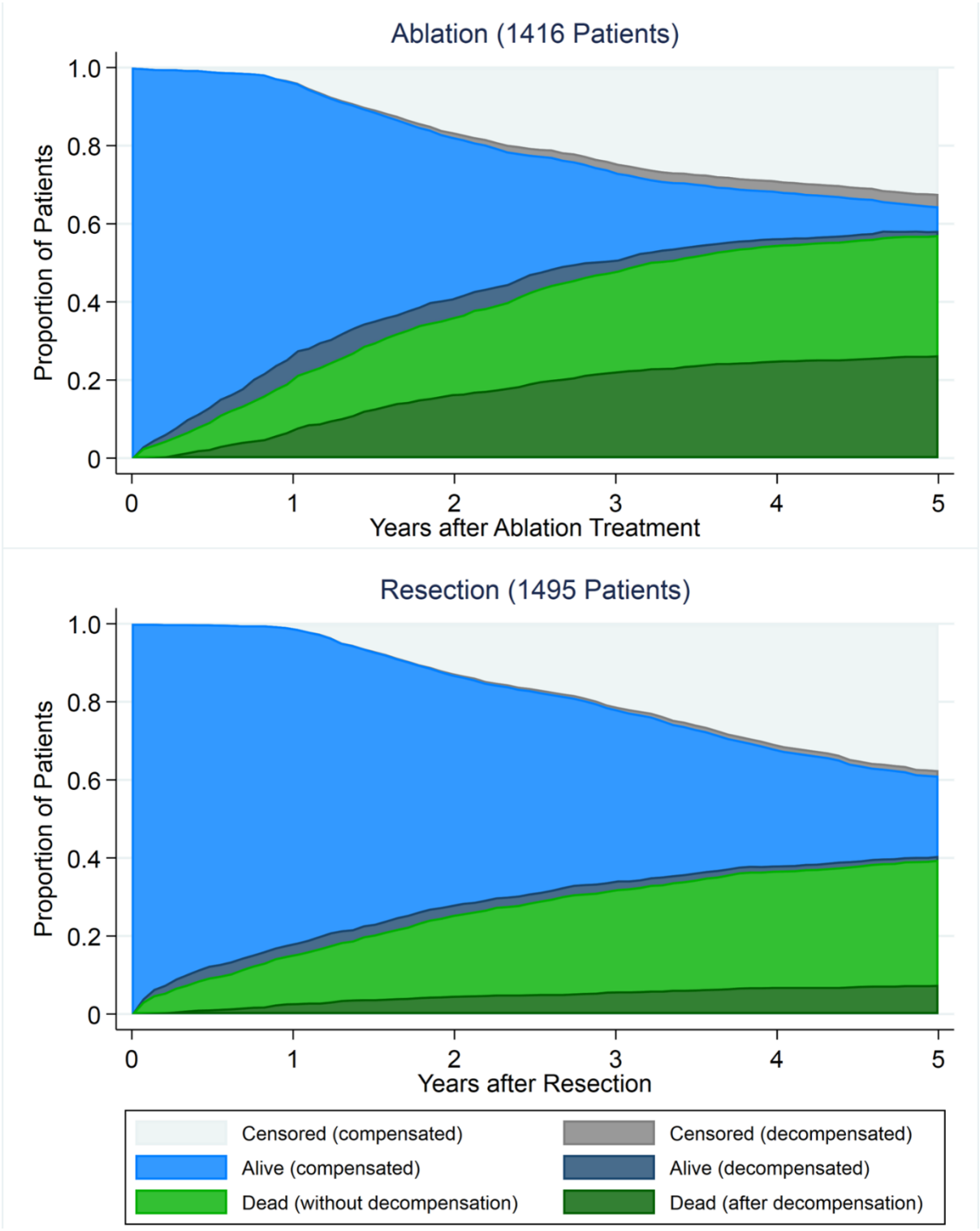

Figure 26. Stacked area graphs representing the cumulative incidence of different disease states following ablation and liver resection.

The CIFs for liver- and cancer-related mortality, stratified by treatment modality, are summarised in Figure 27. The marked increase in overall mortality in the ablation group is associated with a higher liver-related mortality compared with the resection group in univariable analysis, but the cancer-related mortality remains similar in both groups. These findings are reproduced in multivariable analysis using the Fine and Gray model (Table 49), when adjusted for baseline factors. The sub-hazard ratio for liver-related mortality in the ablation group is 3.04 (95% CI 2.39 – 3.86) compared with the resection group.

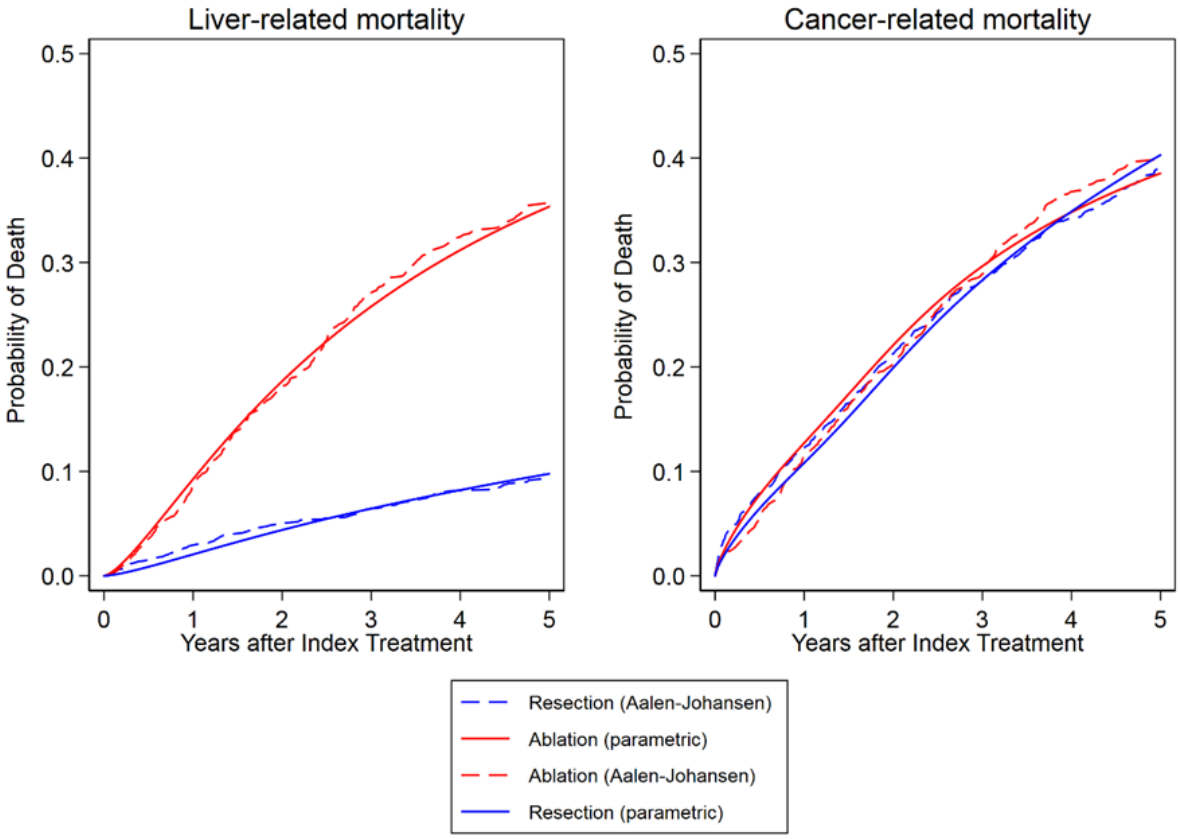

Figure 27. Estimates of the cause-specific cumulative incidence functions for liver- and cancer-related mortality, stratified by treatment modality.

	Liver-related mortality		**Cancer-related Mortality**	
	Sub-hazard Ratio (95% CI)	P value	Sub-hazard Ratio (95% CI)	P value
Resection	Ref		Ref	
Ablation	3.04 (2.39-3.86)	<0.001	0.99 (0.85-1.13)	0.85

Table 49. Results of the Fine and Gray proportional subhazard model for liver- and cancer-related mortality after resection and ablation for HCC. Adjustment was made for potentially confounding baseline variables, including age, sex, Baveno stage, cancer stage, Charlson index and IMD quintile.

11.3.1 Impact of Cirrhosis Severity on Clinical Outcomes after Resection

Most patients who underwent resection did not have clinically significant portal hypertension (Baveno 1). However, for those patients with a Baveno score of ≥ 2, the rates of decompensation post treatment were higher. In the model, the rates of liver-related mortality were higher in this group, as shown in Figure 28.

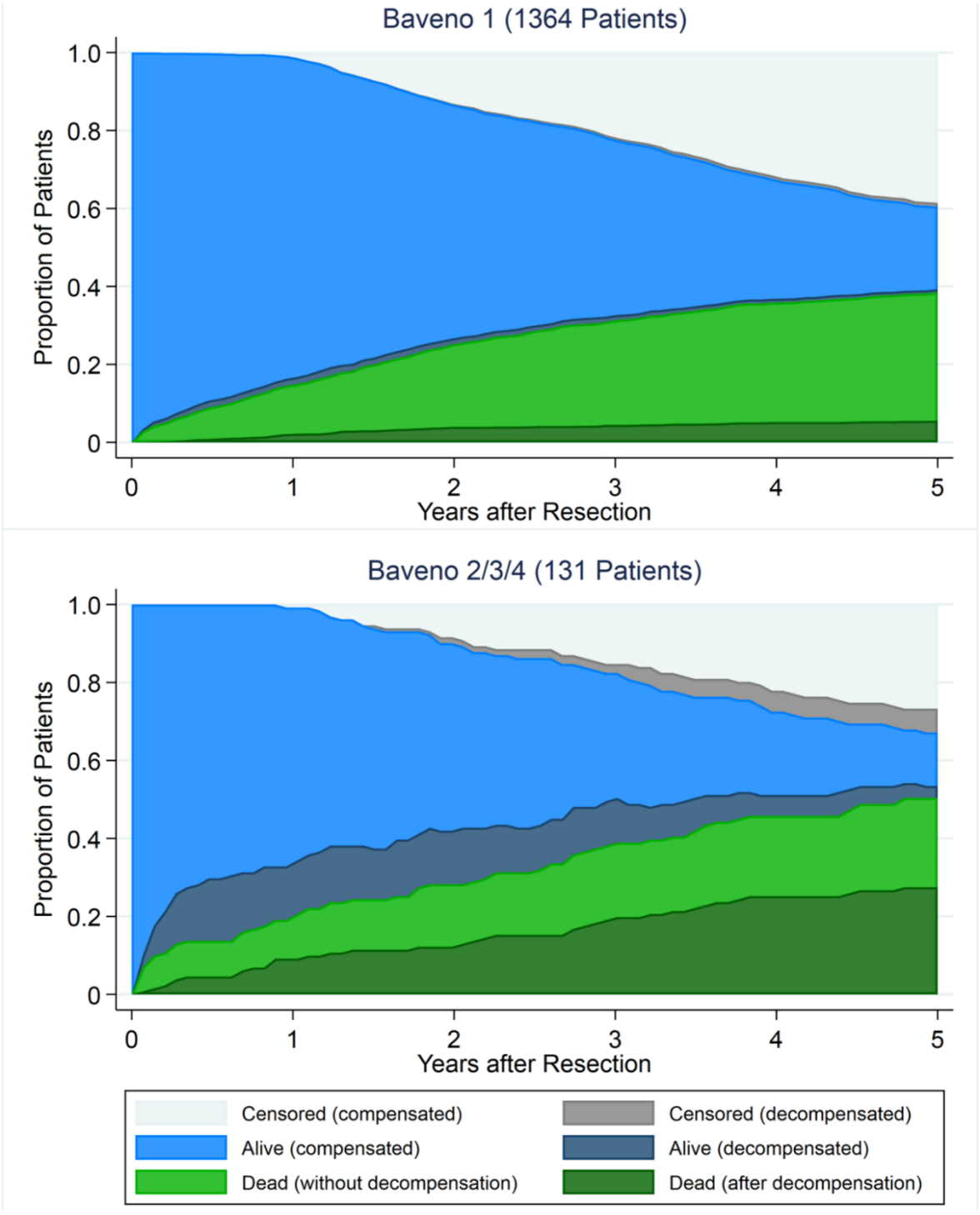

Figure 28. Stacked area graphs representing the cumulative incidence of different disease states following resection for different Baveno stages.

11.4 Discussion of Results

The marked difference in overall survival between the ablation and resection cohorts is associated with an increase in liver-related mortality in those patients who had ablation. In this model, there was no difference between cancer-related death between the two treatments. However, patients undergoing resection had more advanced cancer (larger tumours) and those undergoing ablation had more advanced liver disease (demonstrated by the presence of clinically significant portal hypertension).

This study is limited by the absence of information about cancer recurrence. Previous randomised control trials (Qi et al., 2014, Wang et al., 2014) have demonstrated superior overall survival and recurrence-free survival in resection compared to ablation. However, when considering treatment options for a patient on the borderline of eligibility criteria for resection, these analyses highlight that overall survival may be influenced by liver-related mortality in the presence of significant portal hypertension.

These data demonstrate that the increase in overall mortality after ablation compared with resection is associated with an increase in hepatic decompensation. This can be explained by the presence of more advanced cirrhosis in those who undergo ablation. The high rates of decompensation following surgery for those with more severe portal hypertension support the latest EASL guidelines about suitability for resection (EASL, 2018).

12 National Study - Results and Analysis: Regional Variation in HCC Treatment Allocation in England

This section examined the variation in baseline factors across different geographical regions in England. Subsequently, the regional variation in HCC treatment allocation was investigated, adjusted for differences in baseline factors.

12.1 Baseline Characteristics

The variation in baseline factors amongst the 19 Cancer Alliance (CA) regions is shown in Table 50. Since median age was not available, age has been presented as the percentage aged more than 70 in each CA. To prevent potential disclosure, smaller groups have been removed; only the three most common aetiologies are compared, and ethnicities have been suppressed due to small numbers. The percentage of patients with inpatient cirrhosis codes, together with the proportion with significant portal hypertension are compared. The percentage of patients with multiple co-morbidities in each CA are compared, along with the extremes of IMD quintiles.

Patients were significantly older in North Central and North East London, and South East London – these regions also had the highest proportion patients with hepatitis C-related HCC. In the North East and Cumbria, patients were significantly younger and there was the highest proportion of patients with alcohol-related liver disease, the highest proportion with NAFLD and the lowest proportion with hepatitis C-related HCC. This CA also had the greatest proportion of patients with multiple comorbidities. Since IMD quintile is determined by the postcode of residence, there is an association between this and the broader geographical location defined by CA.

