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Liver transplantation as a treatment for patients with hepatocellular carcinoma: a study using electronic health care data.

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ABSTRACT

Background

Annually over 4,000 new cases of hepatocellular carcinoma (HCC) are being diagnosed in the UK. Overall survival of HCC patients is poor with less than 30% alive at one year. Prognosis is best for patients who receive a liver transplant. The emergence of liver transplantation as a curative option for HCC has resulted it now being the most common indication for liver transplantation. This development has increased the disparity between the number of patients waiting for transplantation and the availability of suitable livers. In response, livers from donation after circulatory death (DCD) are increasingly being used to expand the donor pool, although outcomes have been previously proven to be worse than with livers from donation after brain death (DBD). The overall aim of my research was to use linked large-scale electronic health care data to improve the current evidence base on the best strategy for using liver transplantation in patients with and without HCC.

Methods

In this thesis, national datasets were linked at patient level and analysed to investigate outcomes of patients following liver transplantation. The Standard National Liver Transplant Registry (SNLTR) was used to identify the donor and recipient characteristics of patients with and without HCC and the Hospital Episode Statistics (HES) dataset was used to capture information on clinico-sociodemographic characteristics that included deprivation status, co-morbidity, treatments and length of hospital stay. Throughout the thesis, post-transplant mortality and graft failure for HCC and non-HCC patients were analysed in distinct post-transplantation time-periods ('epochs'). Stepwise case mix adjustment for recipient and then donor factors was used to ascertain determinants of post-transplant outcomes. Multiple imputation methods were used to handle missing data items. The analyses in this thesis were split into three related clinical areas; DCD livers, pre-transplant performance status (PS), and the administration of transarterial chemoembolization (TACE) on the transplant waiting list.

Results

In the last two decades, mortality after liver transplantation in the UK has more than halved for HCC patients despite the increased and preferential use of DCD livers in these patients. However, one in four HCC recipients still die within five years compared to only one in six non-HCC patients. Improvements in survival for HCC and non-HCC recipients has been driven by significant improvements both in short-term mortality and in improvements in outcomes of patients who receive a DCD liver. In fact, mortality in recipients of a DCD liver is now comparable to those receiving a DBD liver.

In non-HCC recipients, impaired PS at the time of transplantation was found to be associated with post-transplant mortality whilst in both HCC and non-HCC recipients poorer PS was also associated with an increased incidence of major post-transplant complications and length of hospital stay. However, the impact of PS on each of the measured post-transplant outcomes was limited only to the early post-transplantation time-period.

In the final analysis, 40% of HCC recipients in the UK received at least one treatment of TACE prior to their transplant. However, there was no evidence that TACE increased the risk of post-operative complications or affected the risk of post-transplant mortality or graft failure. These results did not depend on the number of TACE treatments, the type of donor organ (DBD or DCD), or the time-period after transplantation.

Conclusions

Improvements in peri-operative care and in the use of DCD livers has led to significant improvements in post-transplant mortality for HCC and non-HCC patients. Countries who experience high waiting list mortalities should now consider increasing their utilisation of DCD livers. Measurements of PS scores can improve the ability to predict post-transplant survival, post-transplant complications and length of hospital stay, which may contribute to the assessment of the suitability of HCC and non-HCC patients for transplantation. The use of TACE in HCC patients prior to transplantation does not increase the risk of post-operative complications nor does it improve post-transplant mortality. The benefit of TACE is therefore restricted to its impact on modulating tumour growth before transplantation.

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
BASL	British Association of the Study of the liver
BCLC	Barcelona Clinic Liver Cancer (BCLC) Staging and Treatment System
BMI	Body Mass Index
CAG	Confidentiality Advisory Group
CEU	Clinical Effectiveness Unit
CIT	Cold ischaemic time
CLD	Chronic Liver Disease
DAA	Directly acting antiviral
DARS	Data Access and Request Service
DBD	Donation after brainstem death
DCD	Donation after circulatory death
ECOG	Eastern Cooperative Oncology Group
HAT	Hepatic artery thrombosis
HCC	Hepatocellular carcinoma
HES	Hospital Episode Statistics
HBV	Hepatitis B
HCV	Hepatitis C
HR	Hazard ratio
HRA	Health Research Authority
HTN	Hypertension
ICD-10	International Classification of Disease – Version 10
LOS	Length of stay
LRT	Locoregional therapy
LSHTM	London School of Hygiene & Tropical Medicine
MDT	Multidisciplinary Teams
MELD	Model for End-Stage Liver Disease
NAFLD	Non-alcoholic fatty liver disease

NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NHSBT	NHS Blood & Transplant
NIHR	National Institute of Health Research
ONS	Office of National Statistics
OPCS-4	Office of Population, Census and Surveys Classification of Surgical Operations and Procedures
PH	Proportional Hazards
PLD	Primary liver disease
PS	Performance status
RCS	The Royal College of Surgeons of England
REC	Research Ethics Committee
RFA	Radiofrequency ablation
SEFT	Secure File Transfer
SNLTR	Standard National Liver Transplant Registry
TACE	Transarterial chemoembolization
UK	United Kingdom
US	United States
UKELD	United Kingdom End-Stage Liver Disease
WIT	Warm ischaemic time

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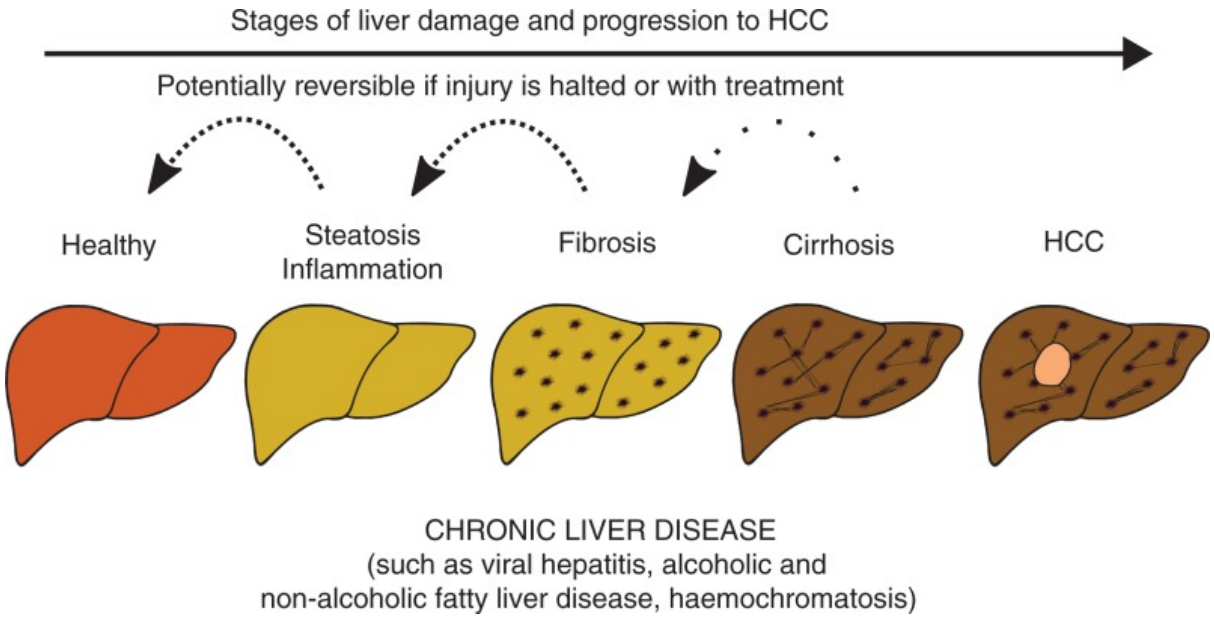
1. INTRODUCTION

1.1 Epidemiology of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for approximately 80% of all primary liver cancers.[1-2] Each year in the United Kingdom (UK), more than four thousand patients are being diagnosed with HCC and age-standardised rates have increased three-fold in the last 20 years.[1-2] This marked escalation in cases of HCC has placed a considerable pressure on global health services and in particular on liver transplantation services in the UK and elsewhere.[3]

Increases in the incidence of HCC are predominantly driven by changes in the prevalence of the aetiological risk factors that precipitate a prolonged disease pathway.[1-3] This pathway usually involves the development of a primary liver disease (PLD) that then leads to cirrhosis – replacement of normal liver tissue with scar tissue – and finally to HCC (Figure 1).[4-5] It is estimated that 80% to 90% of all primary HCCs arises from this pathway.[5]

Figure 1: Stages in the development of HCC[5]



It can often take decades before the exposure to a potential aetiological risk factor results in the occurrence of HCC.[6] This prolonged disease pathway could allow early identification of those at risk of developing HCC. However, HCC often presents symptomatically at a stage that curative intervention is no longer possible.[3] At the point of diagnosis, only 30% of patients with HCC are eligible to receive potentially life-saving surgery[3] and as a result less than 30% of the patients are alive 1 year after diagnosis.[2]

The aetiological risk factors for HCC are well defined,[4-5] and include viral hepatitis, alcohol and obesity.[1-3,7-9] Viral hepatitis is the most prevalent of all the risk factors and accounts globally for 80% of all HCC.[9] The incidence of HCC, both internationally and in the UK, is therefore mapped to the pattern of viral hepatitis.[8]

Internationally, hepatitis B (HBV) is the main driver of HCC but in the UK, protected by effective HBV vaccination and antiviral medications, hepatitis C (HCV) has been responsible for the rising epidemic of liver

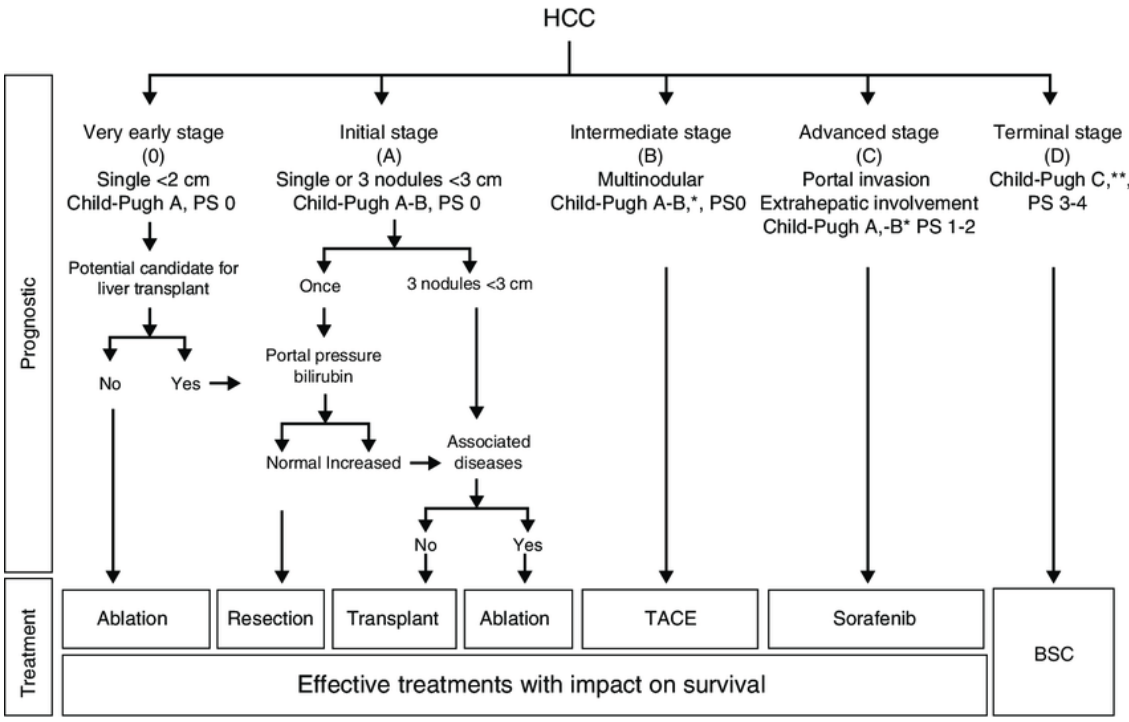
cancer.[4,9] However, there is now strong evidence to suggest that new directly acting anti-virals (DAAs) have decreased the incidence of HCV cirrhosis which is likely to lead to marked reductions in HCC incidence in the future.[10-11] Such is the efficacy of DAAs that patients with HCV cirrhosis are no longer routinely listed for liver transplantation.