Cancer Alliance	Male (%)	Age >70 (%)	HCV (%)	Alcohol (%)	NAFLD (%)	Cirrhosis (%)	Baveno 2 (%)	Baveno 3&4 (%)	Charlson 2 (%)	Charlson 3+ (%)	IMD 1 (%)	IMD 5 (%)	Total
Cheshire and Merseyside	76.4	51.0	13.4	26.9*	13.7	60.8	10.2	21.2	15.2	37.2	13.1	40.6*	**1,187**
East Midlands	77.1	49.9	11.1	17.7	16.2	57.4	8.6	24.0	12.8	34.7	16.8	20.7	**1,213**
East of England	77.7	49.4	14.2	18.1	16.6	58.7	11.5	21.1	16.2	31.1	17.9	12.0*	**2,049**
Greater Manchester	78.9	50.8	14.6	21.9	12.4	58.4	9.9	24.9	13.3	37.9	11.3*	39.1*	**1,271**
Humber, Coast and Vale	78.5	43.5	5.6*	19.3	14.3	49.7*	8.5	20.5	18.2	34.2	19.5	19.9	**483**
Kent and Medway	75.4	48.8	11.7	23.6	14.7	60.9	11.3	24.2	14.1	34.3	16.7	16.1*	**496**
Lancashire and South Cumbria	79.6	46.7	11.0	20.6	12.2	52.0	8.0	19.1	15.5	37.1	11.6	31.5*	**690**
North Central and North East London	79.8	59.5*	28.3*	14.0*	10.8*	64.7	13.1	24.7	11.9	30.6	3.5*	45.5*	**1,098**
North East and Cumbria	79.2	40.5*	6.2*	25.7*	18.7*	57.9	11.9	22.0	15.6	40.8*	13.6	34.4*	**1,426**
North West and South West London	77.0	55.5*	23.5*	19.4	9.8*	64.6*	11.2	25.8	14.5	32.8	11.1*	23.4	**1,118**
Peninsula	78.7	45.6	13.4	23.0	17.7	61.3	10.3	22.5	13.6	36.9	9.0*	14.1*	**610**
Somerset, Wiltshire, Avon and Gloucester	77.6	47.5	11.4	20.7	17.0	58.3	13.9	21.0	16.1	34.9	21.4*	11.7*	**875**
South East London	78.7	60.2*	20.3*	17.4	10.0	62.5	13.0	19.7	11.7	32.3	7.6*	32.5*	**563**
South Yorkshire, Bassetlaw, North Derbyshire	75.4	43.8	10.3	16.3	15.0	50.5	8.8	22.0	14.7	37.9	12.6	31.8*	**841**
Surrey and Sussex	79.1	43.3	12.1	20.9	14.1	55.9	9.0	23.4	13.4	34.2	28.6*	8.7*	**948**
Thames Valley	78.7	50.0	14.3	20.6	12.3	57.8	10.6	21.3	13.8	31.5	37.3*	6.8*	**616**
Wessex	79.9	45.2	10.3	21.7	17.8	61.2	14.7*	20.3	14.1	36.8	24.0*	8.5*	**856**
West Midlands	77.3	47.1	11.1	20.0	15.2	56.7	10.4	21.7	15.3	32.6	11.9*	30.4*	**2,026**
West Yorkshire and Harrogate	77.6	48.4	11.8	20.8	13.7	56.3	10.5	19.5	15.7	33.4	15.2	30.9*	**1,070**
Total	**78.0**	**48.7**	**13.5**	**20.4**	**14.6**	**58.3**	**10.8**	**22.2**	**14.6**	**34.7**	**15.4**	**25.2**	**19,436**

*Table 50. Summary of the variation in baseline factors in all patients diagnosed with HCC across the 19 Cancer Alliance regions of England. * = significant Pearson residual in χ2 analysis.*

12.2 Treatment Allocation

The unadjusted proportion of patients who received HCC treatments in each CA are summarised in Table 51. Those who received best supportive care only are not included.

Cancer Alliance	TACE n (%)	Ablation n (%)	Resection n (%)	Transplant n (%)	Total
Cheshire and Merseyside (1)	175 (14.7)	154 (13.0)	87 (7.3)	49 (4.1)	**1,187**
East Midlands (2)	187 (15.4)	86 (7.1)	86 (7.1)	44 (3.6)	**1,213**
East of England (3)	293 (14.3)	112 (5.5)	150 (7.3)	118 (5.8)	**2,049**
Greater Manchester (4)	206 (16.2)	65 (5.1)	111 (8.7)	47 (3.7)	**1,271**
Humber, Coast and Vale (5)	62 (12.8)	25 (5.2)	36 (7.5)	20 (4.1)	**483**
Kent and Medway (6)	114 (23.0)	41 (8.3)	22 (4.4)	20 (4.0)	**496**
Lancashire and South Cumbria (7)	82 (11.9)	24 (3.5)	59 (8.6)	24 (3.5)	**690**
North Central and North East London (8)	162 (14.8)	74 (6.7)	115 (10.5)	82 (7.5)	**1,098**
North East and Cumbria (9)	261 (18.3)	90 (6.3)	74 (5.2)	67 (4.7)	**1,426**
North West and South West London (10)	143 (12.8)	113 (10.1)	87 (7.8)	62 (5.6)	**1,118**
Peninsula (11)	86 (14.1)	39 (6.4)	66 (10.8)	37 (6.1)	**610**
Somerset, Wiltshire, Avon and Gloucester (12)	116 (13.3)	61 (7.0)	61 (7.0)	41 (4.7)	**875**
South East London (13)	118 (21.0)	59 (10.5)	30 (5.3)	18 (3.2)	**563**
South Yorkshire, Bassetlaw, North Derbyshire (14)	49 (5.8)	55 (6.5)	83 (9.9)	31 (3.7)	**841**
Surrey and Sussex (15)	141 (14.9)	56 (5.9)	61 (6.4)	32 (3.4)	**948**
Thames Valley (16)	66 (10.7)	57 (9.3)	56 (9.1)	47 (7.6)	**616**
Wessex (17)	110 (12.9)	66 (7.7)	58 (6.8)	31 (3.6)	**856**
West Midlands (18)	259 (12.8)	155 (7.7)	134 (6.6)	108 (5.3)	**2,026**
West Yorkshire and Harrogate (19)	186 (17.4)	84 (7.9)	119 (11.1)	75 (7.0)	**1,070**
Total	**2,816 (14.5)**	**1,416 (7.3)**	**1,495 (7.7)**	**953 (4.9)**	**19,436**

Table 51. Crude rates of different HCC treatments in the 19 Cancer Alliance regions in England. The numbers in parentheses next to the CA names relate to the labels in the subsequent funnel plots.

12.2.1 Ablation

The crude (unadjusted) ablation rate across the 19 CA regions is summarised in Figure 29.

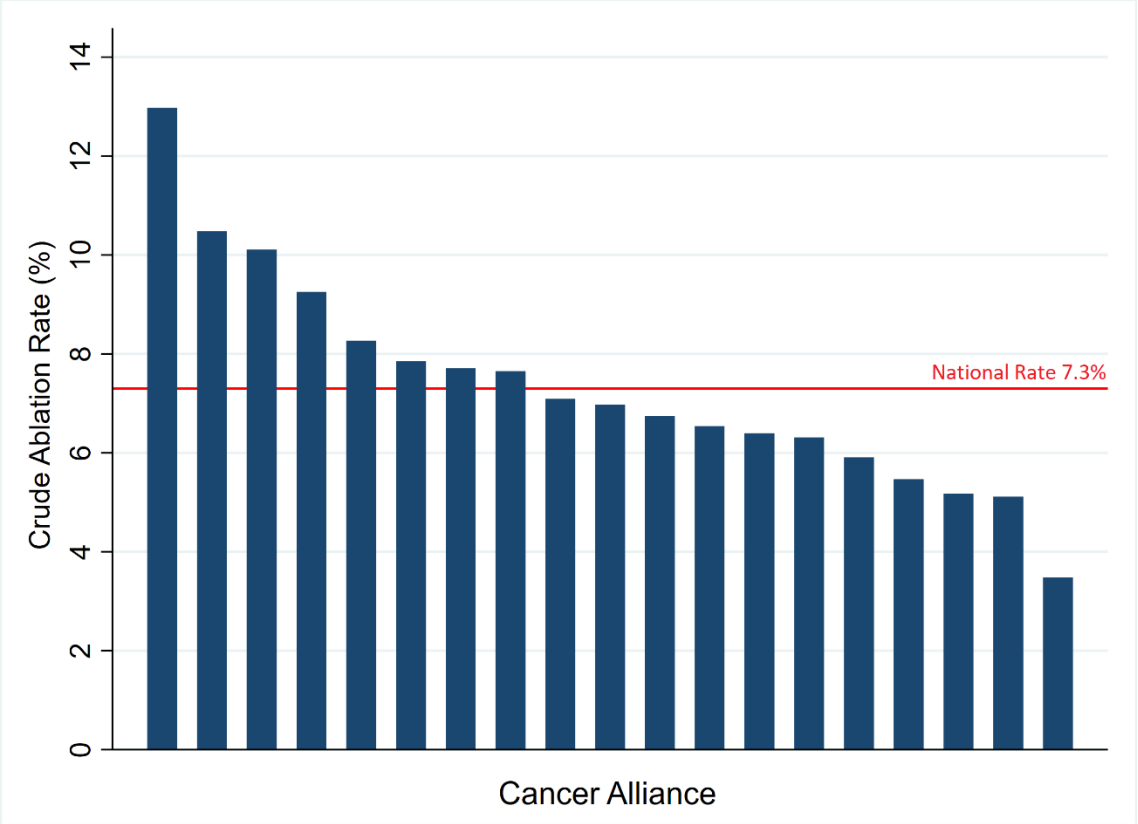

Figure 29. Proportion of patients who received ablation for HCC in each Cancer Alliance region.

In Figure 30, the ablation rate for each CA is displayed, with control limits for 2 and 3 standard deviations, based on the number of HCC cases in each region. Crude and adjusted rates are presented, using the distribution of baseline factors within each CA region. The adjusted ablation rate in Lancashire and South Cumbria (label 7), and in East of England (3) fall just below the 99.8% control limit. The proportion of patients receiving ablation in Cheshire and Merseyside (1) is significantly higher than the remainder of the UK.

The ablation rate in Greater Manchester (4) was between two and three standard deviations below the national rate. In North West and South West London (10) and Thames Valley (16), the adjusted ablation rate was between two and three standard deviations above the mean.

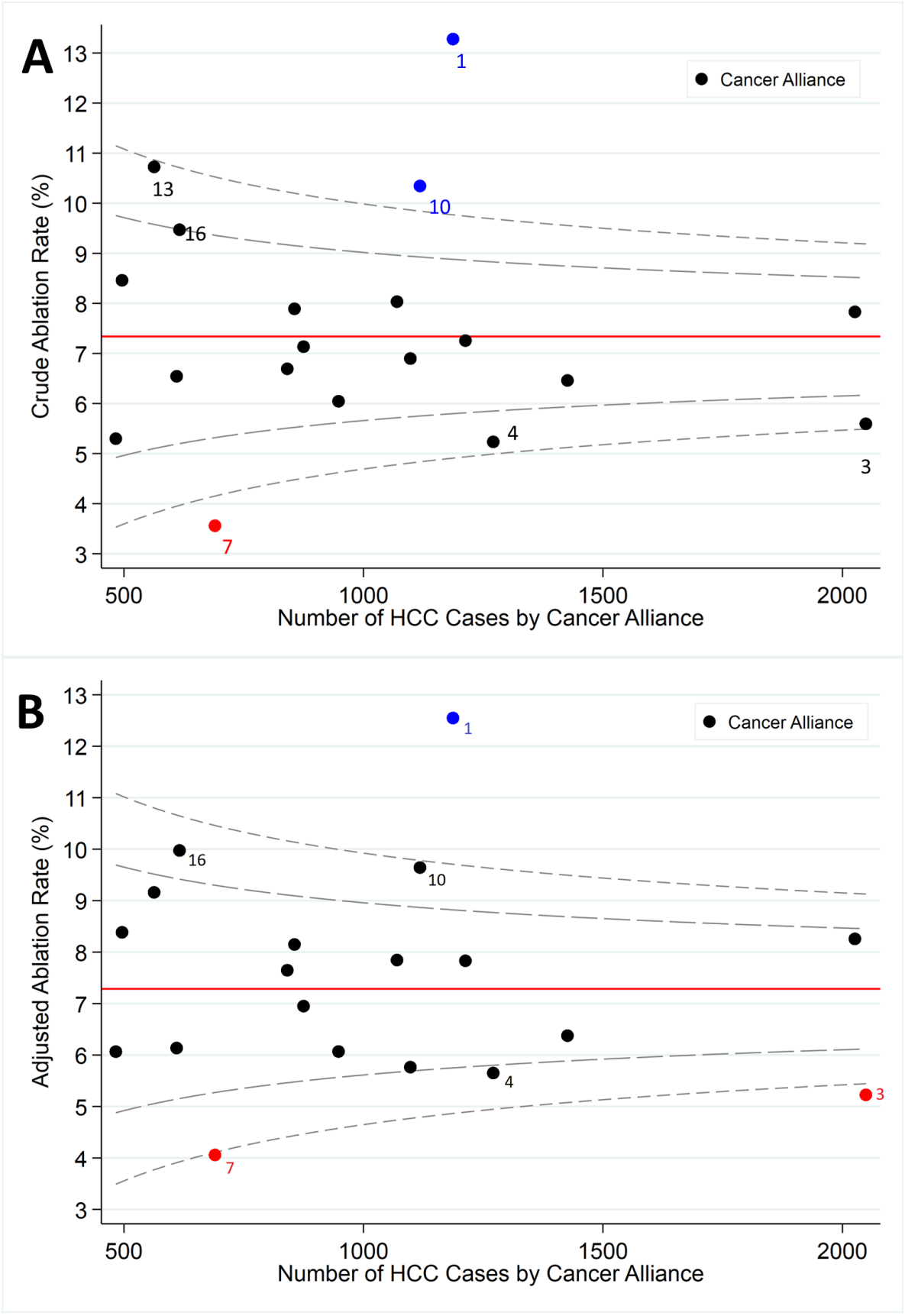

Figure 30. Funnel plots of the proportion of patients who received ablation in each Cancer Alliance. Plot A shows the crude rate and plot B is adjusted by baseline characteristics. Control limits of 2 standard deviations (long dashed lines) and 3 standard deviations (short dashed lines) are shown. The national rate is shown in red.

12.2.2 Resection

The crude resection rate across the 19 CA regions is summarised in Figure 31 and the crude and adjusted funnel plots are shown in Figure 32. West Yorkshire and Harrogate (19) had the highest liver resection rate on both crude and adjusted analyses – it is the only CA which falls outside the 99.8% control limit in the funnel plot.

The resection rates in Kent and Medway (6), and South East London (13) were between two and three standard deviations below the national resection rate. The resection rates in North Central and North East London (8), Peninsula (11), and South Yorkshire, Bassetlaw and North Derbyshire (14) were between two and three standard deviations above the national mean in the adjusted analyses. The crude resection rate in the North East and Cumbria CA (9) lies below 3 standard deviations of the mean, but when adjusted for the baseline factors, it is not an outlier.

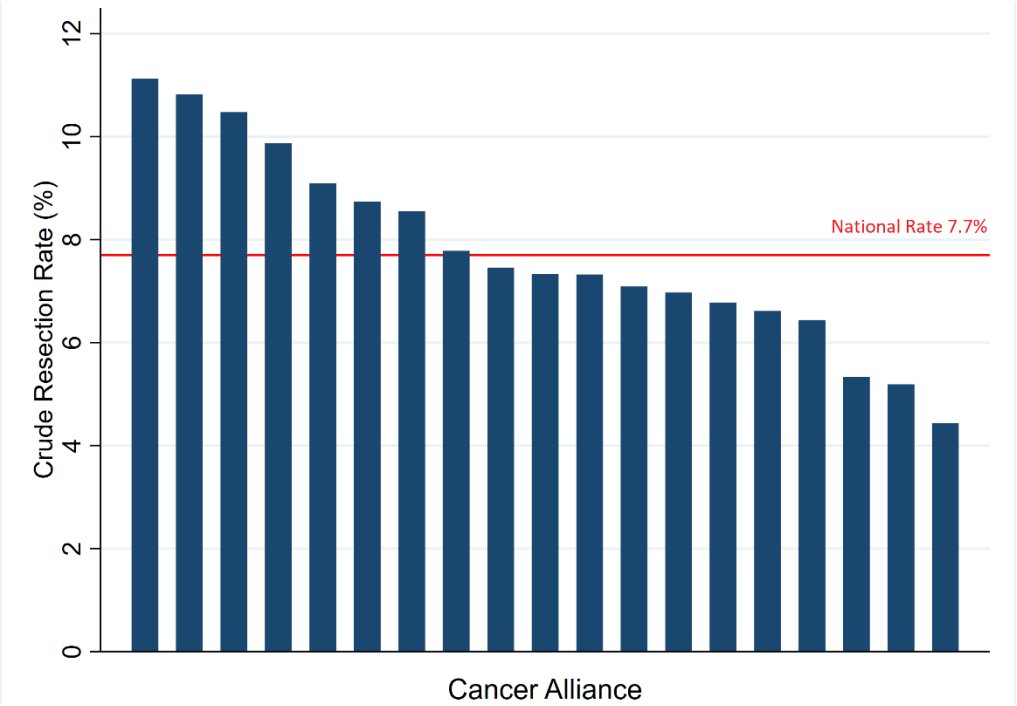

Figure 31. Proportion of patients who underwent resection for HCC in each Cancer Alliance region.

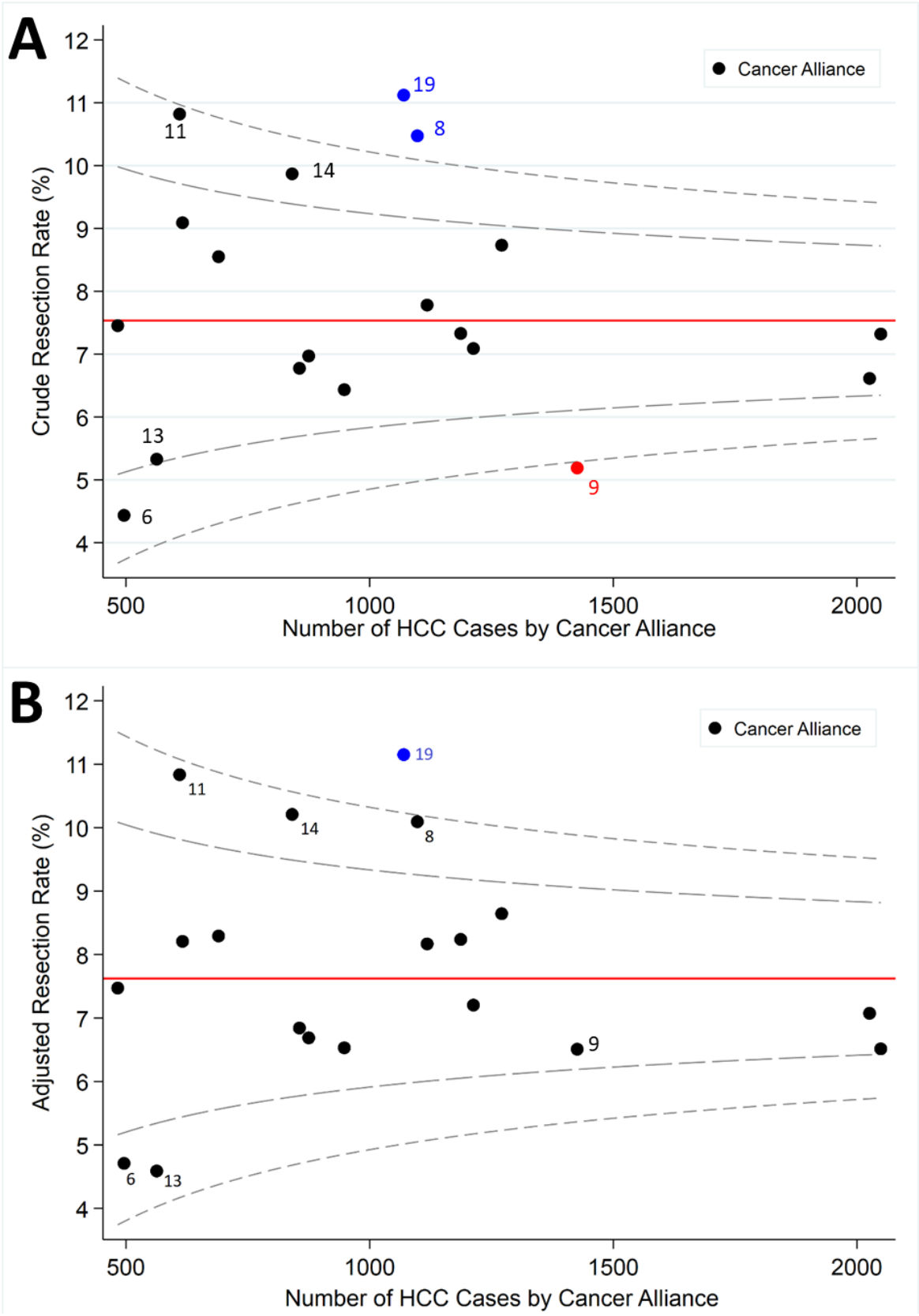

Figure 32. Funnel plots of the proportion of patients who received resection in each Cancer Alliance. Plot A shows the crude rate and plot B is adjusted by baseline characteristics. Control limits of 2 standard deviations (long dashed lines) and 3 standard deviations (short dashed lines) are shown. The national rate is shown in red.

12.2.3 Transplant

The unadjusted transplant rate across the 19 CA regions is summarised in Figure 33 and the crude and adjusted funnel plots are shown in Figure 33.

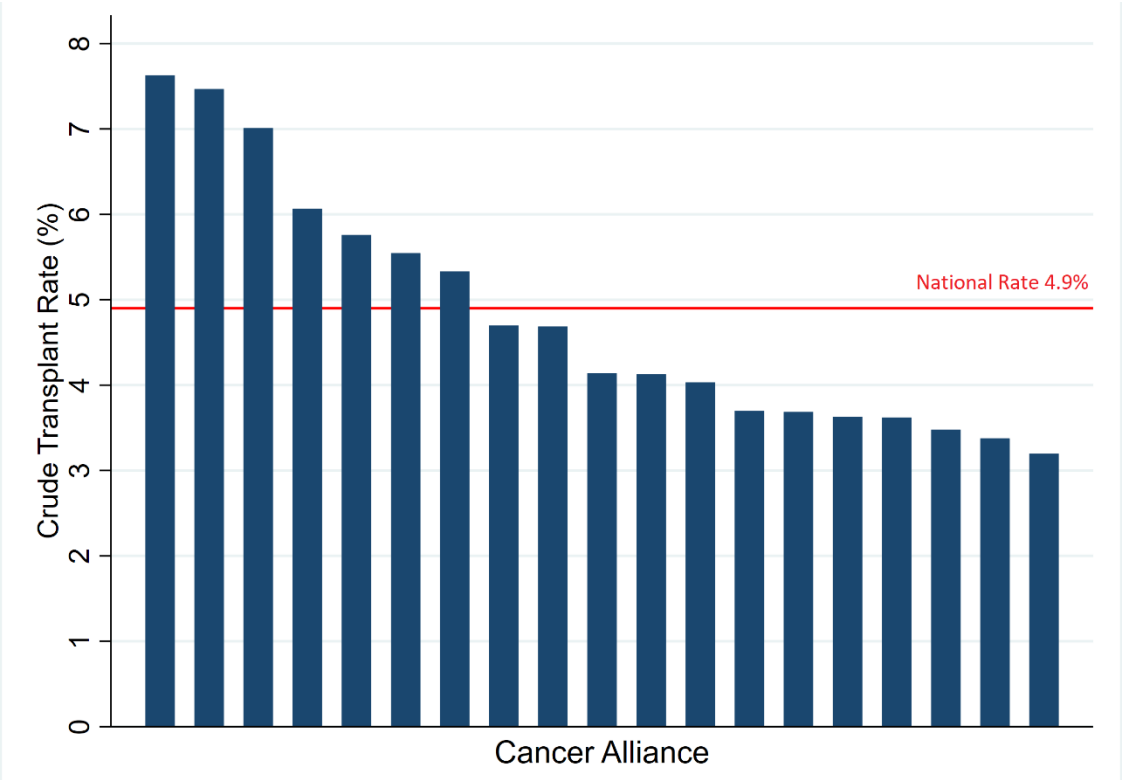

Figure 33. Proportion of patients who received a transplant for HCC in each Cancer Alliance region.

The adjusted transplant rate in West Yorkshire and Harrogate CA (19) was just outside the 99.8% control limit in the funnel plot. Although the crude rate in North Central and North East London (8) appeared to be an outlier, the rate was close to the national average when adjusted for the baseline characteristics in the region.

The transplant rate for West Midlands (18), and North East and Cumbria (9) was between two and three standard deviations above the national mean. Similarly, the transplant rates for South East London (13), Surrey and Sussex (15), Greater Manchester (4) and East Midlands (2) were between two and three standard deviations below the national mean.

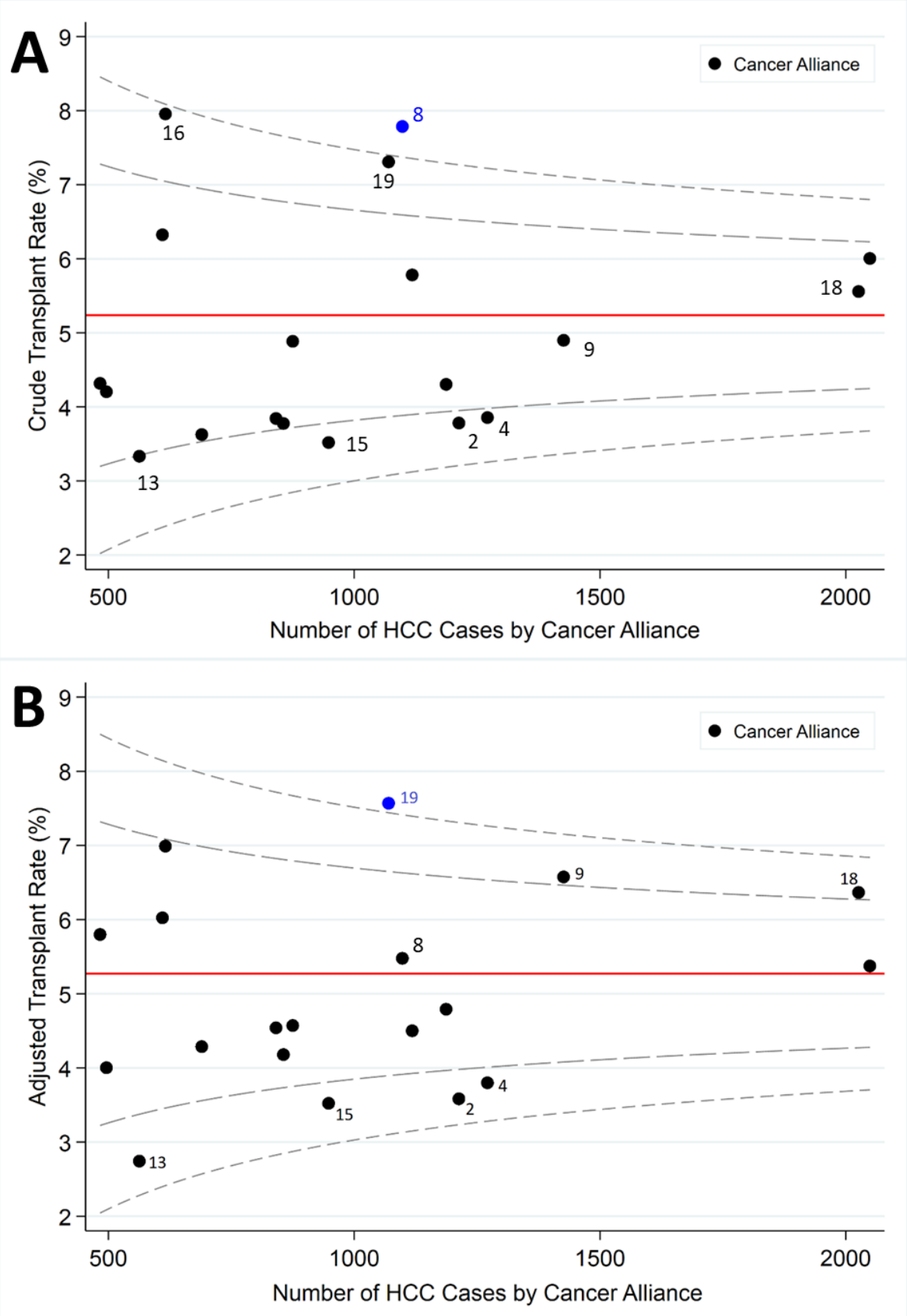

Figure 34. Funnel plots of the proportion of patients who received a liver transplant for HCC in each Cancer Alliance. Plot A shows the crude rate and plot B is adjusted by baseline characteristics. Control limits of 2 standard deviations (long dashed lines) and 3 standard deviations (short dashed lines) are shown. The national rate is shown in red.

12.2.4 Trans-arterial Chemoembolisation

The unadjusted proportions of patients who received TACE as their primary HCC treatment across the 19 CA regions is summarised in Figure 35. The crude and adjusted funnel plots are shown in Figure 36.

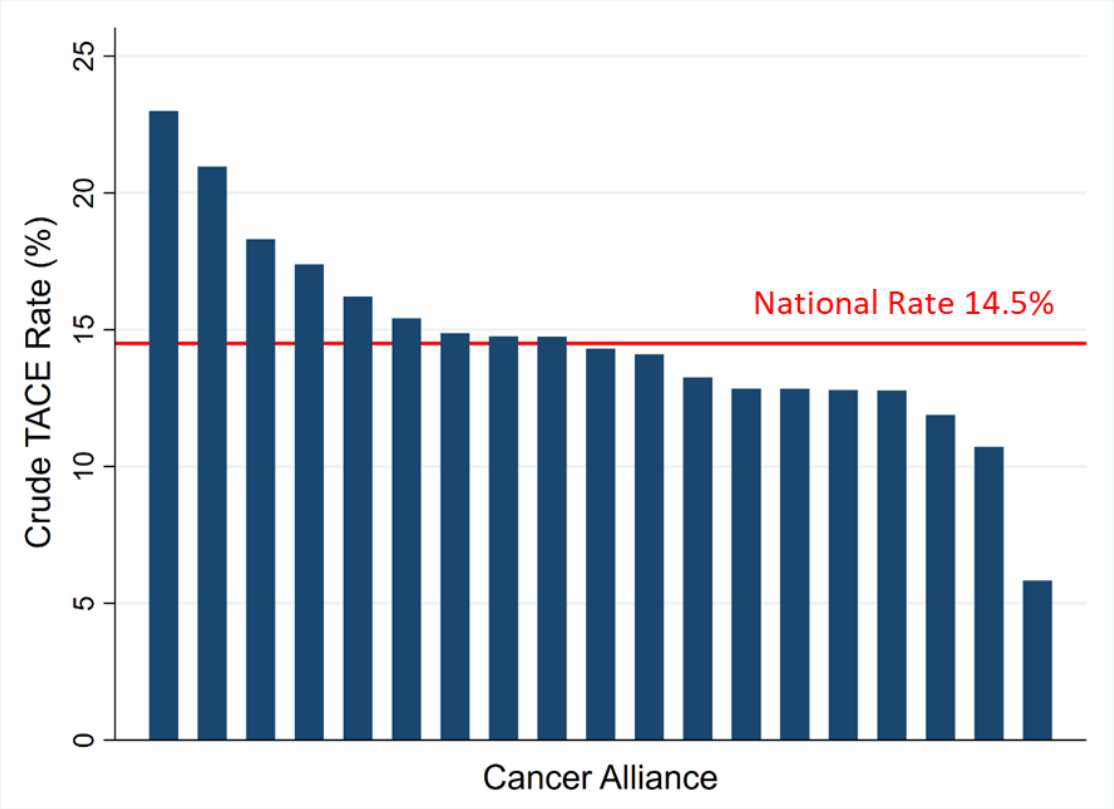

Figure 35. Proportion of patients who received TACE as primary HCC treatment in each Cancer Alliance region.