However, the hope of eventually reducing HCC incidence through advances in the treatment of HCV is matched with equal concern about the emerging impact of obesity-related liver diseases on HCC incidence.[12] There is epidemiological evidence linking components of 'metabolic syndrome' – obesity, hypertension (HTN), type II diabetes and non-alcoholic fatty liver disease (NAFLD), its hepatic manifestation – with HCC,[12-14] and several studies have suggested a key role for obesity, either as an independent cause or through interaction with other co-morbidities.[12-14] In fact irrespective of HCC, NAFLD is now the fastest growing indication for liver transplantation in both the United Status (US) and the UK.[15]. Overall, the increase in cases of HCC is yet to show any sign of abating.[1-2]

1.2 Liver transplantation for HCC

The available treatment options for patients with HCC depend on the size and spread of the cancer at the time of diagnosis (Figure 2).[3,15-16] Several instruments have been developed to help guide clinicians into selecting the most appropriate treatment option for patients with HCC.[3,16] In high income countries, the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy is the most widely endorsed in research and clinical practice (Figure 2).[3,16] The BCLC links cancer staging with prognosis and suggests a first line treatment option for each.[3,16]

Figure 2: Barcelona Clinic Liver Staging and Treatment System.[3]



For those whose HCC has spread beyond the liver, palliative treatment options include the use of systemic chemotherapy in the form of Sorafenib and transarterial chemoembolisation (TACE).[3] TACE is an angiographic procedure that involves both the local administration of chemotherapeutic agent(s) to a specified HCC nodule and embolisation and blockade of the arterial branch that is supplying it.[17] The procedure can induce decompensation of the cirrhotic liver and can also cause damage to the inner lining or the intima of the hepatic artery, potentially increasing the risk of hepatic artery thrombosis (HAT)[18-22] For those who are diagnosed with early stage HCC, it is widely acknowledged that liver transplantation offers the best potentially curative option.[3] However, a solitary HCC lesion within the liver (without evidence of vascular invasion) can also be considered for a curative liver resection or radiofrequency ablation (RFA) where the tumour is ablated using heat generated from medium frequency alternating current.[3,23-26]

The increase in the incidence of HCC and the introduction of the 'Milan' selection criteria – a set of tumour characteristics introduced in 1996 recommending liver transplantation only if a patient has one HCC lesion with a diameter ≤ 5 cm or alternatively no more than three lesions, each with a diameter ≤ 3 – have led to marked increases in the number of patients with HCC who receive a liver transplant.[3,25-26]

Subsequent expansions to the Milan selection criteria[27-28] and the increasing number of patients referred after failure of alternative interventions – such as liver resection or RFA[27] – have led to further (albeit modest) increases in the number of HCC patients accepted for transplantation.[3,27-29] This has put further pressure on transplantation services in many countries because they find it difficult to cope with providing sufficient liver transplant capacity for both HCC and non-HCC patients within an acceptable time frame.[3,29-30]

It remains uncertain how increases in the transplantation of patients with HCC and expansions to selection criteria have affected post-transplantation outcomes. International consensus recommendations published in 2012 suggest that survival of patients transplanted for HCC should be 'comparable' to those transplanted for non-HCC.[26] To the best of my knowledge however, no recent study has tested this assertion. A historical analysis using European wide data from 1988 to 2003 identified outcomes immediately after transplantation to be superior in HCC patients but also found that their survival deteriorates later during follow-up most likely due to tumour recurrence.[31-32] In essence, they described – although without explicitly acknowledging it – that HCC is a time-dependent risk factor for liver transplantation.[31-32]

It was expected that the introduction of the more restrictive Milan selection criteria would reverse the impact of HCC on longer post-transplantation outcomes by reducing the incidence of post-transplant tumour recurrence.[25,31] However, more recent studies do not analyse post-transplant outcomes in different time-periods ('epochs') following transplantation.[32] It is therefore unknown whether recurrence of HCC following transplantation results in HCC itself being a time-dependent risk factor for outcomes after liver transplantation.

The importance of analysing liver transplant outcomes in distinct epochs of follow-up time had been recognised and promoted since the 1980s.[32] For example, the first-ever study to recognise the time-dependency of HCC as a risk factor following liver transplantation was based on the first ever statistical

analysis of the Cambridge-Kings Liver Transplant series.[32] Compared to non-HCC recipients, the prognostic effect associated with HCC switched from being a favourable risk factor in the initial post-operative period to a unfavourable risk factor thereafter.[31-32] In response, clinicians changed clinical practice and started performing staging laparotomies to avoid liver transplantation in patients with evidence of pre-existing metastatic disease and thus at risk of a poorer prognosis later on through tumour recurrence.[32] Since then, advances in radiological techniques have eliminated the need for such invasive pre-transplantation investigations.[32]

The example described in the previous paragraph demonstrates the importance of using models for the analysis of outcomes after liver transplantation that allow the effect of a risk factor to vary with time after transplantation. Nevertheless, it has been recognised this form of statistical analysis appears to have passed into the "folklore" of transplantation and medical statistics.[32] It is therefore a key element of this thesis that it describes a number of studies in which post-transplant outcomes are analysed in distinct epochs of follow-up, as testing the prognostic impact of HCC - as well as other risk factors - in different post-transplant time-periods can be justified by clinically plausible explanations.[31-32]

For example, at the time of transplantation patients with HCC tend to have relatively well-preserved liver function.[31-33] As a consequence, they are in a better physical condition and have less signs of end-stage liver disease than patients with other liver diseases.[31-33] This is a likely explanation of why HCC recipients historically have superior outcomes in the early post-operative period.[31,33] However, as explained earlier, the outcomes of HCC recipients in later post-transplant periods are negatively affected by the recurrence of cancer.[25,31] Yet, it is possible that changes over time in HCC selection criteria as well as era-specific improvements in matching of donor and recipients, immunosuppression, use of anti-viral medications, reductions in cold ischaemic times and overall improvements in peri-operative care could have led to changes in the time-dependent effect of HCC.[23,33] Alternatively, increases in the use of sub-optimal organs and changes in organ allocation policies could have exacerbated the difference in short and longer term outcomes between HCC and non-HCC patients.[3,33-36]

1.3 Liver Transplantation in HCC patients using livers donated after circulatory death

The chronic shortage of donor organs has led to an increase in the use of donors whose organs have a greater risk of initial poor function or failure, including organs donated after circulatory death (DCD).[34] In the case of DCD donation, the poorer initial function is attributed to a period warm ischaemic time (WIT, poor or absent blood flow to liver)[34-37] sustained during their procurement that leads to irreversible cellular damage to the biliary structures of the liver.[34] Livers donated after brainstem death (DBD) do not suffer the same period of warm ischaemia and are therefore often considered to be more optimal grafts.[34]

The role of DCD donors in liver transplantation is ill-defined and it remains unknown to what extent the increase in the number of liver transplants for HCC and the related increased use of DCD and other sub-optimal donor organs have affected post-transplantation outcomes. However, for patients with HCC on the

waiting list, transplantation with a DCD liver may still offer the best chance of curative treatment.[3] This is particularly relevant for organ allocation policies – like those used in the UK until recently – that do not use tumour characteristics to prioritise patients on the waiting list[35-36] or for countries who have a high waiting list mortality.[38-39]

At the time of transplantation, HCC patients are also known to be on average in a better physical condition with less signs of end-stage liver disease.[31,33] One argument is that this may have positive effect on short-term post-transplant outcomes and make them more optimal candidates to receive a DCD liver.[33] On the other hand, the transplantation of relatively high-risk DCD livers into patients with early stage HCC and preserved liver function may jeopardise their outcomes due to the increased risk of biliary complications, early graft failure and patient death.[40-41]

Predictive modelling has indicated that compared to more optimal donor organs there is an increased risk of mortality for up to 2 years in patients with early stage HCC who receive a DCD liver.[40] This supports the argument that high-risk liver transplantation, characterised by the utilisation of sub-optimal and DCD donors, is better served in those non-HCC patients with advanced primary liver disease and poor synthetic liver function.[40] However, a 2014 report issued by NHS Blood & Transplant (NHSBT) – the regulatory body coordinating transplant activity in the UK – indicates that if the use of DCD livers was not prioritised in patients with HCC, then these patients would on average have to wait 2 years to receive a liver transplant.[42] This strategy is therefore not without risk and patients with HCC could be at significant risk of falling off the waiting list as their disease progresses beyond transplantable criteria.[3] This is especially pertinent as there are currently no effective molecular markers that better predict the individual behaviour of a heterogeneous set of tumours.[3]

Disease progression on the waiting list can be managed with bridging loco-regional therapy (LRTs), including TACE.[43-44] However, there are no studies in the UK or elsewhere that have used a representative sample of patients to evaluate the role of TACE as a bridging therapy.[18-22] Also in approximately 25% of cases, computed tomography has now been proven to under-stage HCC patients on the waiting list.[26] This means that there still remains a considerable level of uncertainty about the appropriateness of asking patients with HCC to wait longer to receive a liver transplant with a better quality donor organ.

These arguments must all be balanced against the fact that there is also likely to be a learning curve for the optimal utilisation of DCD grafts.[45] In response to early reports of poorer outcomes,[3,34] the transplant community in the UK are very likely to have modified their practice which may mean the previous deleterious impact of DCD livers on graft failure is no longer so prominent.[45-46] In fact, new evidence suggests that accepting an earlier offer of a 'marginal' DCD liver does not necessarily affect post-transplantation outcome.[45-47] A single-centre analysis in the UK has shown graft type had no effect on 1, 3 and 5-year post-transplantation outcomes in patients with HCC whilst in a more recent analysis it has been demonstrated that accepting a DCD liver rather than waiting for a DBD confers a significantly reduced risk of death irrespective of primary liver diseases.[46-47]

Systematic reviews collating the results of studies that compare post-transplantation outcomes following DCD and DBD donation do exist.[48-49] However, most included studies are either from the US or the UK and the meta-analyses are either methodologically inaccurate or unpublished.[48-49] Novel techniques designed to accurately synthesise the results of published studies have also proved futile.[50] Even with emerging digital software, designed to recreate individual level patient data from graphical images,[50] the published studies do not provide the basic information (numbers of patients at risk and total number of events) to recreate an accurate censoring pattern required to conduct a comprehensive meta-regression.[48]

As a result, the impact of using more DCD livers in patients with HCC remains unknown and important gaps in the literature need to be addressed. Firstly, does the use of DCD livers in HCC patients negatively affect their short- or longer-term post-transplantation outcomes? Secondly, has the increased use of DCD livers over time prevented further improvements in post-transplant mortality? Finally, have improvements in the use of DCD livers been observed in the UK and if so do these improvements vary according to whether the patient was transplanted for an HCC or non-HCC indication?

1.4 Performance status in HCC and non-HCC patients who received a liver transplant

Patients with cirrhotic chronic liver disease (CLD) may develop multiple complications that impact upon their ability to perform activities of daily living (ADL) or their performance status (PS).[51-53] In both HCC and non-HCC patients on the transplant waiting list, impaired PS has been shown to have important adverse effects on quality of life as well as survival.[54-56] However, in patients who have received a liver transplant, the impact of pre-transplant PS on post-transplant survival is not as well described.

Measurements of PS are designed to capture a global assessment of health status as opposed to identifying the specific effects of particular organ dysfunction.[53,55-56] There are a variety of metrics available to quantify PS and one of these is through recording of PS scores – patient-reported or clinician recorded assessments of patients' ability to care for themselves.[53] One commonly used PS score shown to have a strong association with mortality in non-transplanted patients with CLD is the Eastern Cooperative Oncology Group (ECOG) scale.[57]

In one previous study, impaired ECOG status has been shown to be a strong and independent risk factor post-transplant mortality.[53] However, this study used data from almost two decades ago and may now not represent the current outcomes of liver transplantation.[53] Within this analysis they also did not specifically assess whether the impact of PS on post-transplant outcomes varied according to the distinct epochs of follow-up time.[53]Also, since the publication of this study, the number of recipients with HCC has increased,[33,53] and therefore the impact of PS on post-transplant mortality in this particular group of patients needs further attention.[58] It is possible that the impact of pre-transplant PS is very different in HCC patients because at the time of transplantation HCC recipients are often in a better physical condition with fewer manifestations of end-stage liver disease than patients without .[33] Given the increasing appreciation of the clinical impact of frailty on the outcome of transplantation in patients, considering the PS of HCC and non-HCC patients prior to

transplantation may help in the assessment, selection and counselling of patients who are potentially eligible for transplantation.

The use of PS measures in HCC and non-HCC patients waiting for transplantation may also be useful beyond helping to predict post-transplant mortality. For example, it is likely that if frailty on the waiting list can help predict post-transplantation outcomes it will also be able to help predict post-operative length of hospital stay and complications. This has never been analysed before using large-scale datasets but is particularly important at a time when the capacity of the National Health Service (NHS) to provide hospital beds for patients requiring solid-organ transplantation is a cause of concern to service providers.[59-60]

Length of hospital stay is also recognised as an outcome that reflects hospital resource and expenditure in the setting of liver transplantation.[61-62] Identifying in advance potentially modifiable factors predictive of longer hospital admissions and how this differs according to HCC and non-HCC patients has a number of potential implications. First, it could help clinicians counsel their patients on what might be experienced in the post-operative period. Second, it could help service providers plan hospital resource use and maximise resource utilisation. Third, it would potentially incentivise the introduction on the waiting list of prehabilitative interventions, aiming to enhance a patient's functional capacity before transplantation, which may serve to reduce overall LOS following transplantation.

1.5 The use of transarterial chemoembolisation (TACE) in HCC patients waiting for a liver transplant

As highlighted earlier, a rise in the number of patients requiring a liver transplant – driven by increases in the incidence of HCC – has increased the pressure on the transplant waiting list.[3] This means that many HCC patients listed for transplantation are in danger of having to wait longer to receive their transplant, especially in countries where there is a shortage of donor livers.[3] In response, increasing numbers of HCC patients on the waiting list are now receiving TACE to minimise the growth of their tumour and prevent their disease progressing beyond transplantable criteria.[18]

There is little evidence that the administration of TACE on the waiting list has an impact on post-transplant survival.[21-22] Two large multicentre analysis, one from the United States (US) and the other from Europe found no statistically significant difference in post-transplant mortality or graft failure between patients who had received TACE and those who had not. However, these analyses only contained patients from 15% of all transplant centres in the US and 20% of all centres in Europe which raises questions about the representativeness of the included patients.[21-22]

Formal allocation policies in the UK now recommend the use of TACE and other LRTs in all HCC patients who are predicted to have to wait 6 months or more to receive a liver transplant.[3,18] However in the UK, the impact of TACE on post-transplant outcomes has not been assessed using a fully representative cohort of patients with HCC. In addition, the impact of TACE in different epochs of post-transplant follow-up time has never been analysed. Addressing these gaps in the literature in this way would improve the clinical relevance of the

existing evidence by helping to inform clinicians and patients whether the pre-transplantation administration of TACE would affect short and longer-term post-transplant mortality or the incidence of post-procedural complications, including HAT.

2. RESEARCH DESIGN

2.1 Aims and Objectives

Aim:

The overall aim of this research is to use national linked health datasets to inform the best use of liver transplantation as a treatment option for patients with HCC.

Objectives:

1. To identify temporal trends in the number of patients with and without HCC receiving a liver transplantation and to assess how this has affected both organ utilisation and post-transplantation outcomes.
2. To compare the outcomes of liver transplantation for patients with and without HCC, to investigate how the difference in outcomes changes over different periods (epochs) of post-transplant follow-up time, and to assess whether this differences is affected by the use of DCD or DBD donors.
3. To identify temporal trends in the utilisation of DCD and DBD donors and their post-transplantation outcomes and to assess whether this differs according to whether they have been used in HCC or non-HCC patients.
4. To investigate the impact of performance status on post-transplant mortality and to identify whether this differs between recipients with and without HCC and according to thr epoch of post-tranplant follow-up time.
5. To investigate the impact of performance status on hospital resource use and to identify whether this differs according to indication for transplantation (HCC vs non-HCC) and epoch of follow-up time.
6. To identify the impact of TACE on the mortality, graft failure and post-operative complications of HCC patients who receive a liver transplant.