The TACE treatment rate was above the 99.8% control limits in higher in Kent and Medway (6) and in South East London (13). The TACE rate was also higher in North East and Cumbria (9). The South Yorkshire, Bassetlaw and North Derbyshire CA (14) had a significantly lower proportion of patients treated with TACE.

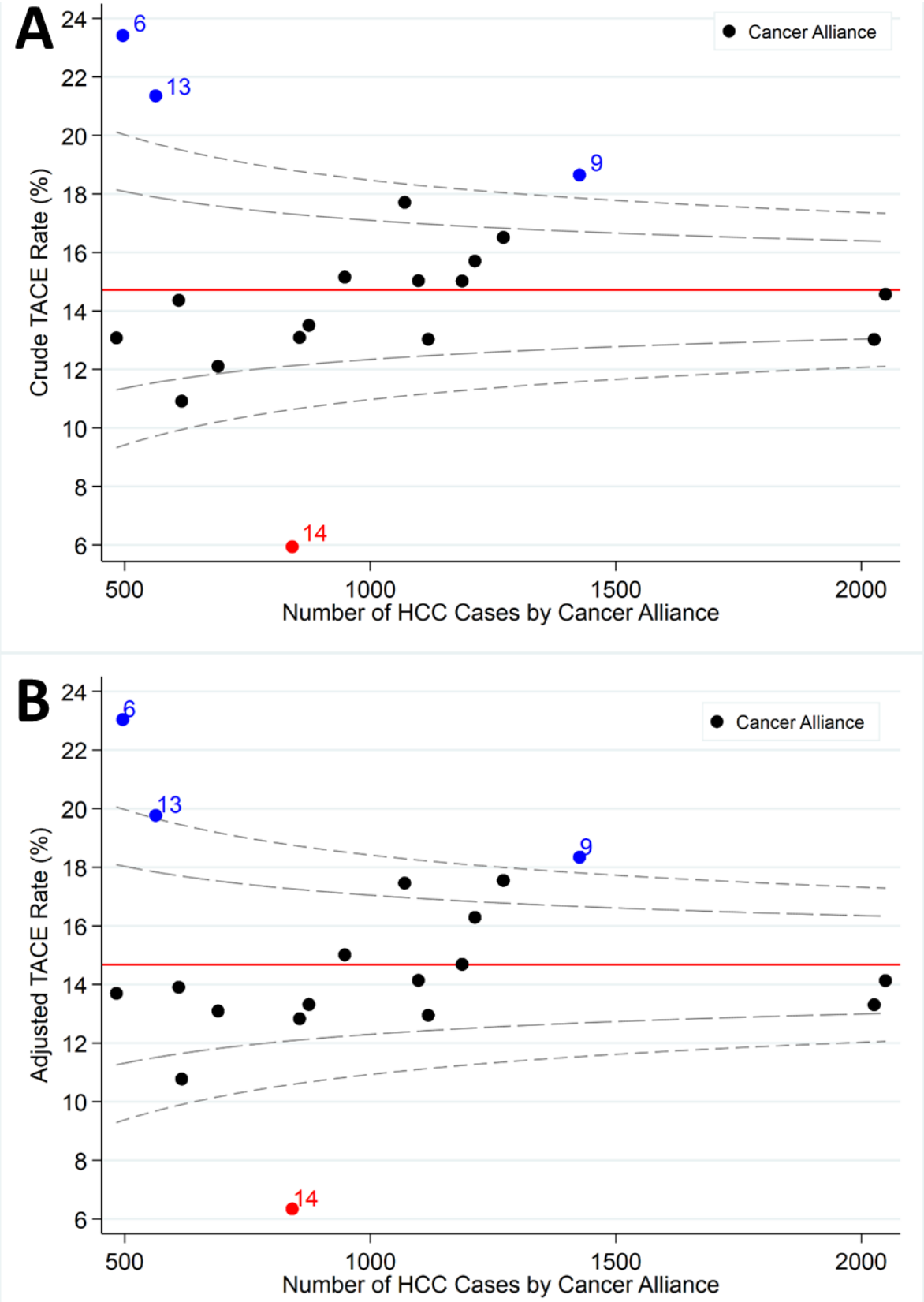

Figure 36. Funnel plots of the proportion of patients who received TACE in each Cancer Alliance, adjusted by baseline characteristics. Control limits of 2 standard deviations (long dashed lines) and 3 standard deviations (short dashed lines) are shown. The national rate is shown in red.

12.3 Discussion of Results

The regional variation in treatment allocation highlights potential differences in service provision across England, as well as differences in baseline factors.

12.3.1 Ablation

The CA region with the highest proportion of patients who received ablation was Cheshire and Merseyside. This region also had the highest proportion of patients with alcohol-related liver disease (26.9%) and the second-highest proportion (40.6%) of individuals in the 5th (most deprived) IMD quintile. This region is known to have a high incidence of cirrhosis (PHE, 2017).

This high proportion of patients receiving ablation suggests a high rate of early detection of smaller tumours, which are amenable to ablation. This may be influenced by local surveillance practice in a population known to have high rates of cirrhosis. Despite this high rate of ablation, the proportion of patients receiving other treatments (including transplant and resection) is in keeping with the national average.

12.3.2 Resection

The liver resection rate in West Yorkshire and Harrogate was higher than the national average. Travel to specialist centres may have a negative impact on the provision of liver resection, particularly for patients in the most deprived IMD quintile. However, the presence of a specialist hepatobiliary surgery centre in Leeds may explain the higher rates of resection, where travel and referral pathways are less of a barrier to access treatment.

North East and Cumbria had a low crude resection rate, but this difference was non-significant in the adjusted analyses. This region had a high proportion of patients with alcohol-related liver disease, NAFLD and a high proportion of patients with multiple co-morbidities (Charlson index of 3 or more). These factors were negatively associated with resection in the previous multinomial logistic regression analysis – the patient characteristics may have influenced the resection rate more than local practice.

12.3.3 Transplant

The rate of liver transplantation was highest in West Yorkshire and Harrogate, the West Midlands and North East and Cumbria. These three regions all contain liver transplant centres. Compared with transplant centres in London and Cambridge, these three centres in Leeds, Birmingham and Newcastle provide liver transplant services for a larger geographical area. Patients local to these centres may experience fewer barriers to access this treatment, including travel distance.

12.3.4 Trans-arterial Chemoembolisation

The TACE treatment rate was above the 99.8% control limits in higher in Kent and Medway (6) and in South East London (13). These two regions also had the lowest adjusted liver resection rate. Local practice and access to specialist surgical centres may explain why some patients received TACE instead of resection. However, the absence of detailed cancer staging information limits the conclusions from these trends.

The TACE treatment rate in South Yorkshire, Bassetlaw and North Derbyshire CA was significantly lower than the national average. This may reflect local practice, but again the absence of cancer staging information limits detailed analysis.

13 General Discussion

13.1 Validation Study - Algorithm Development and Validation

13.1.1 Main Findings

The *Validation Study* successfully demonstrated the ability of an algorithm to utilise HES records to identify and characterise cirrhosis in patients with HCC. Staging of cirrhosis severity from routinely collected administrative data was an essential framework for the study of clinical outcomes in HCC in a population-based study because the information about cirrhosis was not included in the cancer registry.

13.1.2 Strengths

The strength of the *Validation Study* lies in the systematic development of algorithms that utilise inpatient administrative data in order to characterise patients with HCC and cirrhosis. Since all hospitals in England use the same coding format, this is applicable to a large population study in HCC. There is broad capture of codes relating to these patients, as they frequently require inpatient admission to treat complications of cirrhosis as well as to receive HCC treatments.

Extensive case note evaluation was used, involving 289 patients in the development cohort and 50 patients in an external validation cohort. Previous case note evaluation of inpatient cirrhosis coding in the UK was undertaken using free text analysis of primary care and death certification data (Ratib et al., 2014a). The original validation study of the cirrhosis algorithm included the paper case note review of just 36 patients (Fleming et al., 2008a). These previous studies utilised electronic records to assess the prevalence of cirrhosis in the general population, in which the pre-test probability of cirrhosis was lower than in a cohort with known HCC. By limiting the cirrhosis algorithms to inpatient records, the performance characteristics were optimised to the HCC population.

Compared with previous cirrhosis algorithms, this method has the advantage of the ‘anchor point’ of the HCC diagnosis date. This enables the calculation of a time interval to other diagnoses and clinical events. This facilitated optimised cirrhosis detection by specifying when ascites was included in the algorithm relative to the HCC diagnosis date, avoiding the

misinterpretation of malignant ascites. In subsequent analyses, it also enabled the identification of decompensation events following HCC treatments.

As a prognostic marker, the ALBI grade has been validated in population-based studies in HCC (Johnson et al., 2015). Previous studies has shown a correlation between ALBI grade and portal hypertension (Guha et al., 2019) and so the *Validation Study's* findings can be considered as complementary. The algorithm has the advantage that is can be applied to routinely collected diagnostic coding data, which is available in many health systems and does not necessitate blood tests for the assessment of cirrhosis severity in population-based analyses.

Another strength of this study is the provision of a framework to estimate the competing risk of liver- and cancer-related mortality. Although this is an approximation of cause-specific mortality, the identification of post-treatment decompensation is an important outcome for patient experience, and it has a critical impact on future HCC treatment options.

13.1.3 Limitations

The limitations of this *Validation Study* include the setting in two specialist cancer centres. This may not reflect the clinical coding practice in the rest of the country, and these may change over time. The cirrhosis algorithm relied on capturing all inpatient episodes, but this was limited to admission to these centres only. If patients were admitted elsewhere, or if patients moved address, that information would be lost. Although this is a shortcoming of the *Validation Study*, when applied to the national cohort, all inpatient admissions are captured in the HES dataset, irrespective of location.

In the validation cohort, 66% of patients were identified with cirrhosis from their clinical case note review. This is lower than previous reports (El-Serag and Rudolph, 2007, D'Amico et al., 2006). If patients had advanced HCC at presentation, their clinical record may have not explicitly stated the presence of cirrhosis. Additionally, they may have not been investigated further to establish a diagnosis of cirrhosis if the expected prognosis was poor. In the validation cohort, patients with no documented cirrhosis diagnosis in the case notes were significantly older (median age 73 years, compared with 67 years in the cirrhosis group) and 29.6% were aged over 80.

There were 40/289 patients in the *Validation Study* who did not have an inpatient EHR and so additional analysis about cirrhosis was not possible. The performance characteristics of the Identification Algorithm reflect this uncertainty – the PPV for cirrhosis detection was 99%, whereas the NPV was only 79%. When interpreting findings in the *National Study*, it is important to recognise that patients who have no cirrhosis codes may have underlying cirrhosis that has not been captured by the inpatient EHR. Patients who survive longer are more likely to be admitted to hospital and therefore more likely to have cirrhosis codes in their EHR – this introduces a potential survivor bias for the identification of cirrhosis (van Walraven et al., 2004).

Cause-specific mortality is challenging to determine accurately in the setting of HCC and advanced cirrhosis, even in clinical practice. This model is a simplification and only includes the presence or absence of decompensation to determine competing risk. If patients die of another co-morbid condition, the model assumes a cancer death, which is a limitation. However, the advantage of this approach is that the hepatic decompensation events provide a tangible clinical outcome that has important clinical implications for patient care, health economics and the preclusion of further anti-cancer treatment.

The accuracy of Aetiology Algorithm is limited by the accuracy of clinical coding, particularly around the diagnosis of NAFLD. Given the size of the *Validation Study*, the accuracy of the detection of less common aetiologies is less certain. There is no specific ICD10 code for PSC – it can only be identified as 'cholangitis'. These analyses were therefore unable to assess the impact of PSC on the development of HCC. The absence of aetiology codes leads to additional uncertainty – these patients may have an unclassified underlying liver aetiology, or they may have developed HCC on the background of a normal liver.

13.1.4 Implications

This *Validation Study* has demonstrated the utility of coding algorithms to identify and characterise underlying cirrhosis in patients with HCC from their inpatient HES records. This is an essential step in the assessment of clinical outcomes in HCC, given the impact of underlying cirrhosis on treatment allocation and liver-related outcomes. The reliability of the cancer registry data within NCRAS is well established (Henson et al., 2020), and the *Validation Study* provides evidence of a reliable assessment of underlying cirrhosis. The study demonstrates the validity of using inpatient records in this population and justifies the use of a tailored algorithm for cirrhosis assessment.

The *Validation Study* also provides a novel methodology for assessing cirrhosis-related outcomes following cancer diagnosis and treatment. By monitoring clinical events related to decompensated cirrhosis, the rate of liver-related complications can be analysed over time. This gives additional information about clinical outcomes at a population level; not only can overall survival be measured, but the presence of decompensated cirrhosis can be detected, enabling an assessment of post-treatment complications.

This framework also facilitates the use of multi-state disease models in cirrhosis (Jepsen et al., 2015). Identifying patients who experienced decompensation prior to death can be used as an estimation of liver-related mortality and this study validated this approach by case note review. The subsequent analyses of competing risk in the *National Study* demonstrate the utility of this approach and suggest that it can be applied to other settings in cirrhosis (such as the rate of decompensated cirrhosis following abdominal surgery for colorectal cancer).

13.2 National Study - Baseline Characteristics and the Impact on Treatment Allocation

13.2.1 Main Findings

The baseline characteristics of the HCC cohort were similar to previous studies in Western populations (Goutté et al., 2017), but the rates of viral hepatitis were lower than international studies (El-Serag, 2012). Cirrhosis is considered the most important risk factor for HCC and the high prevalence in this cohort compared to a general population is in keeping with this. Nevertheless, the estimated cirrhosis prevalence of 58.3% is lower than previous studies. Although this may relate to the limitations of only using inpatient codes, this raises the possibility that HCC may more commonly occur in the presence of advanced fibrosis or in the setting of subclinical cirrhosis. Previous decompensated cirrhosis was recorded in 22.1% of patients prior to their HCC diagnosis. This finding is similar to previous studies (Goutté et al., 2017) and is a critically important factor in determining HCC treatment options, post-treatment decompensation and overall survival.

HCC treatment allocation was consistent with the BCLC classification in the EASL Clinical Practice Guidelines (EASL, 2018). The majority of patients (61.8%) in this study did not receive HCC treatments and received best supportive care. This finding demonstrates that for most patients, the presence of advanced liver disease, poor performance status, or advanced cancer means that they are not eligible for treatment. Overall, the proportion of patients who received potentially curative treatment (transplant, resection or ablation) was 20% - this is lower than the target of 30-40% suggested in the previous EASL guidelines (EASL, 2012).

13.2.2 Strengths

These analyses provide a detailed description of the baseline characteristics of a large population of patients who were diagnosed with HCC. Utilising the validated algorithms based on routinely collected HES data, characterisation of the cohort provides an insight into the reasons for the differences in treatment allocation and patient outcomes.

The identification of underlying cirrhosis and the assessment of severity is essential to understand why different patients receive different treatments. Most importantly, the finding that most patients (61.8%) received best supportive care is explained by the identification of previous inpatient events related to decompensated cirrhosis in 49.2% of individuals known to

have cirrhosis. This insight has not previously been possible using the NCRAS dataset due to the absence of information related to cirrhosis severity.

This study provides a real-world estimate of the proportion of patients who receive different HCC treatments in England. It demonstrates the high prevalence of baseline factors that preclude HCC treatment. This information is essential in the subsequent analyses into regional variation in treatment allocation, given the distribution of baseline factors across England.

13.2.3 Limitations

Cancer stage was missing in 75% of cases in the cohort, although the proportion of completed staging information in the registry increased over time during the study. This limits the assessment of how many patients had advanced HCC at diagnosis. It is therefore uncertain whether the large proportion of patients who received BSC were ineligible for HCC treatment due to advanced cancer, or due to poor performance status or liver function. It is also not possible to assess how different sized cancers were treated with the different treatment modalities, and how this compares to the BCLC classification.

The analyses are limited in those patients who have limited or absent records in HES. As discussed above, survivor bias may lead to less information about baseline factors derived from the HES record in those who died soon after HCC diagnosis. Among those who received BSC, 5,801/ 12,013 (48.2%) had no cirrhosis codes. It is uncertain whether these patients had HCC in the background of a normal liver, or if cirrhosis was present but not recorded in the HES record. Similarly, limited information from HES leads to uncertainty about ethnicity and underlying liver disease aetiology.

The analysis of HCC treatment was simplified to include only the primary treatment modality. In reality, some patients received more than one treatment. This approach was used because the most definitive treatment was considered the most informative, with subsequent survival analyses based on this. In this manner, the overall survival of a patient who received ablation was measured from the index treatment date, even if they received follow-up treatments. It is possible that patients experienced recurrence of the index cancer, or a new metachronous cancer following resection, ablation or TACE. The NCRAS dataset does not differentiate between these and so these analyses cannot be used to compare the effectiveness of anti-cancer treatments by consideration of cancer-free survival.

13.2.4 Implications

This study of all new cases of HCC in England from 2007-2016 highlights the burden of HCC in the population. The incidence has increased during the study period from 1,284 cases in 2007 to 2,655 in 2016. The majority of these cases relate to preventable diseases, including alcohol, non-alcoholic fatty liver disease and hepatitis C. This supports the need for public health strategies to address lifestyle changes in order to modify risk factors for the development of cirrhosis.

The latest EASL guidelines (EASL, 2018) recommend surveillance for HCC in patients with cirrhosis, although the evidence for this is weak. The purpose of a surveillance programme is to identify patients at risk of HCC at an early cancer stage, in order that they can receive potentially curative treatment. However, this study identified a high proportion of patients who did not have cirrhosis codes in their HES record. These patients may have not been known to have cirrhosis before their HCC diagnosis, or have not previously been admitted to hospital (or attended for a day case procedure such as endoscopy). If the presentation with HCC was the first manifestation of cirrhosis, this may limit the effectiveness of surveillance programmes if many patients are not known to have cirrhosis.

Previous analysis (Trevisani et al., 2007) suggest that surveillance for HCC in the presence of decompensated cirrhosis is not cost-effective, given the limitation of effective HCC treatments. In the clinical trials investigating TACE (Llovet et al., 2002, Lo et al., 2002, Burrel et al., 2012), patients with variceal bleeding or ascites at the time of treatment were excluded. In a meta-analysis of RCTs in radio-frequency ablation (Wang et al., 2014), 3,112/ 4,138 (75%) of patients had a Child Pugh score ≤ 6, indicating preserved liver function. The *National Study* highlights that a significant proportion (15.6%) of patients with previous decompensation were subsequently eligible for HCC treatment such as TACE and ablation – these patients may benefit from early HCC detection if liver function subsequently improved (eg. after achieving abstinence from alcohol). This finding demonstrates the real world experience of treatment allocation and has implications for future surveillance programmes if more patients are eligible for HCC treatment.

The additional insight into treatment eligibility through the analysis of cirrhosis severity using the validated algorithms is applicable to population studies in individuals with other cancers. The analyses in Sections 9, 10 and 11 demonstrate the importance of cirrhosis severity on overall survival and liver-related mortality. In other cancers, patients will be similarly at risk of liver-related mortality due to advanced cirrhosis and these algorithms could provide an

explanation for clinical outcomes. One example of this is the high risk of decompensated cirrhosis following major abdominal surgery; these algorithms could be used to identify cirrhosis-related morbidity and mortality following potentially curative surgery for colorectal cancer, for example.

13.3 National Study - Clinical Outcomes following HCC Treatments

This study provided an assessment of how different baseline factors and HCC treatment modality affected clinical outcomes. Increasing age, medical comorbidities and cancer stage predict survival, and cirrhosis severity has a critical role post-treatment outcomes. Overall survival and an estimate of cause-specific mortality using the model of post-treatment decompensation was assessed for each HCC treatment (apart from transplantation).

13.3.1 Main Findings

13.3.1.1 Best Supportive Care

The overall survival for patients who received BSC was 2.7 months, which is similar to existing estimates of the natural history of HCC. The mortality rate was highest for those patients with severe liver disease (Baveno stage 3 and 4) and this increase is explained by an increase in the 'liver-related' mortality rate in competing risk analysis.

13.3.1.2 Sorafenib

The median overall survival following Sorafenib treatment of 9.1 months was comparable to the estimates from the clinical trials. The majority of patients did not have clinically significant portal hypertension (Baveno 2, 3 or 4), but these patients were more likely to experience liver-related mortality. The 1-year survival in the group with less severe cirrhosis was similar to the original Sorafenib trial (Llovet et al., 2008a). However, the 90-day mortality was significantly higher for all groups who received Sorafenib in the *National Study*. Direct comparison is not possible given the exclusion criteria in the Llovet trial and the limited information about patients in this *National Study*, but these data provide a representation of recent clinical experience.

These findings highlight the risk of decompensation after Sorafenib treatment, which causes unpleasant symptoms for patients, precludes further treatment and increases the risk of short-term mortality. Although patients require compensated cirrhosis to be eligible for Sorafenib, this study suggests that the presence of portal hypertension and a history of previous ascites or variceal haemorrhage is associated with an increased risk of decompensation post-treatment, as well as a reduction in overall survival.

13.3.1.3 Trans-arterial Chemoembolisation

Overall survival following TACE was inferior to previous estimates based on clinical trials and highly selected cohorts (EASL, 2018). However, this was the most common treatment for patients aged 60-79 and in real world clinical practice may be offered to a greater proportion of patients. This study identified that many patients with a history of previous decompensation (Baveno 3 and 4) were eligible for HCC treatment with TACE.

Patients with previous decompensation had a worse overall survival and higher rates of decompensation post-treatment compared to those with less severe cirrhosis. The presence of portal hypertension in compensated cirrhosis (Baveno 2) did not affect overall survival, although the rates of decompensation after treatment were higher than the Baveno 1 group.

13.3.1.4 Ablation

Overall survival following ablation were comparable to previous survival estimates (EASL, 2018). These clinical outcomes were studied in detail because the eligibility criteria for these treatments result a more homogeneous patient cohort for analysis. Increasing cirrhosis severity was associated with worse overall survival and 90-day mortality. By considering post-ablation decompensation events, competing risk analysis demonstrated that the increase in 90-day and overall mortality seen with increasing Baveno stage was related to increased liver-related mortality.

13.3.1.5 Resection vs. Ablation

The overall survival following liver resection was significantly longer than following ablation. Direct comparison between these two treatments was not possible due to the differences in baseline factors, including more advanced liver disease in those who received ablation and larger tumours in those who had resection. The findings are consistent with meta-analyses have demonstrated improved overall survival and recurrence-free survival following resection compared with ablation for small tumours (Qi et al., 2014, Wang et al., 2014). However, using the competing risk model, the difference in overall survival was associated with a significantly increased risk of liver-related mortality following ablation in the *National Study*. This suggests that the mortality benefit in patients who had resection relates to less severe underlying cirrhosis and less liver-related mortality post-treatment.

13.3.2 Strengths

This study provides an estimate of survival outcomes following HCC treatments in routine clinical practice in England. It compliments existing evidence about survival outcomes and provides information for patients and clinicians when considering treatment for HCC. This is a large population-based study, including all patients with a registered HCC diagnosis, so it is not limited by exclusion criteria in clinical trials.

This study has also identified the importance of cirrhosis severity on overall prognosis following all treatment modalities for HCC, which is not possible with conventional cancer registry analyses. Using EHRs to identify clinical outcomes in cirrhosis following treatment is a novel approach developed in this study. This has enabled the identification of clinical events related to hepatic decompensation, which has been used to approximate liver-related mortality in the multi-state model of cirrhosis.

13.3.3 Limitations

The multi-state disease model of cirrhosis is an approximation of the clinical experience of patients with HCC and cirrhosis. This model was necessary in order to distinguish between liver- and cancer-related mortality, in order to use established methods for the investigation of competing risk. However, this distinction is very challenging to make, even in clinical practice and with access to case note review. The classification of a cancer-related death in absence of hepatic decompensation may be inaccurate if the patient died of an unrelated comorbidity. Similarly, a decompensation event after treatment may not necessarily lead to a liver-related death, but the cause-specific mortality validation in Section 6.5 suggests that this is a valid approximation.

The uncertainty over cancer stage is another limitation of these analyses. In particular, knowledge about the size and number of lesions is unknown and this information is likely to influence the response to treatment in all modalities. In particular, comparisons between outcomes following ablation and resection are limited by this information.

The date of diagnosis in the NCRAS dataset is recorded as the most definitive modality. In this manner, a histological diagnosis supersedes a radiological diagnosis in most cancers – the confirmed diagnosis of cancer is made when a biopsy confirms malignancy. However, in HCC in cirrhosis, since most cancers are confirmed using radiological criteria, the recorded

diagnosis date may occur when a histological diagnosis is made at liver resection or ablation. These analyses used survival times from first HCC treatment instead of diagnosis date for uniformity, but this may introduce some uncertainty in survival outcome estimates.

These analyses considered only the most definitive HCC treatment but in reality, many patients received different modalities. Most notably in the original Sorafenib trial, patients had received previous HCC treatment with resection (19%), ablation (15%) and TACE (29%). These analyses included only those patients who received Sorafenib as the primary treatment modality.

13.3.4 Implications

These analyses demonstrate the importance of considering cirrhosis severity when deciding about HCC treatment options. Graphical representations of the competing risk of liver- and cancer-related outcomes have shown the proportion of patients who experienced decompensation prior to death for different HCC treatments. This enables patients and clinicians to understand the expected outcomes and the impact of liver-related symptoms in HCC. This also shows that following HCC treatments, there is a risk of further decompensation, which may influence further HCC treatment and patient experience.

This real-world study highlights that patients with previous decompensated cirrhosis were offered HCC treatment with Sorafenib, TACE and ablation. When patients are the borderline of eligibility for treatment, there may be a tendency to offer the most effective anti-cancer treatment. However, in the presence of advanced cirrhosis, this carries an increased risk of decompensation and liver-related mortality. This is particularly evident in the decision to proceed with ablation or resection – although surgery offers better cancer-related survival in the clinical trials, these data may help patients and clinicians to discuss treatment options, recognising that advanced cirrhosis may be the more significant determinant of overall outcome and post-treatment complications.

From a patient perspective, understanding risk in the setting of cirrhosis and HCC is complex. The priority to treat cancer most definitively needs to be balanced with cirrhosis-related treatment risk and it is hoped that these data can facilitate a clear understanding of this. By estimating the proportion of patient who experience liver-related morbidity and mortality, this may inform decision-making about treatment.

13.4 National Study - Regional Variation in HCC Treatment Allocation

13.4.1 Main Findings

Analysis of the baseline characteristics of patients diagnosed with HCC across England identified some regional variation in the aetiology of underlying liver disease, which has previously been shown to be a determinant of HCC treatment allocation. However, there was little regional variation in cirrhosis severity.

There was a wide variation in the provision of ablation across England; the crude rate was 3.5% in Lancashire and South Cumbria, and it was 13.0% in Cheshire and Merseyside. These differences persist in the adjusted analyses and may suggest differences in local detection of early cancers amenable to curative treatment, or access to local expertise. The need to travel to a centre that can provide ablation may be a barrier to this treatment.

Liver resection was most commonly performed in Cancer Alliance regions that contained a hepatobiliary surgical centre. Kent and Medway, and South East London CAs had the lowest adjusted liver resection rate, but also the highest rate of TACE. This may suggest that some patients received TACE in preference to resection in these regions. Liver transplantation was also most commonly performed in CA regions that contained a liver transplant centre, which may also highlight barriers to referral.

13.4.2 Strengths

These analyses highlight the variation in the provision of HCC treatments across England. These estimates highlight potential differences in clinical practice and access to specialist services across the country. The identification of higher rates of resection and transplantation in regions containing specialist centres suggests that there may be barriers to treatment for patients living further from these centres.

Adjusting for the baseline characteristics of patients in each CA enabled careful interpretation of apparent differences in crude treatment rates. Large differences in baseline characteristics resulted in non-significant differences in the adjusted treatment rates in some regions.

13.4.3 Limitations

The lack of accurate cancer staging information limits the interpretation of variation in treatment allocation. Although trends in treatment rates could be compared, in the absence of cancer stage it is not possible to be certain that there are differences in local practice. These analyses involve the HCC treatments undertaken, but not the survival outcomes in each region. The NCRAS review panel did not approve the use of the PHE data for such analyses as there were concerns that they would not capture pre-referral factors and would be an inaccurate assessment of performance. These analyses are unable to assess the appropriateness of patient selection for HCC treatments in each CA.

13.4.4 Implications

These analyses highlight that there are differences in the allocation of HCC treatments across England. Further investigation into these potential barriers, including referral pathways to specialist centres for surgical treatment and patients travelling to receive treatment, may lead to an improvement in the equity of HCC treatment.

Patients who receive curative treatment for HCC remain in the minority. The critical determinants for this are liver disease severity and HCC detection at an early stage. Public health measures to focus on the early detection of liver disease in high-risk groups is a priority, in order to prevent progression to decompensated cirrhosis and facilitate engagement in HCC surveillance programmes.

There was significant regional variation in alcohol and HCV-related HCC in this study and this was correlated with areas of greatest social deprivation. In recent years, the widespread use of direct-acting antiviral therapy for HCV is expected to reduce the future prevalence of decompensated cirrhosis and the development of HCC (Mennini et al., 2021). Strategies have focussed on case-finding in under-served communities have been successful in finding those most at risk (PHE, 2019). Future public health strategies must focus on identifying those most at risk oh cirrhosis and HCC and improving access to treatment.

14 Conclusions

This thesis includes an investigation into the outcomes of patients with hepatocellular carcinoma (HCC). It analyses contemporary data on the experience of patients diagnosed with this condition in England form 2007 to 2016 and represents the largest cohort study in HCC in the UK to date. It complements the existing evidence of survival outcomes for patients undergoing different HCC treatments and provides an insight into prognostic factors at baseline. It also highlights variability in the provision of different HCC treatments across England and the potential for improvements in the equity of service provision.

The *Validation Study* demonstrates the reliability of using electronic health records to characterise patients with cirrhosis and HCC. It also demonstrates the utility of this method to determine liver-specific clinical outcomes by identifying clinical events related to hepatic decompensation. This novel approach provided additional insight into patients' experience following HCC diagnosis and treatment; the development of decompensation has significant implications for symptom management, subsequent hospitalisation, and the fitness for future HCC treatments. These algorithms are applicable in other population-based studies (including other cancer scenarios) for patients with underlying cirrhosis.

The *National Study* provides a summary of recent clinical practice and outcomes in HCC. Using the presence of hepatic decompensation as an approximation of liver-related mortality, established methods for modelling competing risk have been employed to further investigate clinical outcomes following different HCC treatments. This study provides an insight into the importance of cirrhosis severity on clinical outcomes in HCC, which needs careful consideration by patients and clinicians when discussing treatment options. These data represent real-world experience rather than estimates based on clinical trial outcomes.