2.2 Data sources

a. Overview of datasets and their advantages:

To determine the role of liver transplantation in patients with HCC I have used two national databases linked at patient level. Firstly, I used an extract of the UK liver transplant registry that, for the purposes of this thesis, I named the Standard National Liver Transplant Registry (SNLTR). This dataset was used to identify patients with and without HCC who have undergone a liver transplant and includes information on donor and recipient characteristics as well as highly complete information on the outcomes of patients.[63] In two of the analyses, records were linked to the Hospital Episode Statistics (HES) database which provided important additional information on co-morbidity and length of hospital stay.[64]

b. The Standard National Liver Transplant Registry:

The SNTLR contains records of all patients who received a liver transplant since 1994.[63] The patients included in this database can be considered to form a multi-centred prospective cohort with all six liver transplants units based in England and the single centres in Scotland and Ireland submitting data on all patients who undergo liver transplantation.[63] The registry is separated into three datasets:

1) 'Standard' Liver Transplant Dataset
2) 'Waiting List' Liver Transplant Dataset
3) 'Follow-up' Liver Transplant Dataset

The data submitted to the registry generally come in four separate forms: recipient characteristics and technical aspects of transplant operations in the First Week Transplant Record, which is completed at the time of transplant by the centre-specific transplant teams; general donor characteristics in the Core Donor Data form, which is recorded by organ procurement teams at the time of organ retrieval; and outcomes and follow-up data in the 3-month and Annual Follow-up forms.

The quality of the SNLT is continuously being monitored using computerised consistency checks.[63] A comparison of data of medical records and audit information showed that 98% of the data was complete and 94% of the data fields accurate.[77] The SNTLR has been used to produce numerous high-impact peer review publications.[33-36,53,61,66,72-75]

In this thesis, this dataset provided data on crucial clinical characteristics of the HCC and non-HCC liver transplant recipients including date of transplant, recipient age, sex and BMI, all the clinical parameters that contribute to their UKELD score, and information on cause of death and cause of graft failure.[63] Data on donors and donated livers also included information on age, sex and BMI as well as data detailing organ appearance, graft type (DCD or DBD) and cold and warm ischaemic time.[63] The waiting list dataset contained information on the tumour characteristics of HCC patients at the time of their registration whilst the follow-up dataset provided information on post-operative complications and readmissions.[63]

c. Hospital Episode Statistics (HES) database:

The HES database is an administrative dataset capturing a record of all admissions to English NHS hospitals as well as attendances to outpatient clinics and accident and emergency departments.[64-66] It contains records of episodes, which represent periods of care in hospital under one consultant.[66] Every episode is recorded into the system, ranging from minor conditions such as appendicitis to major surgical procedures such as liver transplantation.[66] HES collects not only diagnosis codes, including those related to the underlying disease and those related to co-morbidity, but also codes that relate to the diagnostic and therapeutic procedures a patient undergoes during the episode.[66] Consequently, each HES record contains up to 20 diagnoses using codes based on the tenth revision of the International Classification of Disease (ICD-10) and up to 24

procedures sing codes from the Office of Population, Census and Surveys Classification of Surgical Operations and Procedures (OPCS-4).[64] During an admission most patients only have one episode, but some patient may have a series of consecutive episodes, also know as a spell, during one admission depending on the complexity of their conditions.[64-66]

Historically, administrative hospital data has been underused as a tool for research for a number of reasons.[66] Firstly, the data are primarily collected for administrative purposes, including the management of reimbursement, and as a result essential clinical detail may be lacking.[66] Secondly, coding systems for diagnoses and procedures may be ambiguous, may lack specificity, and may not be fully up to date.[66] Thirdly, data are being entered by non-clinical conding staff.[66] Fourthly, the data may be incomplete, especially with respect to the patients' conditions.[66] Finally, access to administrative data is only possible if a number of required permissions are in place.[66]

However, the introduction in 2004 of "Payment by Results" – a funding system by which hospitals get reimbursed according to the complexity of the health needs of each individual patient – improvements in quality, accuracy and validity have led to the a wider use of HES as a data source for research.[66] In fact, since this time, the HES database has been shown in numerous peer-reviewed studies to be useful in conducting research in many fields.[64] The patient identifiers held in HES also make it possible to link – at patient level – to more than one database.[66] Linked national datasets enhance the wider utility of administrative and routinely collected data as a research source and beyond this thesis there are many examples of linkage between administrative health dataset and national clinical registries.

In the context of this research, almost all patients who receive a liver transplant are NHS patients and their medical information, including all diagnoses and co-morbidities, are recorded on HES thus making the HES database as valuable resource for the studies in liver transplantation. For example, in this thesis HES records were used to derive information on patient characteristics (ethnicity, socio-economic deprivation), pre-existing liver disease, co-morbid conditions, relevant procedures, treatments and length of hospital stay.

2.3 Data Linkage and flow

Data linkage was performed by the Data Access Request Service (DARS) at NHS Digital.[67] The linkage involved matching patient records using the following patient identifiers: NHS number (the unique patient identifier used in the NHS), gender, date of birth, and postcode.[67] A hierarchical deterministic linkage approach was used, favouring record pairs with a higher likelihood of links being correct.[66-67] If there is a link, each record will include a 'match rank' detailing which linkage variables were matching.[66-67]

To minimise the transfer of large datasets only the required patient identifiers from NHSBT were sent to NHS Digital (see Data flow diagram, appendix 1). NHS Digital then linked and pseudoanonymised the data and sent LSHTM files containing HES-IDs that represent the linked records.[67] Accompanying the linked data files from NHS Digital were data items from the 5 separate HES datasets (Office National Statistics mortality data, inpatient, outpatient and, critical care and Accident & Emergency).[76] The non-identifiable HES extract

contained the linked HES records of patients who underwent liver transplantation. All data transfers involving NHS Digital were conducted using 'Secure File Transfer Accounts' (SEFT) and were co-ordinated by their Data Access and Request (DARS) service.[67] NHSBT the sent their non-identifiable dataset separately via secure transfer to the Clinical Effectiveness Unit at The Royal College of Surgeons of England (RCS-CEU).[63,67] At the RCS-CEU, the pseudoanonymised linked files from NHS Digital were merged with the datasets from NHSBT. The CEU is a collaborative research until between the London School of Hygiene & Tropical Medicine (LSHTM) and the RCS.

Throughout the PhD the data were received, managed, and stored at the RCS-CEU. The data were stored on restricted access folder on a secure server. Only the minimum data that was required to carry out the analyses was requested from NHSBT and NHS Digital (see NHS Digital data sharing agreement, appendix 2).

2.4 Study Design

The study population for each chapter was selected from adults only who were aged 17 years or above and who had undergone a first-time elective liver transplant in the UK and Ireland. When using linked transplant HES-records only those patients who received a transplant in England were included. The thesis did include patients who received a transplant from 1995 up until 31st March 2016. However, the study period described in the chapters varies according to the specific research question. In chapters three and four, the study population that was selected was dichotomised into a cohort of patients who received a liver transplant for HCC and into a cohort of patients who had a liver transplant for other indications. In the studies described in these chapters, post-transplant mortality and graft failure were compared between these cohorts. In chapter three, comparisons were made across different periods of calender time referred to as 'eras of transplantation' and in chapter 4 outcomes were compared over different periods of follow-up time ('epochs).

In the fifth chapter of the thesis, the study population was also dichotomised into two cohorts but in this chapter first-time liver transplant recipients were grouped according to whether patients had received a DCD or DBD donor liver. In this study there were two main analyses. In the first, era-specific comparisons of mortality and graft failure were identified separately for each of the DBD and DCD cohort. In the second, the mortality and graft failure were compared but this time between the cohorts. Also, the statistical models used in each of these analyses were specifically designed to identify whether the post-transplant outcomes of those who had received a DBD or DCD liver differed according to whether they had received their transplant for HCC or a non-HCC indication.

In chapters six and seven, the study population was stratified according to different levels of PS. In chapter six, post-transplant mortality was the main outcome measure and was again assessed in different epochs. In chapter seven, the main outcome measures were post-operative complications and hospital length of stay. To identify length of stay in hospital, linked HES records were required leading to only a slight refinement of the study population as linkage rates of the transplant-HES records were in excess of 85%.

In chapter eight, only patients who had received a first-time liver transplant for HCC were included. In this analysis, the impact of TACE on post-transplant mortality and graft failure were compared between those patients with HCC who had received TACE on the waiting list and those who had not. In this analysis, linked HES records were used to identify information on those recepients with HCC who had received TACE and also to identify the co-morbidity of these patients.

2.5 Statistical methodology

In every analysis in this thesis, outcomes following transplantation, including patient mortality and graft failure, were analysed in distinct time-periods ('epochs').[31-32] This methodological approach does not assume that the proportional hazards (PH) assumption has been met and in doing so does not assume that the effect of a potential risk factor on mortality (or graft failure) is constant over the pre-defined post-transplant time period.[32-33,68] Instead, by individually testing the prognostic impact of different risk factors in different epochs and searching for clinically plausible explanations for the subsequent findings, the relative time-dependent impact of risk factors on post-transplant outcomes can be quantified.[32-33,68]

In this this thesis, I use pre-defined epochs – in most instances up to 90 days, between 90 days and 2 years, and between 2 and 5 years – to investigate the time-dependency of the impact of HCC on patient mortality and graft survival. Patient survival up to 90 days was chosen as it was considered to reflect the occurrence of surgical complications, primary non-function and acute rejection, survival between 90 days and 2 years and between 2 and 5 years as it was considered to reflect tumour recurrence and chronic rejection[23,66] The advantage of this approach is that the hazard ratios (HRs) can be estimated using standard Cox regression methods and, more importantly, that the results are relatively easy to interpret. Its disadvantage is that that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration is arbitrary.

I used multivariable regression to adjust for confounding. In all but one of the analysis Cox regression methods were used to assess post-transplant mortality and graft failure. In chapter seven, linear and logistic regression methods were used to describe the relationship between PS and length of hospital stay and post-operative complication, respectively. Consistently, outcomes were analysed in a stepwise manner first without any adjustment, then with adjustment for recipient characteristics only and then with adjustment for both donor and recipient characteristics. Adjusting for case-mix characteristics in this way allowed me to investigate separately the impact that recipient characteristics and donor characteristics have on in post-transplant outcomes.

I did use interaction terms in many of the Cox models and this allowed me to identify whether the impact of one risk factors on the outcome differed according to the level of another and in particular whether the outcome differed according to whether the patient had received a transplant for an HCC or a non-HCC indication. Importantly, interaction terms were also used to determine whether the effect of a specified risk factor (i.e. HCC, DCD, PS etc) differed according to the epoch of follow-up time.

In most of my analyses, I defined graft failure as a composite of retransplantation or patient death. However, in certain circumstances these two factors could be considered competing events and in this instance a competing risk analysis needs to be considered.[69] A competing risk is an event that precludes the occurrence of the primary event of interest.[69] An example of this in chapter five where I investigate era-specific retransplantation rates, defining patient death as a competing risk and employing Fine and Gray regression methods to estimate adjusted subdistribution hazard ratios to investigate the differences in retransplantation rates between era with adjustment for recipient and then donor characteristics.[69]

To prevent the loss of patients due to missing data values multiple imputation techniques were employed.[70-71] This allowed me to increase the power of the analyses included in the thesis and reduced the risk of systematic bias that might have been introduced if the patients who were excluded due to missing data were systematically different from those who remained.[70] For all analyses, imputation of missing donor and recipient characteristics was carried out using chained equations that created ten complete datasets.[70-71] The Cox regression results for each of these datasets were then pooled using Rubin's rules.[70-71] In the imputation procedure, all of the donor and recipient variables used in the case-mix adjustment were used to predict missing values, including the outcome variables[71] It must be acknowledged however that the SNLTR is a very complete dataset and that only variables 'organ apperance' and 'steatosis' had consistently more than 10% of missing data.

2.6 Ethics

Ethics approval from the Health Research Authority (HRA) Research Ethics Committee (REC) and the Confidentiality Advisory Group (CAG) was sought for this PhD (see appendix 3). Approvals were required from both organisations as the project involved linking datasets and also, in the case of mortality data in HES, the data request included at the time of application sensitive data items – date and cause of death – that could be potentially used to identify an individual.

Ethics approval by the HRA Proportionate Review Sub-committee of Brighton & Sussex REC was granted on the 10th February 2017 (Reference: 17/LO/0231). CAG approval was granted on 20th March 2017 (reference: 17/CAG/0025). Ethics approval was also sought from the London School of Hygiene & Tropical Medicine (Reference: 12043) and obtained on 8th February 2017 (see appendix 3).

2.7 Patient and Public Involvement

A fundamental component of this PhD was the evaluation of health services and outcomes in patients with undergoing liver transplantation for HCC. The project aimed to drive the improvement in outcomes by disseminating its results into the public domain. To achieve these goals, I formed active collaborations with patients and members of the public to help in the design and dissemination of this thesis. To incorporate relevant patient involvement into the project design a patient HCC advisory group formed of two members of the patient support group, LISTEN was created. The advisory group were involved from the very conception of

the project – including the National Institute of Health Research (NIHR) funding application – right up until its completion and were most important in determing which clinical questions were most important from the patient perspective. Meetings took place at a neutral venue on a 3-monthly basis.

3. Results Chapter

Research Paper 1

Title: Short- and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the UK

The results of this chapter have been presented in the form of a published paper. The supplementary information referred to in the paper is available at the end of the manuscript.

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Student ID Number	1605002	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Wallace		
Thesis Title	Liver transplantation as a treatment for patients with hepatocellular carcinoma: a study using electronic health care data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Journal of Surgery		
When was the work published?	3rd March 2020		
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SECTION E

Student Signature	[redacted]
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Original article

Short- and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the UK

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Background: The increasing demand for liver transplantation has led to considerable changes in characteristics of donors and recipients. This study evaluated the short- and long-term mortality of recipients with and without hepatocellular carcinoma (HCC) in the UK between 1997 and 2016.