The study also highlights limitations in the recording of patient data in the cancer registry. These findings demonstrate the importance of considering cirrhosis severity when investigating outcomes in HCC. Despite the validity of the methods employed, they are inferior to contemporary recording of cirrhosis severity, including blood test results and Child Pugh score. Similarly, more accurate recording of cancer stage (including size, number and local invasion), as well as an assessment of performance status, is required to register patients according to the BCLC classification. The latest version of the liver-specific items in the Cancer Outcomes and Services Dataset (COSD) within PHE includes much more detailed information about patients' baseline characteristics (COSD, 2019). This includes BCLC classification,

UKELD score and cirrhosis aetiology, as well as more cancer staging information and the details of HCC treatments received. More detailed recording of cirrhosis severity, cancer staging and HCC treatments in the future may highlight reasons for the regional variation in HCC treatment allocation observed in the *National Study*.

Epidemiological work within the HCC-UK NCRAS/ BASL partnership demonstrated the increasing incidence of HCC from 1997 to 2017 (Burton et al., 2021). Whilst the 1-year survival in HCC increased over the duration of this study, it remained below 50% in 2017. Here, the *National Study* highlighted that nearly two thirds of patients received best supportive care only, and this finding corroborates the epidemiological data.

Since 2017, the emergence of new systemic therapies such as monoclonal antibodies and immune checkpoint inhibitors (eg. bevacizumab and atezolizumab) may offer more treatment options to patients who are ineligible for surgical or loco-regional therapies (Kudo, 2020). The updated liver-specific items in COSD include details about cancer surveillance in patients with cirrhosis; these data may also highlight reasons for the differences in baseline characteristics and treatment allocation observed. The methods developed and demonstrated in this thesis can be used to evaluate clinical outcomes following HCC treatments, utilising EHR to estimate cirrhosis-related morbidity and mortality.

15 References

AALEN, O. O. & JOHANSEN, S. 1978. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics*, 141-150.

AKINYEMIJU, T., ABERA, S., AHMED, M., ALAM, N., ALEMAYOHU, M. A., ALLEN, C., AL-RADDADI, R., ALVIS-GUZMAN, N., AMOAKO, Y. & ARTAMAN, A. 2017. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA oncology,* 3**,** 1683-1691.

ANDERSEN, P. K. & KEIDING, N. 2002. Multi-state models for event history analysis. *Stat Methods Med Res,* 11**,** 91-115.

BARBER, K., MADDEN, S., ALLEN, J., COLLETT, D., NEUBERGER, J. & GIMSON, A. 2011. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation,* 92**,** 469-476.

BEASLEY, R. P. 1988. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer,* 61**,** 1942-56.

BOIGE, V., CASTERA, L., DE ROUX, N., GANNE-CARRIE, N., DUCOT, B., PELLETIER, G., BEAUGRAND, M. & BUFFET, C. 2003. Lack of association between HFE gene mutations and hepatocellular carcinoma in patients with cirrhosis. *Gut,* 52**,** 1178-81.

BRIERLEY, J., GOSPODAROWICZ, M. & WITTEKIND, C. 2017. *TNM Classification of Malignant Tumours,* Chichester, West Sussex, UK, Wiley-Blackwell.

BRUIX, J., REIG, M. & SHERMAN, M. 2016. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology,* 150**,** 835-53.

BURREL, M., REIG, M., FORNER, A., BARRUFET, M., DE LOPE, C. R., TREMOSINI, S., AYUSO, C., LLOVET, J. M., REAL, M. I. & BRUIX, J. 2012. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *Journal of hepatology,* 56**,** 1330-1335.

BURTON, A., TATARU, D., DRIVER, R. J., BIRD, T. G., HUWS, D., WALLACE, D., CROSS, T. J. S., ROWE, I. A., ALEXANDER, G. & MARSHALL, A. 2021. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. *JHEP Rep,* 3**,** 100232.

CABIBBO, G., PETTA, S., BARBARA, M., ATTARDO, S., BUCCI, L., FARINATI, F., GIANNINI, E. G., NEGRINI, G., CICCARESE, F. & RAPACCINI, G. L. 2017. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. *Journal of Hepatology,* 67**,** 65-71.

CANCER RESEARCH UK. 2016. *Liver Cancer Statistics* [Online]. Available: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-Zero [Accessed 18/11/2019].

CHAN, Y. H. 2005. Biostatistics 305. Multinomial logistic regression. *Singapore medical journal,* 46**,** 259.

CHARLSON, M. E., POMPEI, P., ALES, K. L. & MACKENZIE, C. R. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis,* 40**,** 373-83.

CHEN, P.-C. A., CHIU, N.-C. B. C., SU, C.-W. A. C., HUANG, Y.-H. A. D., HOU, M.-C. A. C., LIN, H.-C. A. C. & WU, J.-C. D. E. 2019. Albumin-bilirubin grade may determine the outcomes of patients with very early stage hepatocellular carcinoma after radiofrequency ablation therapy. *Journal of the Chinese Medical Association,* 82**,** 2-10.

CITTERIO, D., FACCIORUSSO, A., SPOSITO, C., ROTA, R., BHOORI, S. & MAZZAFERRO, V. 2016. Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma. *JAMA Surgery,* 151**,** 846-853.

COHEN, J. 1960. A coefficient of agreement for nominal scales. *Educational and psychological measurement,* 20**,** 37-46.

COLEMAN, M. P., FORMAN, D., BRYANT, H., BUTLER, J., RACHET, B., MARINGE, C., NUR, U., TRACEY, E., COORY, M., HATCHER, J., MCGAHAN, C. E., TURNER, D., MARRETT, L., GJERSTORFF, M. L., JOHANNESEN, T. B., ADOLFSSON, J., LAMBE, M., LAWRENCE, G., MEECHAN, D., MORRIS, E. J., MIDDLETON, R., STEWARD, J. & RICHARDS, M. A. 2011. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *The Lancet,* 377**,** 127-138.

COSD. 2019. *COSD Version 8 Liver Section Item Descriptors* [Online]. Available: https://www.basl.org.uk/uploads/Liver-specific%20COSD%20item%20guidance%20v8.1.pdf [Accessed 13/06/2021].

COX, D. R. 1972. Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological),* 34**,** 187-202.

CUCCHETTI, A., PISCAGLIA, F., CESCON, M., COLECCHIA, A., ERCOLANI, G., BOLONDI, L. & PINNA, A. D. 2013. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *Journal of hepatology,* 59**,** 300-307.

D'AMICO, G., GARCIA-TSAO, G. & PAGLIARO, L. 2006. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of Hepatology,* 44**,** 217-31.

DE FRANCHIS, R. 2005. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology,* 43**,** 167-76.

DONATO, F., TAGGER, A., GELATTI, U., PARRINELLO, G., BOFFETTA, P., ALBERTINI, A., DECARLI, A., TREVISI, P., RIBERO, M. L., MARTELLI, C., PORRU, S. & NARDI, G. 2002. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol,* 155**,** 323-31.

DOWNING, A., MORRIS, E. J., CORRIGAN, N., SEBAG-MONTEFIORE, D., FINAN, P. J., THOMAS, J. D., CHAPMAN, M., HAMILTON, R., CAMPBELL, H., CAMERON, D., KAPLAN, R., PARMAR, M., STEPHENS, R., SEYMOUR, M., GREGORY, W. & SELBY, P. 2017. High hospital research participation and improved colorectal cancer survival outcomes: a population-based study. *Gut,* 66**,** 89-96.

DOWNING, A., WEST, R. M., GILTHORPE, M. S., LAWRENCE, G. & FORMAN, D. 2011. Using routinely collected health data to investigate the association between ethnicity and breast cancer incidence and survival: what is the impact of missing data and multiple ethnicities? *Ethn Health,* 16**,** 201-12.

DOYLE, A., GORGEN, A., MUADDI, H., ARAVINTHAN, A. D., ISSACHAR, A., MIRONOV, O., ZHANG, W., KACHURA, J., BEECROFT, R., CLEARY, S. P., GHANEKAR, A., GREIG, P. D., MCGILVRAY, I. D., SELZNER, M., CATTRAL, M. S., GRANT, D. R., LILLY, L. B., SELZNER, N., RENNER, E. L., SHERMAN, M. & SAPISOCHIN, G. 2019. Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3cm in potentially transplantable patients. *J Hepatol*.

EASL 2012. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma.[Erratum appears in J Hepatol. 2012 Jun;56(6):1430]. *Journal of Hepatology,* 56**,** 908-43.

EASL 2018. EASL clinical practice guidelines: management of hepatocellular carcinoma. *Journal of hepatology,* 69**,** 182-236.

EL-SERAG, H. B. 2012. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology,* 142**,** 1264-1273. e1.

EL-SERAG, H. B. & RUDOLPH, K. L. 2007. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology,* 132**,** 2557-76.

ELSAYES, K. M., KIELAR, A. Z., CHERNYAK, V., MORSHID, A., FURLAN, A., MASCH, W. R., MARKS, R. M., KAMAYA, A., DO, R. K. G., KONO, Y., FOWLER, K. J., TANG, A., BASHIR, M. R., HECHT, E. M., JAMBHEKAR, K., LYSHCHIK, A., RODGERS, S. K., HEIKEN, J. P., KOHLI, M., FETZER, D. T., WILSON, S. R., KASSAM, Z., MENDIRATTA-LALA, M., SINGAL, A. G., LIM, C. S., CRUITE, I., LEE, J., ASH, R., MITCHELL, D. G., MCINNES, M. D. F. & SIRLIN, C. B. 2019. LI-RADS: a conceptual and historical review from its beginning to its recent integration into AASLD clinical practice guidance. *Journal of hepatocellular carcinoma,* 6**,** 49-69.

FINE, J. P. & GRAY, R. J. 1999. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association,* 94**,** 496-509.

FINN, R. S., QIN, S., IKEDA, M., GALLE, P. R., DUCREUX, M., KIM, T. Y., KUDO, M., BREDER, V., MERLE, P., KASEB, A. O., LI, D., VERRET, W., XU, D. Z., HERNANDEZ, S., LIU, J., HUANG, C., MULLA, S., WANG, Y., LIM, H. Y., ZHU, A. X. & CHENG, A. L. 2020. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med,* 382**,** 1894-1905.

FLEMING, K. M., AITHAL, G. P., SOLAYMANI-DODARAN, M., CARD, T. R. & WEST, J. 2008a. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study. *Journal of Hepatology,* 49**,** 732-8.

FLEMING, K. M., AITHAL, G. P., SOLAYMANI-DODARAN, M., CARD, T. R. & WEST, J. 2008b. Incidence and prevalence of cirrhosis in the United Kingdom, 1992–2001: A general population-based study. *Journal of Hepatology,* 49**,** 732-738.

FRACANZANI, A. L., CONTE, D., FRAQUELLI, M., TAIOLI, E., MATTIOLI, M., LOSCO, A. & FARGION, S. 2001. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non–iron-related chronic liver disease. *Hepatology,* 33**,** 647-651.

GIMSON, A. 2020. Development of a UK liver transplantation selection and allocation scheme. *Current opinion in organ transplantation,* 25**,** 126-131.

GOLDBERG, D., LEWIS, J., HALPERN, S., WEINER, M. & LO RE, V., 3RD 2012. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. *Pharmacoepidemiol Drug Saf,* 21**,** 765-769.

GOODMAN, L. A. & KRUSKAL, W. H. 1954. Measures of Association for Cross Classifications*. *Journal of the American Statistical Association,* 49**,** 732-764.

GOUTTÉ, N., SOGNI, P., BENDERSKY, N., BARBARE, J. C., FALISSARD, B. & FARGES, O. 2017. Geographical variations in incidence, management and survival of hepatocellular carcinoma in a Western country. *Journal of Hepatology,* 66**,** 537-544.

GUHA, I. N., HARRIS, R., BERHANE, S., DILLON, A., COFFEY, L., JAMES, M. W., CUCCHETTI, A., HARMAN, D. J., AITHAL, G. P., ELSHAARAWY, O., WAKED, I., STEWART, S. & JOHNSON, P. J. 2019. Validation of a Model for Identification of Patients With Compensated Cirrhosis at High Risk of Decompensation. *Clin Gastroenterol Hepatol*.

HENSON, K. E., ELLISS-BROOKES, L., COUPLAND, V. H., PAYNE, E., VERNON, S., ROUS, B. & RASHBASS, J. 2020. Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol,* 49**,** 16-16h.

JAYACHANDRAN, A., SHRESTHA, R., BRIDLE, K. R. & CRAWFORD, D. H. G. 2020. Association between hereditary hemochromatosis and hepatocellular carcinoma: a comprehensive review. *Hepatoma Research,* 6**,** 8.

JEPSEN, P., OTT, P., ANDERSEN, P. K., SORENSEN, H. T. & VILSTRUP, H. 2010. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology,* 51**,** 1675-82.

JEPSEN, P., VILSTRUP, H. & ANDERSEN, P. K. 2015. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. *Hepatology,* 62**,** 292-302.

JOHNSON, P. J., BERHANE, S., KAGEBAYASHI, C., SATOMURA, S., TENG, M., REEVES, H. L., O'BEIRNE, J., FOX, R., SKOWRONSKA, A., PALMER, D., YEO, W., MO, F., LAI, P., INARRAIRAEGUI, M., CHAN, S. L., SANGRO, B., MIKSAD, R., TADA, T., KUMADA, T. & TOYODA, H. 2015. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *Journal of Clinical Oncology,* 33**,** 550-8.

KAPLAN, E. L. & MEIER, P. 1958. Nonparametric estimation from incomplete observations. *Journal of the American statistical association,* 53**,** 457-481.

KRAMER, J. R., DAVILA, J. A., MILLER, E. D., RICHARDSON, P., GIORDANO, T. P. & EL-SERAG, H. B. 2008. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. *Aliment Pharmacol Ther,* 27**,** 274-82.

KUDO, M. 2020. Recent Advances in Systemic Therapy for Hepatocellular Carcinoma in an Aging Society: 2020 Update. *Liver Cancer,* 9**,** 640-662.

KULIK, L. & EL-SERAG, H. B. 2019. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology,* 156**,** 477-491.e1.

LAMBERT, P. C., WILKES, S. R. & CROWTHER, M. J. 2017. Flexible parametric modelling of the cause-specific cumulative incidence function. *Stat Med,* 36**,** 1429-1446.

LANDIS, J. R. & KOCH, G. G. 1977. The measurement of observer agreement for categorical data. *Biometrics,* 33**,** 159-74.

LAPOINTE-SHAW, L., GEORGIE, F., CARLONE, D., CEROCCHI, O., CHUNG, H., DEWIT, Y., FELD, J. J., HOLDER, L., KWONG, J. C., SANDER, B. & FLEMMING, J. A. 2018. Identifying cirrhosis, decompensated cirrhosis and hepatocellular carcinoma in health administrative data: A validation study. *PLoS One,* 13**,** e0201120.

LEON, D. A. & MCCAMBRIDGE, J. 2006. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *The Lancet,* 367**,** 52-56.

LIVRAGHI, T., MELONI, F., DI STASI, M., ROLLE, E., SOLBIATI, L., TINELLI, C. & ROSSI, S. 2008. Sustained complete response and complications rates after

radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology,* 47**,** 82-89.

LLOVET, J. M., REAL, M. I., MONTAÑA, X., PLANAS, R., COLL, S., APONTE, J., AYUSO, C., SALA, M., MUCHART, J. & SOLÀ, R. 2002. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *The Lancet,* 359**,** 1734-1739.