Methods: First-time elective adult liver transplant recipients in the UK were identified and four successive eras of transplantation were compared. Hazard ratios (HRs) comparing the impact of era on short-term (first 90 days) and longer-term (from 90 days to 5 years) mortality were estimated, with adjustment for recipient and donor characteristics.

Results: Some 1879 recipients with and 7661 without HCC were included. There was an increase in use of organs donated after circulatory death (DCD), from 0 per cent in era 1 to 35·2 per cent in era 4 for recipients with HCC, and from 0·2 to 24·1 per cent for non-HCC recipients. The 3-year mortality rate decreased from 28·3 per cent in era 1 to 16·9 per cent in era 4 (adjusted HR 0·47, 95 per cent c.i. 0·35 to 0·63) for recipients with HCC, and from 20·4 to 9·3 per cent (adjusted HR 0·44, 0·36 to 0·53) for those without HCC. Comparing era 4 with era 1, improvements were more marked in short-term than in long-term mortality, both for recipients with HCC (0–90 days: adjusted HR 0·20, 0·10 to 0·39; 90 days to 5 years: adjusted HR 0·52, 0·35 to 0·75; $P = 0·043$) and for non-HCC recipients (0–90 days: adjusted HR 0·32, 0·24 to 0·42; 90 days to 5 years: adjusted HR 0·52, 0·40 to 0·67; $P = 0·024$).

Conclusion: In the past 20 years, the mortality rate after liver transplantation has more than halved, despite increasing use of DCD donors. Improvements in overall survival can be explained by decreases in short-term and longer-term mortality.

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Introduction

The rise in incidence of hepatocellular carcinoma (HCC), and the introduction of selection criteria that identify patients with HCC who are likely to achieve acceptable results with liver transplantation, have led to a marked increase in the number of patients with HCC who receive a liver transplant[1–5]. This has put pressure on transplantation services in many countries because it is felt to be more difficult to cope with transplanting both patients with HCC and those without HCC in an acceptable time frame[1]. The chronic shortage of donor organs has led to an increase in the use of donors whose organs have a greater risk of initial poor function or failure, including organs donated after circulatory death (DCD)[6].

It is currently unknown to what extent the increase in the number of liver transplants for HCC and the related increased use of suboptimal donors have affected post-transplantation outcomes. A study[6] carried out in the UK, including patients transplanted between 2005 and 2010, has suggested that recipients of a DCD liver have poorer post-transplantation outcomes. However, for some patients on the waiting list, especially those with HCC, transplantation with a DCD liver may still offer the best chance of curative treatment[1]. This is particularly relevant for organ allocation policies – like those used in the UK

until recently – that do not use tumour characteristics to prioritize patients on the waiting list[7,8], or for countries with a high waiting list mortality[9,10].

It has been shown previously that patients who receive a liver transplant as treatment for HCC are on average in better physical condition with fewer signs of end-stage liver disease than patients who receive a liver transplantation for other reasons. This in turn may have a positive effect on short-term post-transplant outcomes[11]. However, survival of recipients with HCC in the longer term is affected negatively by recurrence of cancer[11]. Therefore, a national population-based cohort study that explored time trends in short-term and longer-term post-transplant mortality was carried out, separately for recipients with and those without HCC.

Methods

Standard National Liver Transplant Registry

Since 1984, the Standard National Liver Transplant Registry has assembled detailed information about all liver transplants performed in the seven liver transplant centres in the UK[12]. Regular checks indicate that the data are consistently more than 93 per cent complete and accurate, and several studies[13–15] have confirmed the validity of the data set.

Study population

All patients aged 17 years or older who received a first-time elective liver transplant between 1 January 1997 and 31 December 2016 were eligible for inclusion. Recipients were categorized into two groups: transplanted patients with HCC recorded in any of three diagnosis fields available in the Standard National Liver Transplant Registry (HCC group) and transplanted patients with other liver disease diagnoses (non-HCC group). To limit heterogeneity of the study cohort, patients who had transplantation for types of liver cancer other than HCC and those who underwent multivisceral, superurgent domino or living-related liver transplantations were excluded (*Fig. S1*, supporting information), as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). Patients whose survival data were missing were also excluded. Information on explant pathology was not available[12].

Patients were grouped according to date of transplantation into one of four successive 5-year transplantation periods: era 1, 1 January 1997 to 31 December 2001; era 2, 1 January 2002 to 31 December 2006; era 3, 1 January 2007 to 31 December 2011; and era 4, 1 January 2012 to 31 December 2016. Recipients' functional status at the time of transplantation was assessed using a five-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'[15]. The UK Model for End-stage Liver Disease score, derived from the international normalized ratio, and serum creatinine, serum bilirubin and serum sodium levels, was used to score the recipients' severity of liver disease[8]. Ethnicity was dichotomized into white and non-white groups. Changes over time in overall donor quality were measured using the UK Donor Liver Index (DLI), derived from donor age, sex, height, type (DCD donor or not), serum bilirubin concentration, smoking history, and whether the liver was split; larger values represented poorer donor livers[16].

UK allocation policy, 1997–2016

During the study interval, the allocation of DCD livers and livers donated after brainstem death (DBD) was organized locally and centres selected recipients according to local criteria[7,8]. Patients on local waiting lists were prioritized according to waiting list mortality predicted on the basis of a scoring system capturing the severity of liver disease. The scoring system did not award additional points to patients with HCC on the waiting list[7,8].

Statistical analysis

Categorical variables are presented as proportions and were compared using χ^2 tests; continuous variables are presented as mean(s.d.) and were analysed using *t* tests. Patients transplanted for non-HCC indications who were subsequently found to have HCC, according to explant pathology, were analysed on an intention-to-treat basis and remained in the non-HCC group.

Kaplan–Meier methods were used to compare patient and graft survival between successive eras of transplantation. Follow-up was censored at 5 years after transplantation or on the last follow-up visit before 31 December 2016, whichever occurred earlier. Graft failure was defined by either retransplantation or patient death. To account for limited follow-up in era 4, post-transplantation outcomes for all eras are presented up to 3 years after transplantation.

Multivariable Cox regression models were used to estimate hazard ratios (HRs) representing relative differences in the primary outcome measures post-transplant mortality and graft failure between eras of transplantation. Era 1 (1997–2001) was chosen as the reference group. To determine whether changes in donor and recipient characteristics influenced the impact of era of transplantation on post-transplant survival, HRs were

initially estimated without adjustment for recipient or donor characteristics, then with adjustment for recipient characteristics only, and finally with adjustments for both recipient and donor characteristics. All characteristics included in the risk adjustment were based on clinical plausibility of being a potentially confounding factor for post-transplantation mortality or graft failure.

Interaction terms were included in the Cox regression models to determine whether the prognostic impact of era varied according to HCC status, hepatitis C virus (HCV) status in the HCC group only, and time interval after transplantation. Two post-transplant intervals were used: the first 90 days after transplantation, reflecting the occurrence of surgical complications, acute rejection and primary non-function[17], and from 90 days to 5 years, reflecting longer-term outcomes, including recurrence of primary liver disease[17,18]. The significance of interaction terms was tested using the Wald test.

Missing donor and recipient characteristics were imputed using chained equations creating ten complete data sets[19]. In the imputation procedure, the donor and recipient variables used in the case-mix adjustment were used to predict missing values, including those for outcome variables[20]. The Cox regression results for each of these data sets were pooled using Rubin's rules[19]. $P < 0{\cdot}050$ was considered statistically significant. Stata® version 15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

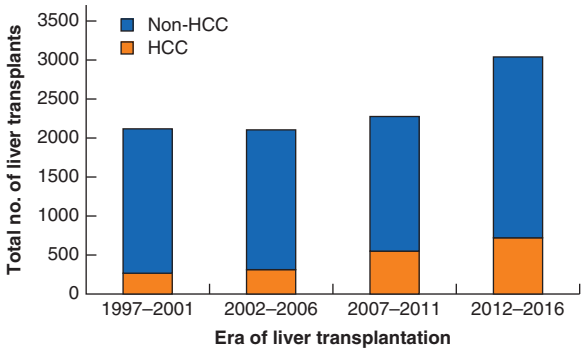
Results

Time trends in post-transplant mortality

Between 1 January 1997 and 31 December 2016, 9540 first-time single-organ elective adult liver transplants were performed. Over this interval, the number of adult recipients with HCC almost tripled, from 275 of a total of 2117 liver transplantations (13·0 per cent) in era 1 (1997–2001) to 727 of 3042 (23·9 per cent) in era 4 (2012–2016). The increase in total number of liver transplants for the first three eras of transplantation was fully explained by the increase in the number of liver transplants in patients with HCC (*Fig. 1*). In contrast, the proportion of all patients with HCC in England who received a liver transplant remained stable, despite substantial increases in the number of patients diagnosed with HCC from 4029 in era 1 to 12 142 in era 4 (*Fig. S2*, supporting information).

The use of DCD livers greatly increased during the study period from 0 among 275 recipients with HCC and four among 1842 recipients without HCC (0·2 per cent) in era 1 to 256 of 727 (35·2 per cent) and 557 of 2315 (24·1 per cent) respectively in era 4 (*Table 1*). Over the entire study interval, recipients with HCC were slightly more likely to receive donor livers that were considered steatotic or abnormal in appearance (*Table 1*). These findings are in line with the trend in the DLI, which showed that liver donor quality deteriorated over time in both cohorts, but that the deterioration was most marked in the HCC group (*Table 1*).

Fig. 1 Time trends in the number of liver transplants in patients with or without hepatocellular carcinoma performed in the UK, stratified by era of transplantation



The analysis included a total of 9540 transplants. HCC, hepatocellular carcinoma.

The number of recipients with HCC who had HCV antibodies decreased over time (from 49·5 per cent in era 1 to 41·8 per cent in era 4) and there was a corresponding decrease for those without HCC (from 19·4 to 10·5 per cent respectively) (*Table 1*). The mean(s.d.) time on the transplant waiting list increased from 105(112) days in era 1 to 146(150) days in era 4 among recipients with HCC, and from 145(160) to 165(221) days respectively for recipients without HCC.

Era-specific changes in post-transplantation outcomes

Kaplan–Meier survival analysis

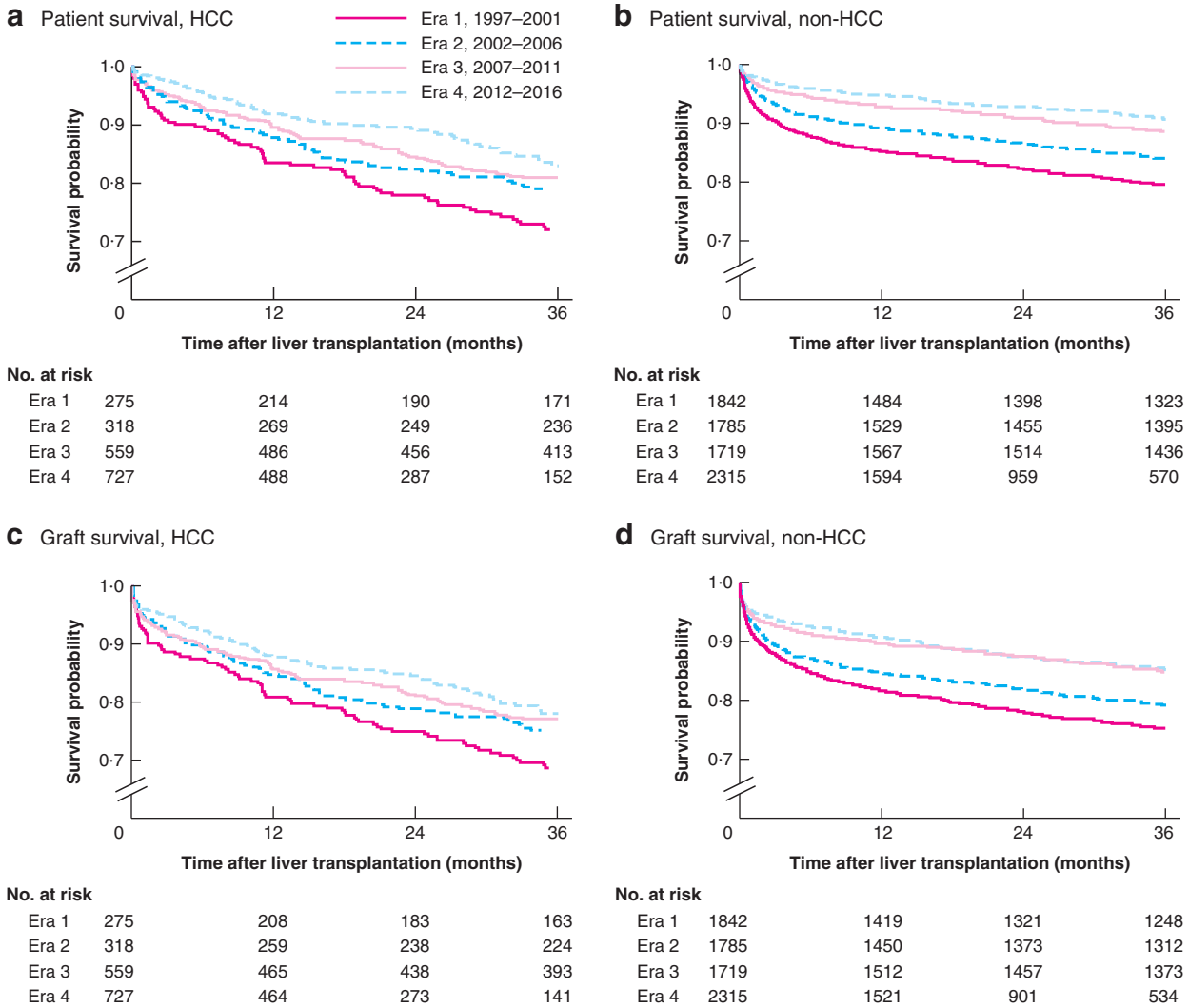
Across the four eras of transplantation, successive improvements in post-transplantation patient and graft survival were identified in both HCC and non-HCC recipients (*Fig. 2*). In recipients with HCC, the 3-year mortality rate decreased from 28·3 (95 per cent c.i. 23·2 to 34·3) per cent in era 1 to 21·3 (17·1 to 26·3) per cent in era 2, 19·0 (16·0 to 22·6) per cent in era 3 and 16·9 (13·5 to 21·1) per cent in era 4 (*Fig. 2a*). In recipients without HCC, mortality decreased from 20·4 (18·6 to 22·4) per cent in era 1, to 15·8 (14·2 to 17·6), 11·3 (9·9 to 12·9) and 9·3 (7·9 to 10·9) per cent in eras 2, 3 and 4 respectively (*Fig. 2b*). Similarly, the 3-year graft failure rate decreased from 31·7 (26·4 to 37·7) per cent in era 1 to 22·0 (18·3 to 26·3) per cent in era 4 (*Fig. 3c*) among recipients with HCC, and from 24·7

Table 1 Donor and recipient characteristics according to era of transplantation

		Era of transplantation				
	Recipient group	Era 1 1997–2001	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	Missing values
No. of transplants	HCC	275	318	559	727	
	Non-HCC	1842	1785	1719	2315	
Donor characteristics						
Women	HCC	46 (16·7)	59 (18·6)	106 (19·0)	138 (19·0)	0 (0)
	Non-HCC	742 (40·3)	725 (40·6)	664 (38·6)	831 (35·9)	0 (0)
Age (years)*	HCC	46·8(14·1)	46·4(15·5)	48·0(15·6)	50·6(15·9)	0 (0)
	Non-HCC	43·0(14·9)	45·2(14·9)	46·6(15·7)	50·1(16·3)	0 (0)
BMI (kg/m^2)*	HCC	25·4(3·8)	25·6(4·3)	26·6(4·9)	26·5(5·1)	40 (2·1)
	Non-HCC	24·8(4·3)	25·6(4·6)	26·0(4·9)	26·4(4·8)	290 (3·8)
Trauma as cause of death	HCC	62 (22·6)	43 (13·5)	63 (11·3)	65 (8·9)	0 (0)
	Non-HCC	398 (21·6)	274 (15·4)	192 (11·2)	139 (6·0)	0 (0)
DCD donor	HCC	0 (0)	16 (5·0)	142 (25·4)	256 (35·2)	0 (0)
	Non-HCC	4 (0·2)	79 (4·4)	272 (15·8)	557 (24·1)	0 (0)
Hepatic steatosis	HCC	54 (47·0)	128 (41·7)	264 (47·6)	335 (46·9)	187 (10·0)
	Non-HCC	237 (36·6)	697 (40·3)	752 (44·5)	1019 (44·8)	1320 (17·2)
Presence of capsular damage	HCC	19 (17·3)	31 (10·2)	67 (12·1)	113 (15·9)	197 (10·5)
	Non-HCC	88 (13·8)	229 (13·5)	250 (14·8)	298 (13·1)	1362 (17·8)
Abnormal donor liver appearance	HCC	59 (21·5)	64 (22·1)	136 (30·9)	164 (26·4)	254 (13·5)
	Non-HCC	307 (16·7)	384 (23·0)	348 (25·1)	445 (22·2)	761 (9·9)
Segmental graft type	HCC	9 (3·3)	18 (5·7)	46 (8·2)	33 (4·5)	0 (0)
	Non-HCC	78 (4·2)	141 (7·9)	167 (9·7)	197 (8·5)	0 (0)
Cold ischaemia time (min)*	HCC	666(175)	599(164)	521(163)	491(156)	138 (7·3)
	Non-HCC	6845(188)	615(169)	533(154)	510(159)	402 (5·2)
Donor Liver Index*†	HCC	1·13(0·23)	1·13(0·23)	1·31(0·41)	1·46(0·49)	278 (14·8)
	Non-HCC	1·14(0·32)	1·16(0·28)	1·24(0·37)	1·38(0·45)	1539 (20·1)
Recipient characteristics						
Female	HCC	46 (17·0)	59 (18·6)	106 (19·0)	138 (19·1)	8 (0·4)
	Non-HCC	742 (41·9)	725 (40·3)	664 (38·8)	36·2 (831)	103 (1·3)
Age (years)*	HCC	54·4(8·7)	56·1(8·6)	56·9(7·7)	58·8(7·8)	0 (0)
	Non-HCC	50·3(10·9)	51·1(11·0)	51·0(11·6)	51·4(12·0)	0 (0)
Non-white ethnicity	HCC	60 (21·8)	75 (23·6)	98 (17·6)	15·7 (114)	1 (0·1)
	Non-HCC	251 (13·6)	242 (13·6)	214 (12·5)	10·1 (234)	1 (< 0·1)
BMI (kg/m^2)*	HCC	26·7(3·6)	27·1(4·6)	26·6(5·0)	28·2(4·9)	44 (2·3)
	Non-HCC	25·4(4·9)	26·3(4·9)	27·6(4·6)	27·4(5·4)	313 (4·1)
UKELD score*	HCC	52·1(5·5)	51·5(4·7)	51·0(4·9)	51·0(4·9)	44 (2·3)
	Non-HCC	56·0(5·8)	55·8(5·6)	56·0(5·7)	55·8(5·3)	215 (2·8)
Functional status: self-care‡	HCC	134 (49·1)	175 (55·2)	217 (39·5)	271 (37·7)	20 (1·1)
	Non-HCC	1081 (58·9)	1116 (62·8)	834 (49·0)	1087 (47·6)	61 (0·8)
Ascites	HCC	103 (37·5)	98 (30·9)	159 (28·4)	218 (30·0)	2 (0·1)
	Non-HCC	1132 (61·8)	993 (55·7)	1021 (59·5)	1439 (62·5)	30 (0·4)
Previous variceal bleed	HCC	57 (20·7)	71 (22·3)	101 (18·2)	100 (13·9)	11 (0·6)
	Non-HCC	662 (35·9)	590 (33·2)	511 (29·7)	608 (26·7)	64 (0·8)
Encephalopathy	HCC	27 (9·8)	25 (7·9)	71 (12·8)	113 (15·9)	24 (1·3)
	Non-HCC	406 (22·0)	392 (22·0)	562 (32·9)	834 (36·7)	64 (0·8)
Presence of HCV antibodies	HCC	136 (49·5)	129 (43·6)	235 (45·5)	291 (41·8)	106 (5·6)
	Non-HCC	357 (19·4)	262 (16·9)	243 (15·3)	233 (10·5)	545 (7·1)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Includes the following donor factors: donated after circulatory death (DCD), segmental graft, height, age, smoking status and bilirubin level. ‡Third level of five-point scale assessing patient's functional status before transplantation. HCC, hepatocellular carcinoma; UKELD, UK Model for End-stage Liver Disease.

Fig. 2 Post-transplant patient and graft survival according to era of transplantation



a,**b** Patient and **c**,**d** graft survival among 1879 patients with hepatocellular carcinoma (HCC) (**a**,**c**) and 7661 without (**b**,**d**). **a**–**d** $P < 0{\cdot}001$ (log rank test).

(22·7 to 26·8) to 15·0 (13·3 to 16·9) per cent respectively in the non-HCC group (*Fig. 3d*).

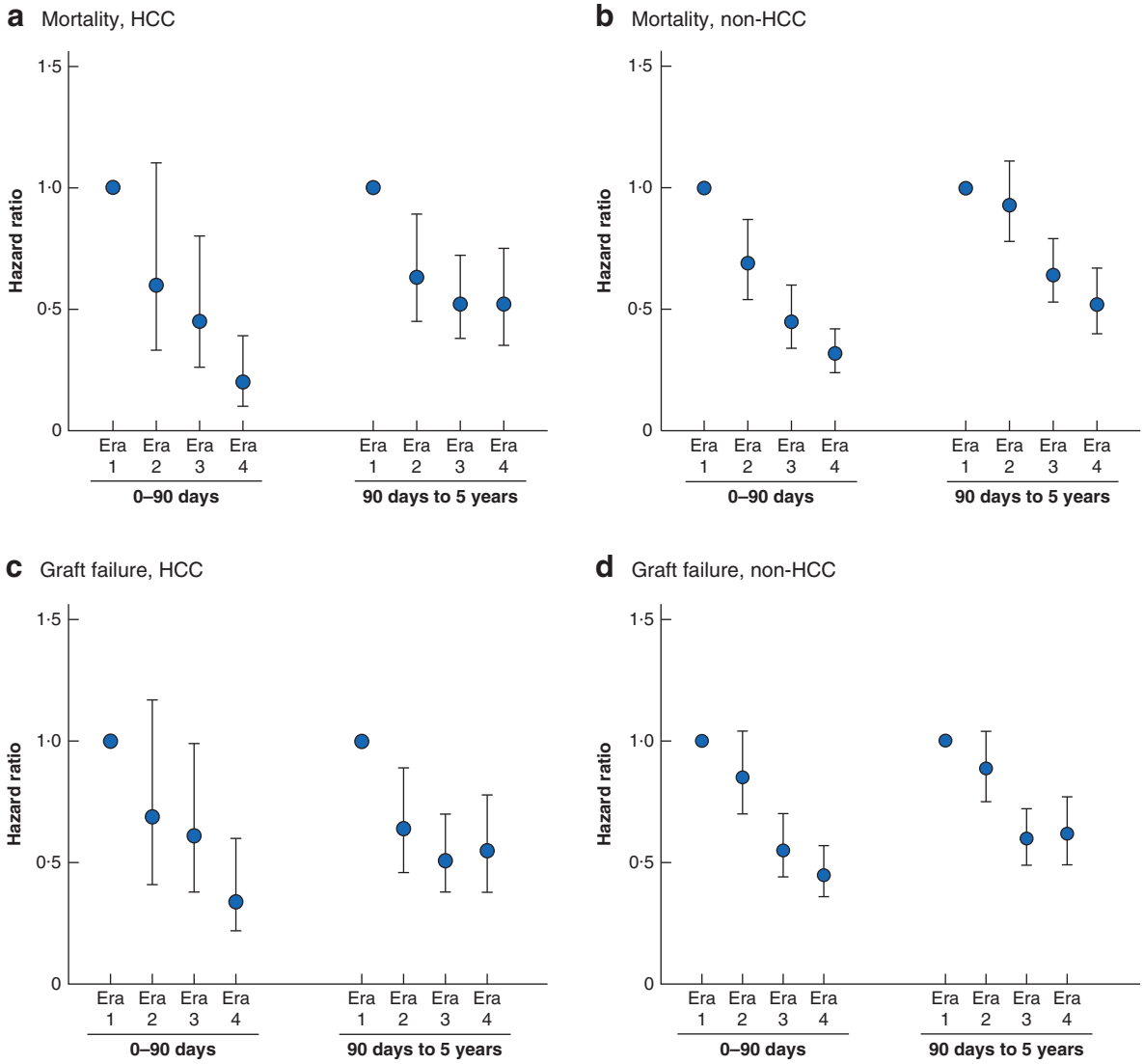
The mortality rate in the first 90 days after transplantation decreased from 9·1 (6·3 to 13·2) per cent in era 1 to 2·2 (1·4 to 3·6) per cent in era 4 for recipients with HCC, and from to 9·6 (8·3 to 11·1) to 3·1 (2·5 to 3·9) per cent respectively for recipients without HCC.

Cox regression analysis

Comparing era 4 with era 1, post-transplant mortality in the first 5 years after transplantation decreased by 50 per cent for patients with HCC (unadjusted HR 0·50, 95 per cent c.i. 0·46 to 0·55) (*Table 2*) and graft failure decreased by 42 per cent (unadjusted HR 0·58, 0·45 to 0·76) (*Table 3*). Among patients without HCC, mortality decreased by 56 per cent (unadjusted HR 0·44, 0·37 to 0·53) (*Table 2*) and graft failure decreased by 41 per cent (unadjusted HR 0·59, 0·51 to 0·68) (*Table 3*). Adjustment for recipient characteristics, and for both recipient and donor characteristics combined had only a small impact on the time trends observed in post-transplant mortality or graft failure in both HCC and non-HCC groups (*Tables 2* and *3*).

The effect of era on mortality and graft failure did not vary according to HCC status (P for interaction = 0·268

Fig. 3 Impact of era of transplantation on post-transplantation outcomes from 0 to 90 days and from 90 days to 5 years in patients with or without hepatocellular carcinoma



Hazard ratios, with 95 per cent confidence intervals, for **a**,**b** mortality and **c**,**d** graft failure among 1879 patients with hepatocellular carcinoma (HCC) (**a**,**c**) and 7661 without (**b**,**d**). Era 1 is the reference group. The analysis was adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, United Kingdom Model for End-Stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery) and donor characteristics (sex, age, BMI, cause of death, donor type (donation after cardiac death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time).

and $P = 0{\cdot}373$ respectively), or according to whether recipients with HCC had a concomitant diagnosis of HCV (P for interaction = 0·124) (*Table S1*, supporting information).