LLOVET, J. M., RICCI, S., MAZZAFERRO, V., HILGARD, P., GANE, E., BLANC, J.-F., DE OLIVEIRA, A. C., SANTORO, A., RAOUL, J.-L. & FORNER, A. 2008a. Sorafenib in advanced hepatocellular carcinoma. *New England journal of medicine,* 359**,** 378-390.

LLOVET, J. M., RICCI, S., MAZZAFERRO, V., HILGARD, P., GANE, E., BLANC, J. F., DE OLIVEIRA, A. C., SANTORO, A., RAOUL, J. L., FORNER, A., SCHWARTZ, M., PORTA, C., ZEUZEM, S., BOLONDI, L., GRETEN, T. F., GALLE, P. R., SEITZ, J. F., BORBATH, I., HAUSSINGER, D., GIANNARIS, T., SHAN, M., MOSCOVICI, M., VOLIOTIS, D., BRUIX, J. & GROUP, S. I. S. 2008b. Sorafenib in advanced hepatocellular carcinoma. *New England Journal of Medicine,* 359**,** 378-90.

LO, C.-M., NGAN, H., TSO, W.-K., LIU, C.-L., LAM, C.-M., POON, R. T.-P., FAN, S.-T. & WONG, J. 2002. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology,* 35**,** 1164-1171.

MA, W.-L., LAI, H.-C., YEH, S., CAI, X. & CHANG, C. 2014. Androgen receptor roles in hepatocellular carcinoma, cirrhosis, and hepatitis. *Endocrine-related cancer,* 21**,** R165.

MALINCHOC, M., KAMATH, P. S., GORDON, F. D., PEINE, C. J., RANK, J. & TER BORG, P. C. 2000. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology,* 31**,** 864-871.

MAZZAFERRO, V., LLOVET, J. M., MICELI, R., BHOORI, S., SCHIAVO, M., MARIANI, L., CAMERINI, T., ROAYAIE, S., SCHWARTZ, M. E., GRAZI, G. L., ADAM, R., NEUHAUS, P., SALIZZONI, M., BRUIX, J., FORNER, A., DE CARLIS, L., CILLO, U., BURROUGHS, A. K., TROISI, R., ROSSI, M., GERUNDA, G. E., LERUT, J., BELGHITI, J., BOIN, I., GUGENHEIM, J., ROCHLING, F., VAN HOEK, B. & MAJNO, P. 2009. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol,* 10**,** 35-43.

MAZZAFERRO, V., REGALIA, E., DOCI, R., ANDREOLA, S., PULVIRENTI, A., BOZZETTI, F., MONTALTO, F., AMMATUNA, M., MORABITO, A. & GENNARI, L. 1996. Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. *New England Journal of Medicine,* 334**,** 693-700.

MENNINI, F. S., MARCELLUSI, A., ROBBINS SCOTT, S., MONTILLA, S., CRAXI, A., BUTI, M., GHEORGHE, L., RYDER, S. & KONDILI, L. A. 2021. The impact of direct acting antivirals on hepatitis C virus disease burden and associated costs in four european countries. *Liver Int,* 41**,** 934-948.

MINISTRY OF HOUSING COMMUNITIES AND LOCAL GOVERNMENT. 2015. *National Statistics: English indices of deprivation 2015* [Online]. Available: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [Accessed 07/2022].

MITTAL, S., EL-SERAG, H. B., SADA, Y. H., KANWAL, F., DUAN, Z., TEMPLE, S., MAY, S. B., KRAMER, J. R., RICHARDSON, P. A. & DAVILA, J. A. 2016.

Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans is Associated With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol,* 14**,** 124-31.e1.

NAUGLER, W. E., SAKURAI, T., KIM, S., MAEDA, S., KIM, K., ELSHARKAWY, A. M. & KARIN, M. 2007. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science,* 317**,** 121-4.

NEHRA, M. S., MA, Y., CLARK, C., AMARASINGHAM, R., ROCKEY, D. C. & SINGAL, A. G. 2013. Use of administrative claims data for identifying patients with cirrhosis. *J Clin Gastroenterol,* 47**,** e50-4.

OKEN, M. M., CREECH, R. H., TORMEY, D. C., HORTON, J., DAVIS, T. E., MCFADDEN, E. T. & CARBONE, P. P. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* 5**,** 649-55.

ONS. 2016. *Cancer registration statistics QMI 2016* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/cancerregistrationstatisticsqmi [Accessed 07/2022].

PEARSON, K. 1900. X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science,* 50**,** 157-175.

PHE 2017. THE 2ND ATLAS OF VARIATION IN RISK FACTORS AND HEALTHCARE FOR LIVER DISEASE IN ENGLAND.

PHE. 2019. *Hepatitis C: interventions for patient case-finding and linkage to care* [Online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829331/Hepatitis_C_interventions_for_patient_case-finding_and_linkage_to_care.pdf [Accessed 07/2022].

PUGH, R. N., MURRAY-LYON, I. M., DAWSON, J. L., PIETRONI, M. C. & WILLIAMS, R. 1973. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg,* 60**,** 646-9.

QI, X., TANG, Y., AN, D., BAI, M., SHI, X., WANG, J., HAN, G. & FAN, D. 2014. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol,* 48**,** 450-7.

RAMAKRISHNA, G., RASTOGI, A., TREHANPATI, N., SEN, B., KHOSLA, R. & SARIN, S. K. 2013. From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. *Liver Cancer,* 2**,** 367-83.

RATIB, S., FLEMING, K. M., CROOKS, C. J., AITHAL, G. P. & WEST, J. 2014a. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. *Journal of Hepatology,* 60**,** 282-9.

RATIB, S., WEST, J., CROOKS, C. J. & FLEMING, K. M. 2014b. Diagnosis of Liver Cirrhosis in England, a Cohort Study, 1998–2009: A Comparison With Cancer. *The American Journal Of Gastroenterology,* 109**,** 190.

RATIB, S., WEST, J. & FLEMING, K. M. 2017. Liver cirrhosis in England—an observational study: are we measuring its burden occurrence correctly? *BMJ Open,* 7.

RIPOLL, C., GROSZMANN, R. J., GARCIA-TSAO, G., BOSCH, J., GRACE, N., BURROUGHS, A., PLANAS, R., ESCORSELL, A., GARCIA-PAGAN, J. C., MAKUCH, R., PATCH, D., MATLOFF, D. S. & PORTAL HYPERTENSION COLLABORATIVE, G. 2009. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *Journal of Hepatology,* 50**,** 923-8.

ROBERTS, M. S., ANGUS, D. C., BRYCE, C. L., VALENTA, Z. & WEISSFELD, L. 2004. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl,* 10**,** 886-97.

RULLI, E., GHILOTTI, F., BIAGIOLI, E., PORCU, L., MARABESE, M., D'INCALCI, M., BELLOCCO, R. & TORRI, V. 2018. Assessment of proportional hazard assumption in aggregate data: a systematic review on statistical methodology in clinical trials using time-to-event endpoint. *British Journal of Cancer,* 119**,** 1456-1463.

SAPISOCHIN, G. & BRUIX, J. 2017. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nature Reviews Gastroenterology &Amp; Hepatology,* 14**,** 203.

SCHLESINGER, S., ALEKSANDROVA, K., PISCHON, T., JENAB, M., FEDIRKO, V., TREPO, E., OVERVAD, K., ROSWALL, N., TJØNNELAND, A. & BOUTRON-RUAULT, M. 2013. Diabetes mellitus, insulin treatment, diabetes duration, and risk of biliary tract cancer and hepatocellular carcinoma in a European cohort. *Annals of oncology,* 24**,** 2449-2455.

SHANKER, M. D., LIU, H. Y., LEE, Y. Y., STUART, K. A., POWELL, E. E., WIGG, A. & PRYOR, D. I. 2021. Stereotactic radiotherapy for hepatocellular carcinoma: Expanding the multidisciplinary armamentarium. *Journal of gastroenterology and hepatology,* 36**,** 873-884.

SPIEGELHALTER, D. J. 2005. Funnel plots for comparing institutional performance. *Statistics in medicine,* 24**,** 1185-1202.

STIGLIANO, R., MARELLI, L., YU, D., DAVIES, N., PATCH, D. & BURROUGHS, A. 2007. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome?: Seeding risk for percutaneous approach of HCC. *Cancer treatment reviews,* 33**,** 437-447.

TAKAYASU, K., ARII, S., KUDO, M., ICHIDA, T., MATSUI, O., IZUMI, N., MATSUYAMA, Y., SAKAMOTO, M., NAKASHIMA, O. & KU, Y. 2012. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. *Journal of hepatology,* 56**,** 886-892.

TATARU, D., SPENCER, K., BATES, A., WIECZOREK, A., JACK, R. H., PEAKE, M. D., LIND, M. J. & LÜCHTENBORG, M. 2018. Variation in geographical treatment intensity affects survival of non-small cell lung cancer patients in England. *Cancer Epidemiology,* 57**,** 13-23.

THYGESEN, S. K., CHRISTIANSEN, C. F., CHRISTENSEN, S., LASH, T. L. & SØRENSEN, H. T. 2011. 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 Medical Research Methodology,* 11**,** 83.

TOVIKKAI, C., CHARMAN, S. C., PRASEEDOM, R. K., GIMSON, A. E., WATSON, C. J. E., COPLEY, L. P. & VAN DER MEULEN, J. 2014. Linkage of a National Clinical Liver Transplant Database With Administrative Hospital Data: Methods and Validation. *Transplantation,* 98**,** 341-347.

TREVISANI, F., SANTI, V., GRAMENZI, A., DI NOLFO, M. A., DEL POGGIO, P., BENVEGNU, L., RAPACCINI, G., FARINATI, F., ZOLI, M. & BORZIO, F. 2007. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? *American Journal of Gastroenterology,* 102**,** 2448-2457.

UCLA. 2020a. *Mixed Effects Logistic Regression - Stata Data Analysis Examples* [Online]. Available: https://stats.idre.ucla.edu/stata/dae/mixed-effects-logistic-regression/ [Accessed 19/06/2020].

UCLA. 2020b. *Multinomial Logistic Regression - Stata Annotated Output* [Online]. Available: https://stats.idre.ucla.edu/stata/output/multinomial-logistic-regression/ [Accessed 18/06/2020].

UHLIG, J., SELLERS, C. M., STEIN, S. M. & KIM, H. S. 2018. Radiofrequency ablation versus surgical resection of hepatocellular carcinoma: contemporary treatment trends and outcomes from the United States National Cancer Database. *European Radiology,* 17**,** 17.

VAN WALRAVEN, C., DAVIS, D., FORSTER, A. J. & WELLS, G. A. 2004. Time-dependent bias was common in survival analyses published in leading clinical journals. *Journal of Clinical Epidemiology,* 57**,** 672-682.

VITALE, A., PECK-RADOSAVLJEVIC, M., GIANNINI, E. G., VIBERT, E., SIEGHART, W., VAN POUCKE, S. & PAWLIK, T. M. 2017. Personalized treatment of patients with very early hepatocellular carcinoma. *J Hepatol,* 66**,** 412-423.

WANDS, J. 2007. Hepatocellular carcinoma and sex. *N Engl J Med,* 357**,** 1974-6.

WANG, Y., LUO, Q., LI, Y., DENG, S., WEI, S. & LI, X. 2014. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. *PLoS One,* 9**,** e84484.

WHITE, D. L., KANWAL, F. & EL-SERAG, H. B. 2012. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol,* 10**,** 1342-1359.e2.

WILLIAMSON, P. R., SMITH, C. T., HUTTON, J. L. & MARSON, A. G. 2002. Aggregate data meta-analysis with time-to-event outcomes. *Statistics in Medicine,* 21**,** 3337-3351.

WONG, V. W.-S. & CHAN, H. L.-Y. 2010. Transient elastography. *Journal of gastroenterology and hepatology,* 25**,** 1726-1731.

WORLD HEALTH ORGANISATION. 2013. *European health for all database (HFA-DB)* [Online]. Available: www.euro.who.int/en/data-and-evidence/databases/european-health-for-all-family-of-databases-hfa-db [Accessed 08/06/2020].

YE, Q., QIAN, B. X., YIN, W. L., WANG, F. M. & HAN, T. 2016. Association between the HFE C282Y, H63D Polymorphisms and the Risks of Non-Alcoholic Fatty Liver Disease, Liver Cirrhosis and Hepatocellular Carcinoma: An Updated Systematic Review and Meta-Analysis of 5,758 Cases and 14,741 Controls. *PLoS One,* 11**,** e0163423.

YU, M.-W. & CHEN, C.-J. 1993. Elevated serum testosterone levels and risk of hepatocellular carcinoma. *Cancer research,* 53**,** 790-794.

16 Appendix

16.1 National Cancer Registration and Analysis Service – analysis proposal

Understanding the outcomes of patients with cirrhosis and hepatocellular carcinoma (HCC) in the England

- Part of HCC-UK/ NCRAS Partnership

Version 1.0 18th January 2017

Dr. Robert Driver[1,2]

[1]Leeds Liver Unit, Leeds Teaching Hospitals NHS Trust

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds

Background

Liver disease is increasing and is a leading cause of death in individuals of working age. The incidence of HCC is also increasing and the outcomes for patients with HCC are poor. The most recent survival figures published by Public Health England indicate 5-year survival of approximately 15%.

Diagnosis and treatment of HCC in the setting of cirrhosis is complex and depends not only of the stage of cancer but also on the underlying cirrhosis. For example, treatments with the greatest chance of providing cure for the patient are often contra-indicated by the severity of the underlying cirrhosis. Assessment of liver disease severity at a population level is therefore crucial to understanding clinical outcomes in HCC.

Since HCC develops in the setting of cirrhosis in more than 80% of cases (El-Serag, 2011), individuals with HCC are at ongoing risk of deterioration in liver function and liver related (non-cancer) mortality. This continues to be the case after potentially curative treatment of HCC where, in individuals with progressive liver disease, liver failure is a frequent cause of death (Cabibbo et al., 2017). The rate of development of liver failure is dependent on the underlying stage of cirrhosis. In a previous analysis

(D'Amico et al., 2006), pooled data from two large natural history studies including 1649 patients were used to identify four clinical states represented by the Baveno classification, determined by the presence of oesophageal varices and ascites (de Franchis, 2005). For each of these states, the annual mortality rate was calculated as well as the cumulative annual rate of transition between states. There is a significant increase in mortality with increasing Baveno stage.
Previous work in health data research has identified methods to use the electronic record to assess cirrhosis severity according to the Baveno stage (Ratib et al., 2014). Since the complications related to liver failure result in admitted patient care, these events are captured by the Hospital Episode Statistics dataset (HES), which will enable the stratification of liver disease severity in HCC.

Project aim – include hypotheses if relevant

To exploit routine health data to investigate how variation in baseline characteristics at HCC diagnosis and geographical location influence treatment allocation and clinical outcomes. In addition to overall survival, the rate of progression of underlying liver disease will also be investigated, to understand the competing mortality of HCC and cirrhosis.

Relevance to NCRAS strategic priorities and functional teams

Assessment of variation in survival outcomes and treatment are key elements of NCRAS's work programme, as well as an assessment of the NHS's performance against other healthcare systems. In addition to the goal of improving cancer care through understanding the long-term effects of treatment and ensuring all patients have access to the best care, the following NCRAS strategic priorities are directly relevant to this project:

1. *Spearhead a radical upgrade in prevention and public health*

Liver disease and its progression to cirrhosis and HCC are major public health problems. The most common aetiologies are associated with preventable diseases, including alcohol, obesity and viral hepatitis. This project will aim to highlight variation in the severity of cirrhosis at the time of cancer diagnosis and the influence this and other factors has on anti-cancer treatment and outcomes. In turn, these findings may help to shape future public health initiatives by highlighting areas of inequality.