Analyses adjusted for both recipient and donor characteristics showed that mortality in the first 90 days after transplantation decreased by 80 per cent between era 1 and era 4 for HCC recipients (adjusted HR 0·20, 0·10 to 0·39) and by 68 per cent for recipients without HCC (adjusted HR 0·32, 0·24 to 0·42) (*Fig. 3a*,*b*; *Table S2*, supporting information). In the subsequent follow-up period, from 90 days to 5 years, decreases in mortality between eras 1 and 4 were not as substantial, being 48 per cent for both HCC (adjusted HR 0·52, 0·35 to 0·75) and non-HCC (adjusted HR 0·52, 0·40 to 0·67) groups respectively. In both recipients with

Table 2 Cox regression analysis of risk of post-transplant mortality among 1879 recipients with and 7661 without hepatocellular carcinoma in the first 5 years after liver transplantation according to era of transplantation

	Hazard ratio (*versus* era 1, 1997–2001)			
	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	*P* for effect of era
Recipients with HCC				
Unadjusted	0·67 (0·61, 0·73)	0·58 (0·54, 0·63)	0·50 (0·46, 0·55)	< 0·001
Adjusted for recipient characteristics only*	0·65 (0·48, 0·87)	0·56 (0·43, 0·73)	0·47 (0·35, 0·63)	< 0·001
Adjusted for recipient and donor characteristics†	0·65 (0·49, 0·87)	0·54 (0·42, 0·70)	0·44 (0·33, 0·60)	< 0·001
Recipients without HCC				
Unadjusted	0·85 (0·74, 0·97)	0·60 (0·51, 0·69)	0·44 (0·37, 0·53)	< 0·001
Adjusted for recipient characteristics only*	0·86 (0·74, 0·98)	0·59 (0·50, 0·69)	0·44 (0·36, 0·53)	< 0·001
Adjusted for recipient and donor characteristics†	0·83 (0·72, 0·96)	0·56 (0·47, 0·66)	0·41 (0·34, 0·50)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, UK Model for End-stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery). †Adjusted for recipient characteristics listed above and donor characteristics (sex, age, BMI, cause of death, donor type (donated after circulatory death or donated after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time). HCC, hepatocellular carcinoma.

Table 3 Cox regression analysis of risk of graft failure among 1879 recipients with and 7661 without hepatocellular carcinoma in the first 5 years after liver transplantation according to era of transplantation

	Hazard ratio (*versus* era 1, 1997–2001)			
	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	
Recipients with HCC				
Unadjusted	0·70 (0·53, 0·92)	0·63 (0·50, 0·81)	0·58 (0·45, 0·76)	< 0·001
Adjusted for recipient characteristics only*	0·69 (0·52, 0·91)	0·63 (0·49, 0·81)	0·57 (0·44, 0·74)	< 0·001
Adjusted for recipient and donor characteristics†	0·68 (0·52, 0·90)	0·56 (0·44, 0·73)	0·48 (0·37, 0·65)	< 0·001
Recipients without HCC				
Unadjusted	0·90 (0·79, 1·01)	0·63 (0·55, 0·72)	0·59 (0·51, 0·68)	< 0·001
Adjusted for recipient characteristics only*	0·91 (0·80, 1·03)	0·63 (0·55, 0·73)	0·60 (0·51, 0·70)	< 0·001
Adjusted for recipient and donor characteristics†	0·87 (0·76, 1·00)	0·57 (0·49, 0·67)	0·52 (0·44, 0·62)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, UK Model for End-stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery). †Adjusted for recipient characteristics listed above and donor characteristics (sex, age, BMI, cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time). HCC, hepatocellular carcinoma.

and those without HCC, the impact of era on mortality was different for the two follow-up periods (*P* for interaction = 0·043 and *P* = 0·024 respectively).

Similar differences were observed in improvements in graft survival in the first 90 days and from 90 days to 5 years (*Fig. 3c,d*; *Table S2*, supporting information), but the impact of era on graft survival did not differ between the two follow-up periods (*P* = 0·136 and *P* = 0·191 for HCC and non-HCC groups respectively).

Era-specific changes in causes of death

The percentage of recipients with HCC who died from tumour recurrence within the first 5 years after transplantation remained stable during the first three eras of transplantation: era 1, 21·0 per cent (21 of 100); era 2, 22 per cent (19 of 88); and era 3, 18·5 per cent (25 of 135) (*Table S3*, supporting information). In era 4 (2012–2016), the percentage of recipients with HCC who died from tumour recurrence was slightly lower at 14 per cent (13 of 91). This decrease in era 4 is almost certainly explained by the fact that most patients in this cohort had been followed up for less than 5 years. Overall, 11 of the 78 recipients with HCC who died from tumour recurrence (14 per cent) had received a DCD liver, compared with 403 of the 1801 recipients with HCC (22·4 per cent) who died from causes other than tumour recurrence (*P* = 0·154). In recipients without HCC, sepsis was consistently the most common cause of death, with the rate increasing from 36·0 per cent (161 of 447) in era 1 to 39·5 per cent (70 of 177) in era 4.

Discussion

The number of first-time single-organ elective liver transplantations in adult recipients performed in the UK has increased continually over the past 20 years, and until recently this rise has been driven by increases in the transplantation of patients with HCC. In the same period, increases in the use of DCD and other suboptimal donor livers have been identified, particularly in patients with HCC. However, mortality in the first 5 years after transplantation has more than halved both for patients with HCC who need a liver transplant before disease progresses beyond transplantable criteria, and for those without HCC who need a liver transplant because of deteriorating liver function related to end-stage liver disease. There were decreases in mortality in the first 90 days after transplantation as well as between 90 days and 5 years.

A limitation of the study was that it compared recipients with HCC with a heterogeneous cohort of recipients without HCC. This approach may have masked specific post-transplant mortality patterns in the non-HCC group related to the primary liver disease. However, the dichotomy between recipients with and without HCC reflects the fundamental difference in why patients were selected for transplantation. A liver transplant is used to remove a malignancy with curative intent in patients with HCC, and as a treatment for liver failure in patients with end-stage liver disease[7,8].

A second limitation might be that the adjustment for recipient and donor characteristics may not have fully captured variations in how patients were selected for liver transplantation over the 20 years of the study. However, given that a wide range of characteristics were adjusted for, it is unlikely that changes in patient selection and organ allocation criteria over time are major explanations for the substantial improvements in post-transplant survival.

In addition, the time after transplantation was divided arbitrarily into two intervals, within the first 90 days and between 90 days and 5 years, to investigate whether there were differences in time trends for short- and long-term post-transplant mortality. A 90-day time interval is being used increasingly to capture short-term surgical outcomes. A study[21] exploring the timing of surgical outcomes after hepatopancreatobiliary surgery in 4000 patients supports the legitimacy of the use of this 90-day limit because it demonstrated that surgery-related deaths accounted for all early deaths and that about 85 per cent of all surgery-related deaths occurred in the first 90 days. In addition, 90-day mortality is commonly used as a short-term outcome after liver transplantation because, in addition to surgical mortality, it reflects the occurrence of acute rejection and primary non-function of the donor liver[22].

Studies from the USA[23] and Europe[24] have described changes over time in the characteristics and outcomes of patients receiving a liver transplant. Analyses of the United Network for Organ Sharing database in the USA, including transplantations carried out between 1994 and 2009[23], and the European Liver Transplant Registry between 1988 and 2009[24], demonstrated marked increases in the number of liver transplantations in patients with HCC. These studies also found that recipients with HCC had worse long-term patient survival than those without. However, no study could be identified that explicitly investigated differences in time trends of short- and longer-term post-transplant outcomes in recipients with and those without HCC, or one that quantified to what extent the increased use of DCD livers affected time trends in outcomes separately for HCC and non-HCC cohorts.

It is important to note that between 1997 and 2016 the incidence of HCC increased threefold but that the proportion of patients with HCC who received a potentially curative liver transplant remained static. As a result, the number of patients with HCC who received a liver transplant increased accordingly. Significant increases in the use of DCD livers reflect increases in the total number of liver transplantations, relative decreases in the overall donation of DBD livers[24], and – for recipients with HCC especially – the clinical requirement to provide liver transplantations in an acceptable time frame for those on the waiting list. However, post-transplantation mortality across the 20-year study interval more than halved for both recipients with and those without HCC.

The improvements in overall patient and graft survival are most likely explained by a combination of factors, which initially includes the introduction of the Milan criteria followed by better matching of donors and recipients, developments in immunosuppression and anaesthesia, decreases in cold ischaemia time, and, more recently, the introduction of directly acting antiviral medications for patients with HCV cirrhosis[13,23]. However, the present analysis was able to demonstrate more specifically than before that factors associated with early post-transplant outcomes, potentially including surgical technique and perioperative care, are likely to have had a substantial impact on improved overall survival.

Adjustment for differences in recipient characteristics only or for both recipients and donor characteristics had minimal effects on the observed time trends in post-transplantation outcomes of recipients with or without HCC. Instead, tumour recurrence was identified as the main factor responsible for the consistently poorer long-term survival among recipients with HCC[11,18]. Accordingly, improvements in the longer-term survival

of recipients with HCC are more likely to be influenced by changes in the selection of such patients for liver transplantation than by donor-related factors[11,18].

Over the study, the number of patients without HCC who had HCV cirrhosis receiving a liver transplant decreased, whereas the number of recipients transplanted for HCV-induced HCC increased. This is consistent with the wider accessibility to newer directly acting antiviral medications, leading to a cascade of events that includes further reductions in patients with HCV requiring a liver transplant and eventual reductions in the incidence of HCV-induced HCC[25,26].

Between 1997 and 2016, the number of patients receiving a liver transplant increased considerably. Most importantly, this study demonstrated that mortality in adult patients undergoing a first-time single-organ elective liver transplantation has more than halved in the past two decades, despite a marked increase in the use of suboptimal donor organs. Decreases in both short- and long-term mortality are responsible for improvements in overall survival, irrespective of whether recipients have HCC with relatively preserved liver function or a failure of liver function linked to end-stage liver disease.

The increasing use of DCD livers over a period with substantial improvement in post-transplant outcomes is a guiding example for countries with a high waiting list mortality and a low DCD utilization[10] as well as those in which a high proportion of liver transplant recipients have HCC[1,23,24]. In the context of the ongoing improvement in post-transplant outcomes, the risk of using DCD livers or livers from donors whose organs have a greater risk of failure must be balanced against the consequence of not using these potentially poorer livers leading to higher waiting list mortality and drop-outs owing to HCC progression.

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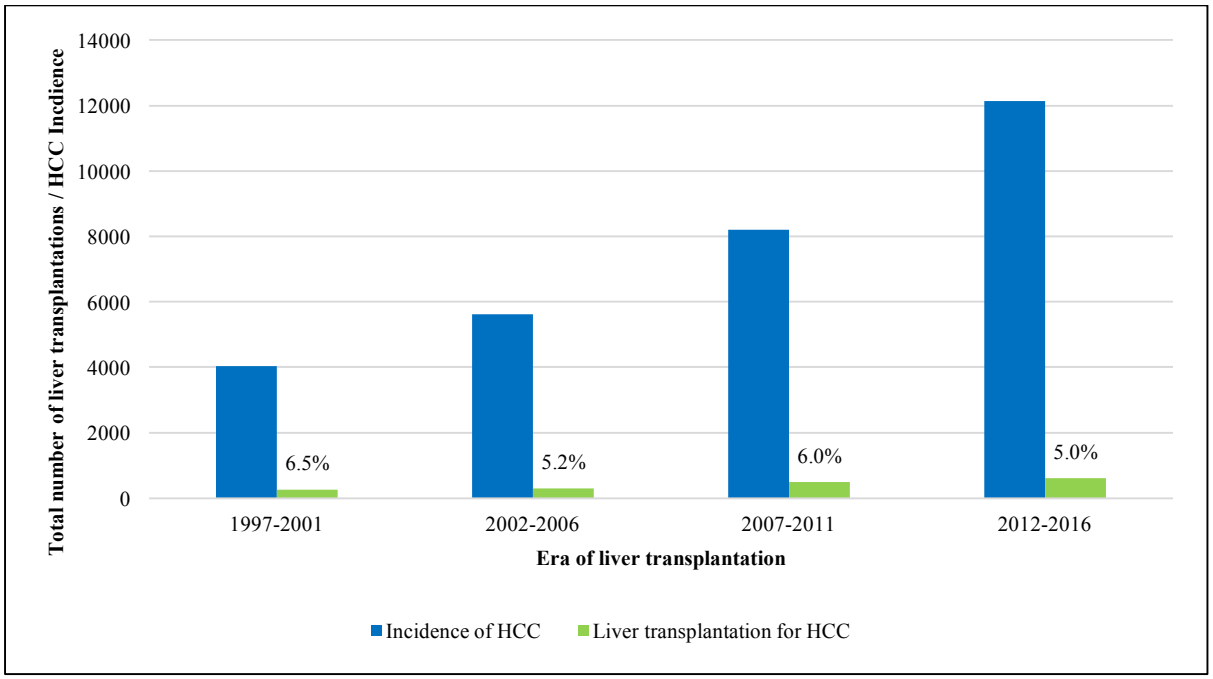
Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

SUPPLEMENTAL INFORMATION:

FIGURES

Figure S1: Proportions of patients with HCC who receive a liver transplantation in England, stratified by era of transplantation (n=1656).



**Incidence of HCC for England provided by data from the National Cancer Registration and Analysis service*
**Incidence of HCC Era 1: 4029, Era 2: 5623, Era 3: 8211, Era 4: 12142*

TABLES

Table S1: The effect of era on 5-year patient survival for patients with HCC, HCV and HCC&HCV combined (n=1 879).

	ERA 1: 1997-2001	ERA 2: 2002-2006	ERA 3: 2007-2011	ERA 4: 2012-2016	P-value for the effect of era
HCC (n=1 027)	**1** (n=139)	0·79 (0·54-1·17) (n=181)	0.53 (0.34-0.75) (n=305)	0.39 (0.25-0.62) (n=402)	<0.001
HCC&HCV (n=852)	**1** (n=136)	0·44 (0·27-0·70) (n=137)	0.50 (0.33-0.74) (n=254)	0.43 (0.27-0.67) (n=325)	<0.001

***Adjusted for recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery, waitlist time, and donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time.*

Table S2: The impact of era of transplantation on the post-transplantation outcomes in first 90 days and from 90 days to 5 years in HCC (n= 1 879) and non-HCC recipients (n= 7 661).

	TIME PERIOD AFTER TRANSPLANTATION	
Patient mortality	**First 90 days**	**From 90 days to 5-years**
HCC recipients		
Era 1:	1	1
Era 2:	0.60 (0.33 - 1.10)	0.63 (0.45 – 0.89)
Era 3:	0.45 (0.26 - 0.80)	0.52 (0.38 – 0.72)
Era 4:	0.20 (0.10 - 0.39)	0.52 (0.35 – 0.75)
Non-HCC recipients		
Era 1:	1	1
Era 2:	0.69 (0.54 – 0.87)	0.93 (0.78 – 1.11)
Era 3:	0.45 (0.34 – 0.60)	0.64 (0.53 – 0.79)
Era 4:	0.32 (0.24 – 0.42)	0.52 (0.40 – 0.67)
Graft failure		
HCC recipients		
Era 1:	1	1
Era 2:	0.69 (0.41 – 1.17)	0.64 (0.46 – 0.89)
Era 3:	0.61 (0.38 – 0.99)	0.51 (0.38 – 0.70)
Era 4:	0.34 (0.22 – 0.60)	0.55 (0.38 – 0.78)
Non-HCC recipients		
Era 1:	1	1
Era 2:	0.85 (0.70 – 1.04)	0.89 (0.75 – 1.04)
Era 3:	0.55 (0.44 – 0.70)	0.60 (0.49 – 0.72)
Era 4:	0.45 (0.36 – 0.57)	0.62 (0.49 – 0.77)

***Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery and donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after cardiac death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time.*

Table S3: Cause of death at 5-years following liver transplantation, stratified by era of transplantation (n=1 699).

Cause of Death	Era 1: 1997-2001		Era 2: 2002-2006		Era 3: 2007-2011		Era 4: 2012-2016	
	HCC (n=100)	Non-HCC (n=447)	HCC (n=88)	Non-HCC (n=388)	HCC (n=135)	Non-HCC (n=273)	HCC (n=91)	Non-HCC (n=177)
Recurrent primary disease - malignant*	21.0% (21)	2.2% (10)	22.0% (19)	1.3% (5)	18.5% (25)	2.6% (7)	14.3% (13)	0.6% (1)
Recurrent primary disease - benign**	5.0% (5)	3.8% (17)	1.1% (1)	1.6% (6)	2.2% (3)	3.3% (9)	0.0% (0)	0.0% (0)
Malignancy – other***	12.0% (12)	9.6% (43)	23.9% (21)	16.0% (62)	14.1% (19)	11.7% (32)	17.5% (16)	10.1% (18)
Sepsis	20.0% (20)	34.5% (154)	20.4% (18)	32.7% (127)	24.4% (33)	36.7% (100)	34.1% (31)	39.0% (69)
Graft Failure	0.0% (0)	4.0% (18)	0.0% (0)	1.8% (7)	1.5% (2)	1.5% (4)	3.3% (3)	3.4% (6)
Haemorrhage	4.0% (4)	6.0% (27)	2.3% (2)	3.4% (13)	3.1% (4)	2.9% (8)	3.3% (3)	4.5% (8)
Pulmonary Failure	3.0% (3)	6.0% (27)	7.9% (7)	7.2% (28)	6.7% (9)	7.0% (19)	5.5% (5)	7.9% (14)
Renal Failure	0.0% (0)	1.6% (7)	1.0% (1)	0.8% (3)	0.7% (1)	1.1% (3)	0.0% (0)	0.0% (0)
Cardiac Failure	6.0% (6)	8.5% (38)	6.8% (6)	7.2% (28)	4.5% (6)	7.4% (20)	2.2% (2)	8.5% (15)
Post-transplant liver failure	5.0% (5)	1.3% (6)	1.0% (1)	2.1% (8)	0.7% (1)	0.7% (2)	2.2% (2)	1.7% (3)
Gastrointestinal	3.0% (3)	2.0% (9)	0.0% (0)	1.3% (5)	0.7% (1)	0.7% (2)	0.0% (0)	0.6% (1)
Infection	1.0% (1)	1.6% (7)	0.0% (0)	1.0% (4)	2.2% (3)	0.7% (2)	0.0% (0)	0.6% (1)
CVA	3.0% (3)	2.5% (11)	0.0% (0)	3.3% (13)	1.5% (2)	1.8% (5)	1.1% (1)	3.4% (6)
Other	12.0% (12)	13.0% (58)	11.3% (10)	10.5% (41)	9.6% (13)	12.4% (34)	14.3% (13)	15.2% (27)
Unknown	5.0% (5)	3.4% (15)	2.3% (2)	9.8% (38)	9.6% (13)	9.5% (26)	2.2% (2)	4.5% (8)
P-value**	**<0.001**		**<0.001**		**0.001**		**0.001**	

** Recurrence of malignant disease for patients transplanted for non-HCC indications likely represents recurrence of a intrahepatic malignancy only identified on explant pathology or an error in the recording cause of death.*

*** Includes the recurrence of HCV and cholestatic liver disease (PSC & PBC).*

**** Includes both lymphoid and non-lymphoid malignant disease.*

*****p value of chi squared test comparing distribution of causes of death in HCC and non-HCC patients in each era of transplantation.*

4. Results Chapter

Research Paper 2

Title: Assessing the Impact of Suboptimal Donor Characteristics on Mortality after Liver Transplantation: A Time-dependent Analysis Comparing HCC With Non-HCC Patients.

The results of this chapter have been presented in the form of a published paper. The supplementary information referred to in the paper is available at the end of the manuscript.

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SECTION A – Student Details

Student ID Number	1605002	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Wallace		
Thesis Title	Liver transplantation as a treatment for patients with hepatocellular carcinoma: a study using electronic health care data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Transplantation		
When was the work published?	April 2019		
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SECTION E

Student Signature	[redacted]
Date	04/01/2021

Supervisor Signature	[redacted]
Date	04/01/2021

Assessing the Impact of Suboptimal Donor Characteristics on Mortality After Liver Transplantation: A Time-dependent Analysis Comparing HCC With Non-HCC Patients

David Wallace, MSc,[1,2] Kate Walker, PhD,[1] Susan Charman, MSc,[1] Abid Suddle, MD,[2] Alex Gimson, MD,[3] Ian Rowe, PhD,[4,5] Chris Callaghan, PhD,[6] Tom Cowling, PhD,[1] Nigel Heaton, FRCS,[2] and Jan van der Meulen, PhD[1]

Background. Patients who receive a liver transplant for hepatocellular carcinoma (HCC) often receive poorer-quality livers. Tumor recurrence also has a negative effect on posttransplant outcomes. We compared mortality of HCC and non-HCC recipients in different posttransplant time periods (epochs) to separate the impact of these different risk factors on short-term and longer-term posttransplant survival. **Methods.** We identified a population-based cohort of first-time liver transplant recipients (aged ≥16 years) between 2008 and 2016 in the United Kingdom. We used Cox regression to estimate hazard ratios (HRs) comparing posttransplant mortality between HCC and non-HCC patients in 3 posttransplant epochs: 0 to 90 days, 90 days to 2 years, and 2 to 5 years, with adjustment first for recipient and later also for donor characteristics. **Results.** One thousand two hundred seventy HCC and 3657 non-HCC transplant recipients were included. Five-year posttransplant survival was 74.5% (95% confidence interval [CI] 71.2%–77.5%) in HCC patients and 84.6% (83.0%–86.1%) in non-HCC patients. With adjustment for recipient characteristics only, mortality of HCC patients was lower but not statistically significantly different in the first 90 days (HR, 0.76; 95% CI, 0.53–1.09; $P = 0.11$), but significantly higher thereafter (90 days to 2 years: HR, 1.99; 95% CI, 1.48–2.66; $P < 0.001$; 2 to 5 years HR, 1.77; 95% CI, 1.30–2.42; $P < 0.001$). Further adjustment for donor characteristics had little impact on these results. **Conclusions.** HCC recipients have poorer 5-year posttransplant survival than non-HCC recipients, most likely because of tumor recurrence. The more frequent use of poorer-quality donor organs for HCC does not explain this difference.

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INTRODUCTION

The rising incidence of hepatocellular carcinoma (HCC) has led to a marked increase in the number of patients with HCC receiving a liver transplant.[1] This has put pressure on transplantation services in many countries as they struggle to cope with transplanting patients with HCC in an acceptable oncological time frame given the limited availability of donor organs.[1] In response, livers with suboptimal donor characteristics are increasingly being used.[2]

It is unknown to what extent the increase in the number of liver transplants for HCC and the related increased use of marginal livers have affected posttransplantation outcomes. International consensus recommendations only indicate that posttransplant outcomes of patients transplanted for HCC should be comparable to those transplanted for non-HCC indications.[3]

A study including patients transplanted between 1988 and 2003 in a number of European countries suggested that posttransplant survival immediately after transplantation is often better in patients transplanted for HCC compared with those who had liver transplant for other reasons.[4,5] However, survival in HCC patients can deteriorate later during follow-up, most likely as a result of tumor recurrence. It has been argued that the introduction of the Milan criteria—a set of tumor characteristics introduced in the late 1990s to identify HCC patients in whom liver transplantation may provide curative treatment (1 lesion with a diameter ≤5 cm, or alternatively 3 lesions each with a diameter ≤3 cm)—will have reduced tumor recurrence and in that way will have canceled the reversal of HCC's impact on posttransplant outcomes.[5-7] There has been no recent large-scale study that has empirically tested this assertion.

In the United Kingdom, the Milan criteria for listing patients with HCC for liver transplantation were expanded in response to studies that suggested that less restrictive criteria would not negatively affect cancer recurrence rates and posttransplant survival.[8,9] As a result, a set of expanded criteria were formally accepted in the United Kingdom in 2008 (1 lesion with a diameter ≤5 cm, or up to 5 tumors each with diameter ≤3 cm, or 1 lesion with a diameter >5 and ≤7 cm with no evidence of tumor progression, extrahepatic spread, or new nodule formation over a 6-month period).[10,11]

Our aim was to examine the prognostic impact of HCC over different time periods (epochs) after liver transplantation using recent data from the Standard National Liver Transplant Registry. To correlate with the introduction of expanded selection criteria, our analysis focused on a cohort of patients who received a liver transplant between 2008 and 2016. We investigated whether the impact of HCC varied over 3 epochs of follow-up: patient survival up to 90 days was chosen to reflect the occurrence of surgical complications, primary nonfunction and acute rejection,[12] survival between 90 days and 2 years and between 2 and 5 years to reflect tumor recurrence and chronic rejection.[3,7,12,13] These results were first adjusted for recipient characteristics and in a second step also for donor characteristics to investigate the impact that the use of livers with suboptimal donor characteristics has on differences in posttransplant survival between HCC and non-HCC recipients. In a series of sensitivity analyses, we also tested whether the effect of HCC on mortality differed according to a previous diagnosis of hepatitis C (HCV) and, more specifically, whether mortality from tumor recurrence differed according to the use of donation after circulatory death (DCD) donors.

MATERIALS AND METHODS

Standard National Liver Transplant Registry

Since 1968, the Standard National Liver Transplant Registry contains information about all liver transplants done in the 6 liver transplant centers in England and 1 center in Scotland. The data set is managed by National Health Service (NHS) Blood and Transplant,[14] and regular checks indicate that the data are consistently >93% complete and accurate and results from several studies confirm the validity of the data set.[14-17]

Study Population

The study population included all recipients aged 16 years or older who received the first elective orthotopic liver transplant in the United Kingdom between January 1, 2008, and December 31, 2016. The diagnostic category of each patient was identified from the 3 diagnostic fields available in the Standard National Liver Transplant Registry and patients were categorized into 2 groups, patients transplanted with HCC and patients transplanted with other liver disease diagnoses according to their primary liver diagnosis at the time of transplantation (non-HCC patients). In the event of multiple diagnoses, patients were considered to have HCC if HCC was mentioned in any of 3 diagnosis fields. There was no information in the UK transplant registry on explant pathology.

To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multivisceral, superurgent, domino, or living-related liver transplantations were excluded as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). We also excluded patients whose survival data were missing.

Donor and recipient characteristics and primary cause of death were compared between HCC and non-HCC recipients. Recipient's lifestyle activity was assessed using a 5-point scale ranging from able to carry out normal activity without restriction to completely reliant on nursing/medical care,[17] and United Kingdom Model for End-Stage Liver Disease (UKELD) was used to score the severity of the liver disease.[18] Cold ischemic time was defined as the duration between the start of cold perfusion in the donor to the start of blood flow through the organ in the recipient.[19] Values for ethnicity were grouped into white and non-white groups.

Statistical Analysis

To describe the prognostic impact of HCC, we included patients who received a liver transplant over a 9-year period between January 1, 2008, and December 31, 2016. Categorical variables were presented as proportions and compared using chi-squared tests and continuous variables presented as means with SDs and compared using *t* tests. Patients transplanted for non-HCC indications who were

subsequently found to have an HCC on explant pathology were analyzed on an intention-to-treat basis and remained in the non-HCC cohort.

The Kaplan-Meier method was used to compare posttransplant patient and graft survival in HCC and non-HCC recipients and to compare posttransplant patient and graft survival in patients with HCC who were transplanted within the Milan criteria and those transplanted within the expanded criteria. Follow-up data were available until December 31, 2016. Patients with a functioning graft or alive at their last follow-up visit were considered to be censored observations. Graft loss was defined as either retransplantation or patient death. Differences in survival were assessed with the log-rank test.

We used multifactorial Cox regression to build 3 separate models. All models were designed to examine the prognostic impact of HCC status on patient survival in 3 separate epochs of follow-up time: up to 90 days after transplantation, between 90 days and 2 years, and between 2 and 5 years. In the first model, hazard ratios (HRs) comparing posttransplant survival in liver transplant recipients with and without HCC were estimated without adjustment for the donor and recipient characteristics. In the second model, HRs were estimated with adjustment for recipient factors only, and in the final model, HRs were estimated after adjustment for both donor and recipient factors. We performed a series of sensitivity analysis that first explored the effect of partitioning the epochs into posttransplantation time periods that included 90 days to 1 year and 1 to 2 years and second determined whether the effect of HCC on mortality differed according to HCV status by testing the interaction between HCC and HCV.

In all Cox models, adjustment for specific tumor characteristics was not included as comparisons of posttransplantation survival in HCC patients were made with a cohort of non-HCC patients. All donor and recipient factors were selected on the basis of their clinical plausibility of being a risk factor for posttransplant survival.[16] The time dependency of HCC as a risk factor for posttransplant survival and the interaction effect between HCC and HCV were tested with Wald tests.