2. *Drive a national ambition to achieve earlier diagnosis*

Central to achieving early diagnosis in HCC is an understanding of the role of HCC surveillance in cirrhosis. This project will give an insight into key parameters involved in optimising surveillance programmes, such as the competing mortality of advanced cirrhosis and regional variation in the characteristics of patients presenting with HCC.

3. *Increase in 1-year survival, with a reduction in CCG variation*

Understanding the complex factors that influence survival in HCC is central to this project. These factors include the stage and aetiology of underlying liver disease,

age, co-morbidity, and cancer-specific treatments which will all be considered in this analysis. Once these factors have been considered, regional variation in treatment allocation and clinical outcomes can also be assessed.

Specific project objectives

The following questions will be specifically addressed in the analyses:

1. *Which baseline factors determine treatment allocation and overall survival in HCC?*

The aim is to assess the baseline factors at HCC diagnosis which may influence HCC treatment allocation (and therefore overall survival). The factors which are independent determinants of survival will also be identified, along with the cause of death. The baseline factors to be considered (in collaboration with the HCC UK-PHE Analyst team) are:

a. Age
b. Sex
c. Ethnicity
d. Cancer stage
e. Medical co-morbidities
f. Aetiology of underlying liver disease
g. Presence of cirrhosis at HCC diagnosis
h. Cirrhosis stage at HCC diagnosis (according to Baveno stage)

2. *How is HCC treatment allocation associated with overall survival and decompensation of cirrhosis?*

The aim is to determine the first and subsequent HCC treatments given to patients and the associated clinical outcomes, including:

a. Overall survival, adjusted for baseline factors
b. Rate of decompensation of cirrhosis following different treatments

3. *What is the nature of regional variation in baseline factors and treatment allocation in HCC?*

The aim is to assess potential regional variation in:

a. Baseline factors at HCC diagnosis, including the influence of income deprivation (in collaboration with the University of Liverpool)
b. HCC treatment allocation at different centres, and
c. Apply the described variation in baseline factors and treatment allocation to understand regional differences in survival (in collaboration with the University of Liverpool)

Analytical approach

To include use of existing Standard Operating Procedures (SOPs) and/or how the project will generate new SOPs that can be used by others

Data Collection

HCC will be defined using ICD-10 code C22.0. The cohort of patients will be defined by those patients with a new diagnosis of HCC between 01/01/2007 and 31/12/2016. This dataset will be linked to the Hospital Episode Statistics (HES) database. A HES extract will be obtained containing information on Finished Consultant Episodes (FCEs) for those individuals in the HCC cohort. This extract period will start from 5 years prior to the HCC diagnosis date and continue until death or the end of the study period.
A focussed HES extract will be retrieved and analysed in order to achieve the specific aims of the study, as described in the following sections:

1. *Which baseline factors determine treatment allocation and overall survival in HCC?*

In order to assess the baseline factors, the following non-identifiable data will be extracted:

a. *Age at diagnosis in 5 year age bands* (from Cancer Registry)
b. *Sex* (from Cancer Registry)
c. *Ethnic category and broad ethnic group* (from Inpatient HES).
   This is required because it may be associated with some aetiologies of liver disease, including viral hepatitis which is more common in migrant populations.
d. *Cancer stage* (using “Best ‘registry’ stage at diagnosis of the tumour” from Cancer Registry)
   There is an expectation that the data quality of HCC cancer stage is poor due missing values, but this will be included to comparison purposes.
e. *Medical co-morbidities*
   Diagnostic codes related to medical comorbidities contained within Inpatient HES will be extracted, along with the time interval from HCC diagnosis date to the start of the associated episode. In addition to Inpatient HES Charlson Index, codes for individual co-morbidities will be extracted because they impact the progression of liver disease.
f. *Aetiology of underlying liver disease*
   Specific diagnostic codes relating to different liver disease aetiologies will be extracted from episodes contained within the total study period.
g. *Presence of cirrhosis at HCC diagnosis*
   Specific diagnostic and procedure codes relating to cirrhosis or its complications (ascites, oesophageal or gastric varices and hepatic encephalopathy) will be extracted from episodes within the total study period. The time interval from HCC diagnosis to the start of the associated episode will be extracted. If these codes appear at any point during the study, it will be assumed that the HCC occurred in the background of cirrhosis.

h. *Cirrhosis stage at HCC diagnosis*
Diagnosis and procedure codes specific to cirrhosis-related complications (along with the time interval from HCC diagnosis to the start of the associated episode) will be extracted from Inpatient HES. Analysing a time interval from 5 years before HCC diagnosis to 3 months after will enable the calculation of the baseline Baveno stage. We expect that this algorithm will generate a new SOP for the classification of liver disease severity from Inpatient HES for use by others:
    - Stage 1: No varices, no ascites
    - Stage 2: Varices, no ascites
    - Stage 3: Ascites +/- varices
    - Stage 4: Bleeding +/- ascites

Overall survival in relation to these baseline factors will be established by extracting the time interval from HCC diagnosis date to death from the Cancer Registry. The certified cause of death and 'underlying cause of death' will be extracted from the Cancer Registry.

2. *How is HCC treatment allocation associated with overall survival and decompensation of cirrhosis?*

An Inpatient HES extract spanning the total study period will be used to identify specific HCC-related treatments. The procedure codes and time interval from HCC diagnosis to the episode containing the treatment will be recorded. The site code of treatment will also be collected.

In order to assess the use of sorafenib, data held within the cancer registry (AV_treatment) and within the Systemic Anti-Cancer Therapy Data Set (SACT) will be analysed. Sorafenib will be searched within the '*raw regimen'* data item in SACT, along with the time interval from HCC diagnosis until the start of the drug regimen. The 'organisation code of provider' will be recorded to identify the treating centre.

Clinical outcomes will be determined including:

a. *Overall survival*
Survival post-treatment will be inferred from the time interval from HCC diagnosis date to death and the interval from HCC diagnosis to each HCC treatment
b. *Rate of decompensation of cirrhosis following different treatments*
Diagnosis and procedure codes specific to complications of cirrhosis which occur after the HCC diagnosis will be extracted, along with the time interval from HCC diagnosis date to the start of the associated episode. An updated cirrhosis stage will be calculated using the new Baveno stage SOP.

3. *What is the nature of regional variation in baseline factors and treatment allocation in HCC?*

a. *Baseline factors at HCC diagnosis* (in collaboration with the University of Liverpool)

The 'broader geographical area' and index of multiple deprivation (IMD) quintiles will be extracted from Inpatient HES. The baseline factors for each area will be assessed using the data items extracted in Section 1.

b. *HCC Treatment allocation at different centres*

The code of the NHS Trust in which the HCC treatment took place ('site code of treatment') will be extracted from the Inpatient HES episode associated with the specific HCC treatment. This is a necessary additional data item to a patient's broader geographical area because it will also demonstrate where patients actually receive their HCC treatment. The variation in treatment allocation at different specialist centres can then be established and this will be correlated with the baseline factors.

c*. Apply the described variation in baseline factors and treatment allocation to understand regional differences in survival* (in collaboration with the University of Liverpool)

The factors described above will be used to identify predictors of regional variation in survival that may relate for instance to stage of liver disease at presentation or differences in treatment allocation.

Statistical Analysis

For each of the study sections, the following statistical analysis will be performed:

1. This analysis will be informed by the Cohort Overview, undertaken by the HCC-UK partners in Bristol (AB), which will describe the patient characteristics. Descriptive statistics will be used to characterise the baseline factors of the HCC cohort, assessing for significant associations between variables.
   A two-state disease model (dead or alive) will be used for standard survival analysis: univariate analysis will be performed using the Kaplan-Meier method, with patients stratified by the baseline factors of interest such as cirrhosis stage. A Cox proportional hazards regression will be used to calculate a hazard ratio for the baseline determinants of overall survival.

2. a. Survival analysis will be performed using the Kaplan-Meier method, stratified by treatment allocation. Survival between the groups will be compared using the log-rank test. Patient numbers are expected to be large enough to allow further stratification by baseline factors of interest, such as liver disease aetiology.

b. The rate of decompensation of cirrhosis following different HCC treatments will be determined by calculating the risk of hospital readmission with complications of decompensated cirrhosis within 30 days. The baseline characteristics of those patients who have decompensation events will be compared using multivariate logistic regression in order to identify predictive factors.
A competing risk analysis will be performed using a cumulative incidence function (CIF) to describe the rate of cirrhosis decompensation events admission following different HCC treatments. The clinical states used in a multi-state disease model will be: compensated cirrhosis, decompensated cirrhosis, death related to HCC and death related to liver disease (from death certification).

3. a. The baseline factors will be cross-tabulated with broader geographical area and tested for significant associations. Analysis performed by HCC-UK partners in Liverpool (VK, TC, DP) will lead to an estimate of the median overall survival for each broader geographical area and linked IMD and travel time to destination. Significant differences in median survival between areas and the association with IMD quintile will be tested and adjusted for the variation in baseline factors.

   b. For each centre treating patients with HCC, the proportion of patients receiving different HCC modality will be calculated. The statistical significance of any variation in treatment allocation between centres will be tested and adjusted for baseline characteristics.

   c. Baseline factors and treatment allocation will be used in Cox proportional hazard models to investigate the potential differences in survival.

Expected outputs or deliverables

Publications that include interpretation or are likely to be politically sensitive will need to be flagged with the PHE publication standard team (excluding press releases, blogs, academic papers, posters, presentations and data/spreadsheets).

We expect that the development of the Baveno stage SOP will be applicable to a wide number of future population-based studies that require an assessment of cirrhosis severity.

We expect to publish these findings in peer reviewed scientific journals and present at scientific conferences. The two main publications include the description of regional variation in HCC treatment and survival (adjusted for cirrhosis severity) and the competing risk analysis of HCC treatment outcomes.

We hope that the project will inform future research and ongoing work within the HCC-UK/ NCRAS partnership on understanding variation in access to treatments

and clinical trials, as well as cost-effectiveness analyses. An understanding of the natural history of cirrhosis in the setting of HCC provided by our analysis will inform the planning of surveillance programmes for HCC in cirrhosis. These analyses have the potential to identify variations in clinical practice and therefore to improve future resource allocation and clinical outcomes.

Breakdown of project timescales

To include realistic expectations of planning, analytical time, QA, write up etc. as well as any externally driven timescales e.g. relevant conferences.

We have undertaken pilot work using the same ICD10/ OPCS4 codes using local audit data. The algorithm for determining Baveno stage has been validated using this dataset and will form the basis of the tool to be used in the national dataset. We therefore envisage a timescale of 6 months from receipt of the data to submission of first publication. We expect it to take a further 6 months to complete the analyses of the whole project and submit publications. We would expect to present preliminary results at the British Association of the Study of the Liver (BASL) meeting in September 2018.

Comms planning

To include how the comms planning will be managed and who intended audience is for the work. Comms plan to be drafted at early stages of project.

The audience will mainly be academic/clinical.

As well as academic publications, blogs on the PHE, BASL and/or BSG website highlighting the work may be written.

The institute leading the research (University of Leeds) will also lead the communications plan however the PHE communications team will be informed well in advance of any publication or presentation of work resulting from the HCC-UK-NCRAS partnership. This may include press releases, blogs, conference presentations, report publications or academic journal publications

Press releases will either be written in conjunction with or reviewed by the PHE comms office.

Risks

Risks will be managed by limiting analysis to pseudonymised data. All potentially identifiable data will be analysed within PHE premises. There may be the possibility to analyse non-identifiable data by a secure VPN-type link, which has previously been used done at Leeds Institute of Data Analytics. Published data will be aggregate data with suppression of small numbers.

Geographical scope i.e. regional, England, UK, International

National outputs should be accompanied by a geographic breakdown of results

This project will comprise the outcomes for patients with HCC in England. The regional variation in disease prevalence, aetiology, cirrhosis severity and treatment allocation, as well as clinical outcomes will be broken down into geographical region.

Equality aspects included e.g. sex, age, ethnicity etc

The purpose of this project is to identify variation in disease and allocation of treatment. Analysis of the HES extract will include demographic information including age, sex and ethnicity.

Costs (if relevant)

The PHE analyst time falls within the auspices of the HCC-UK/ NCRAS partnership. The project team are funded by Leeds Teaching Hospitals NHS Trust and the University of Leeds. We do not envisage any additional costs, but expenses will be covered by Dr Rowe's University budget.

Project Team and roles

To include for each person involved (internal and external) who would be undertaking which aspect of the work

Analysts including QA: Dr Anya Burton (internal), Dr Robert Driver (external)
Project advisors: Dr Tim Cross, Prof Dan Palmer, Dr Aileen Marshall and the HCC-UK/NCRAS Steering Group
Clinical lead (external): Dr Ian Rowe
NCRAS Clinical Lead:
Other relevant people including patients / carers:

Dr Anya Burton (HCC-UK/NCRAS) will establish the HCC cohort, prepare the data and describe the baseline patient characteristics. The NCRAS Survival team have advised on analyses.
Dr Robert Driver will be leading the analysis when data is released from PHE. He will be supported by Dr Amy Downing, Prof Eva Morris and Dr Rowe, alongside the research group within the Leeds Institute for Data Analytics, who have a wealth of experience in conducting population-based studies that quantify variation in the processes of management and outcome of cancer patients.
Dr Vinay Kumar, Dr Tim Cross and Prof Dan Palmer (Liverpool) will perform the survival analysis utilised in Section 3c – describing the regional variation in HCC survival in England (with the linked index of multiple deprivation quintiles). This work will be supported in Liverpool by Dr Sue Povall (Public Health and Policy) and Dr Mark Green (Health Geography).

A provisional authorship (dependent upon forthcoming input) is:
Driver RJ, Burton A, Kumar V, Aileen Marshall & HCC/ NCRAS Steering Group,

Povall S, Green M, Palmer D, Downing A, Cross T, Morris E, Rowe IA.

References and literature review

CABIBBO, G., PETTA, S., BARBARA, M., ATTARDO, S., BUCCI, L., FARINATI, F., GIANNINI, E. G., NEGRINI, G., CICCARESE, F., RAPACCINI, G. L., DI MARCO, M., CATURELLI, E., ZOLI, M., BORZIO, F., SACCO, R., VIRDONE, R., MARRA, F., MEGA, A., MORISCO, F., BENVEGNU, L., GASBARRINI, A., SVEGLIATI-BARONI, G., FOSCHI, F. G., OLIVANI, A., MASOTTO, A., NARDONE, G., COLECCHIA, A., PERSICO, M., CRAXI, A., TREVISANI, F., CAMMA, C. & ITALIAN LIVER CANCER, G. 2017. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. Journal of Hepatology, 67, 65-71.

D'AMICO, G., GARCIA-TSAO, G. & PAGLIARO, L. 2006. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. Journal of Hepatology, 44, 217-31.

D'AMICO, G., MORABITO, A., D'AMICO, M., PASTA, L., MALIZIA, G., REBORA, P. & VALSECCHI, M. G. 2017. Clinical states of cirrhosis and competing risks. Journal of Hepatology, 27, 27.

DE FRANCHIS, R. 2005. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology, 43, 167-76.

EL-SERAG, H. B. 2011. Hepatocellular carcinoma. New England Journal of Medicine, 365, 1118-27.

JEPSEN, P., VILSTRUP, H. & ANDERSEN, P. K. 2015. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology, 62, 292-302.

RATIB, S., FLEMING, K. M., CROOKS, C. J., AITHAL, G. P. & WEST, J. 2014. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. Journal of Hepatology, 60, 282-9.