In the regression models in which we adjusted for donor and recipient characteristics, we also explored possible nonlinear relationships between the recipient and donor characteristics measured as continuous variables and posttransplant survival, by including these as both linear and quadratic terms in the model. Missing patient and donor characteristics were imputed using chained equations creating 10 complete data sets.[20] The Cox regression results for each of these data sets were pooled using Rubin rules.[20] No patient or donor characteristic had >15% of missing values.

Stata V15 (StataCorp, College Station, TX) was used for all statistical analyses. A P <0.05 was considered significant for each statistical analysis.

RESULTS

A total of 4927 first adult elective liver transplants were performed between 2008 and 2016, of which 1270 liver transplants were for HCC recipients and 3657 for non-HCC recipients (Figure 1). Compared with non-HCC recipients, those who received a liver transplantation for HCC between 2008 and 2016 were more likely to be male, from non-white ethnic backgrounds, and positive for HCV infection (Table 1). Despite being significantly older at the time of transplantation, HCC patients were physically more active (according to their recorded lifestyle activity), had better liver function (exhibited by lower UKELD scores), and were less likely to show signs of end-stage liver disease (varices, encephalopathy, and ascites). They were also less likely required ventilation or hospital admission immediately before transplantation and less likely to have undergone previous abdominal surgery. Patients with HCC received more grafts from organs DCD or grafts in which the appearance had been documented as abnormal or steatotic. Cold ischemic time was marginally lower in HCC recipients, and there were only small differences between the cohorts in the frequency of capsular damage in the donor organ. Of the 1270 HCC recipients who were included in our study, only 81 (6.4%) had tumor characteristics that were beyond the Milan but within the expanded criteria at the time of registration on the transplant waiting list.

Kaplan-Meier survival curves comparing outcomes in HCC and non-HCC patients showed that patient and graft survival in the first months following liver transplantation is very similar (Figure 2). After about 3 to 4 months, HCC patients seem to have progressively worse patient survival, resulting in a 5-year patient survival of 74.5% (95% CI, 71.2%–77·5%) for HCC patients and 84.6% (95% CI, 83.0%–86.1%, P < 0.001) for non-HCC patients. A similar time pattern was observed for prognostic impact of HCC on graft survival with corresponding 5-year estimates of 70.2% (95% CI, 66.8%–73.3%) for HCC patients and 79.1% (95% CI, 77.4%–80.7%, P < 0.001) for non-HCC patients.

We did not find a difference in the 5-year patient survival between the 1189 HCC patients who met the Milan criteria (74.6%; 95% CI, 71.1%–77.7%) and the 81 who did meet the expanded criteria (74.5%; 95% CI, 58.6%–85.0%; P = 0.76 (Figure 3). Neither did we find differences in graft survival between these patient groups (70.4%; 95% CI, 67.0%–73.6% and 67.8%; 95% CI, 55.2%–79.3%, respectively; P = 0.81).

The first Cox regression model, comparing HCC and non-HCC patients without adjustment for donor or recipient characteristics, did not find a statistically significant difference in survival in the first 90 days after transplantation (HR, 0.88; CI, 0.63–1.23; Table 2). In the subsequent 2 epochs of follow-up time, patients with HCC had a significantly poorer survival (HR, 2.27 between 90 days and 2 years and HR, 2.00 between 2 and 5 years). In the second Cox regression model, only adjusting for recipient characteristics did not dramatically change the impact of HCC on survival in either the first 90 days after transplantation (adjusted HR, 0.76; CI, 0.53–1.09) or in the 2 later epochs of follow-up time (adjusted HR, 1.99 between 90 days and 2 years and adjusted HR, 1.77 between 2 and 5 years). In the third Cox model, additional adjustment for donor characteristics also had little effect on the impact of HCC in each of the epochs of follow-up time (adjusted HR, 0.74 between 0 and 90 days; adjusted HR, 1.96 between 90 days and 2 years; and adjusted HR, 1.74 between 2 and 5 years). The results of the Cox regression analysis of graft

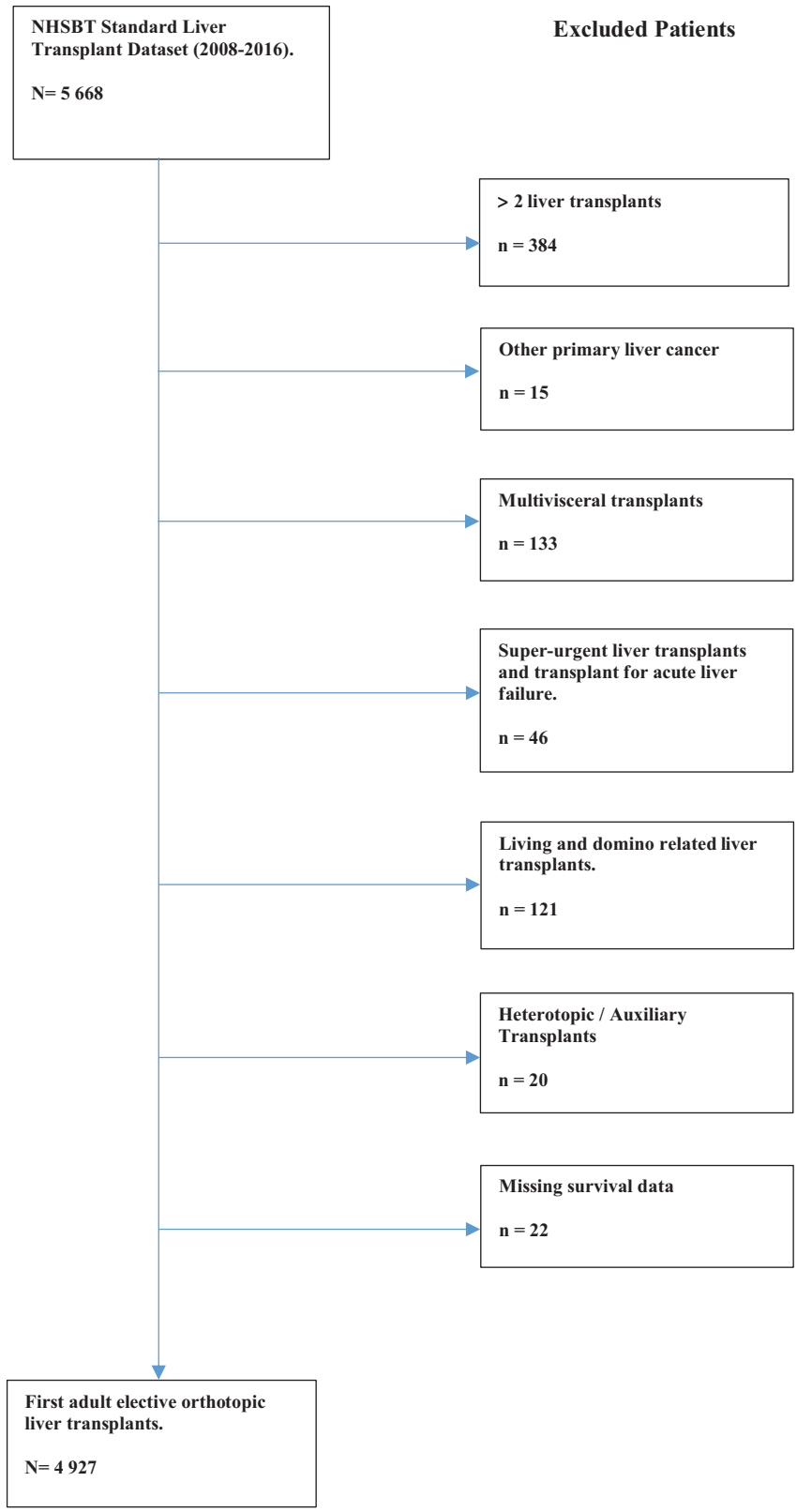

FIGURE 1. Flow chart detailing selection of study population (2008-2016). NHSBT, National Health Service Blood and Transplant.

survival (Table 3) closely mirrored the results found for patient survival (Table 2).

In the sensitivity analysis that explored the impact of HCC in 4 separate epochs, we found that it was highest between 90 days and 1 year after transplantation (adjusted HR, 2.10; 95% CI, 1.47–3.00) and that it remained at a very similar level thereafter (Table S5, SDC, http://links.lww.com/TP/B665). The sensitivity analysis testing the interaction between HCC and HCV status did not show that the effect of HCC on mortality differed significantly according

TABLE 1.

Donor and recipient patient characteristics (N = 4927)

Indication group	HCC	Non-HCC		
Number	n = 1270	n = 3657	Missing values[a]	*P*
Donor	% (N)	% (N)	N	
Sex				
Female	42.8% (544)	47.6% (1740)	0	0.003
Cause of death				
Trauma	9.1% (115)	7.7% (281)		0.21
Cerebrovascular accident	62.6% (796)	64.8% (2371)		
Others	28.3% (359)	27.5% (1005)	0	
Donor type				
DCD	31.9% (405)	21.2% (774)	0	<0.001
ABO match				
Identical	98.0% (1245)	98.6% (3606)		0.34
Compatible	1.9% (24)	1.3% (48)		
Incompatible	0.1% (1)	0.1% (3)	0	
Graft type				
Segmental	6.0% (76)	8.9% (324)	0	0.001
Organ appearance				
Abnormal	29.8% (308)	22.8% (709)	776	<0.001
Steatosis				
Presence	48.2% (604)	44.6% (1603)	84	0.03
Capsular damage				
Presence	14.3% (178)	14.1% (507)	92	0.91
Donor age, y				
Mean (SD)	50 (16)	49 (16)	0	0.07
Donor BMI, kg/m^2				
Mean (SD)	27 (5.0)	26 (5.0)	10	0.15
Cold ischemic time (min)				
Mean (SD)	502 (158)	517 (158)	392	0.01
Recipient				
Sex				
Female	19.8% (251)	37.3% (1363)	1	<0.001
Recipient ethnicity				
Non-white	16.5% (209)	11.1% (407)	2	<0.001
HCV status				
Positive	42.6% (509)	12.1% (418)	285	<0.001
Pretransplant in patient status				
Inpatient	4.9% (62)	16.6% (608)	6	<0.001
Ascites				
Presence	29.8% (378)	61.8% (2251)	17	<0.001
Encephalopathy				
Presence	15.2% (189)	36.1% (1300)	82	<0.001
Pretransplant renal support				
Yes	4.7% (60)	4.6% (170)	13	0.9
Pretransplant ventilation requirement				
Yes	0.2% (3)	0.9% (31)	8	0.02
Previous abdominal surgery				
Yes	10.0% (127)	12.4% (453)	17	0.02
Previous variceal bleed				
Presence	15.7% (199)	27.4% (1002)	56	<0.001
Life style activity				
Normal	12.9% (161)	3.8% (139)		<0.001
Restricted	44.2% (554)	31.5% (1136)		
Self-care	37.4% (469)	47.7% (1724)		
Reliant	4.5% (56)	14.0% (505)		
Confined	1.0% (13)	3.0% (107)	63	

Continued next page

TABLE 1. (Continued)

Indication group	HCC	Non-HCC		
Number	n = 1270	n = 3657	Missing values	*P*
Age (y)				
Mean (SD)	58 (8.0)	51 (11.8)	0	<0.001
BMI, kg/m^2				
Mean (SD)	28 (4.8)	27 (5.3)	5	<0.001
UKELD				
Mean (SD)	51 (4.9)	56 (5.4)	38	<0.001

[a]No data item had >15% of missing values.
BMI, body mass index; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; HCV, hepatitis C; SD, standard deviation; UKELD, United Kingdom Model for End-Stage Liver Disease.

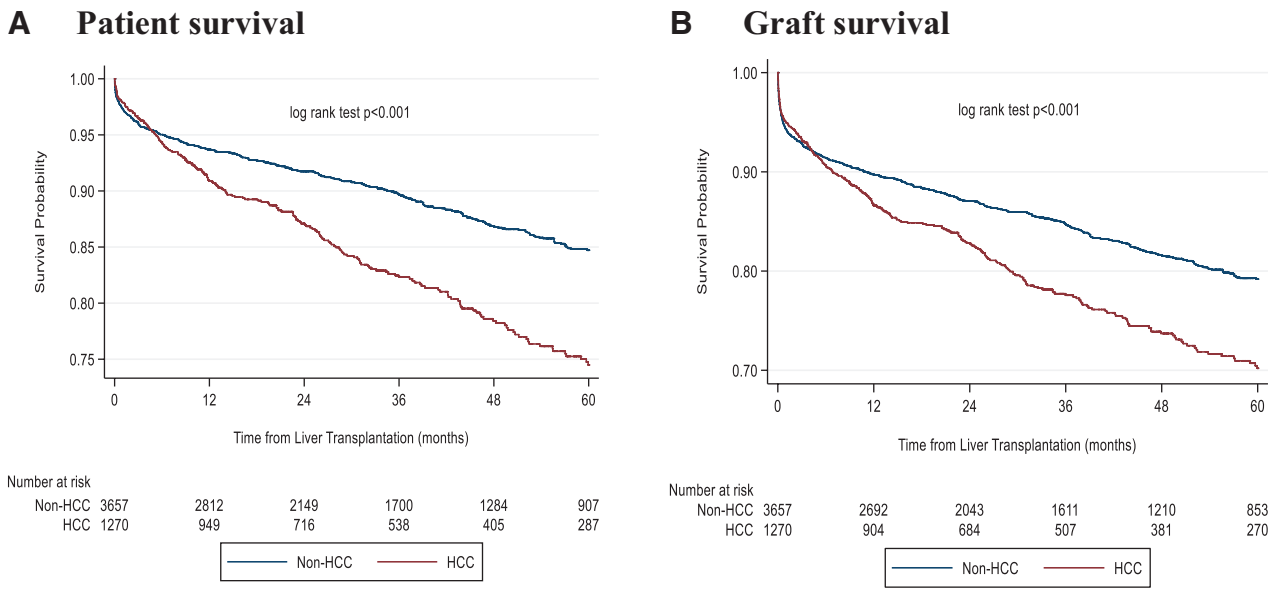

FIGURE 2. Five-year patient and graft survival stratified by hepatocellular carcinoma (HCC) status 2008-2016 (N = 4927).

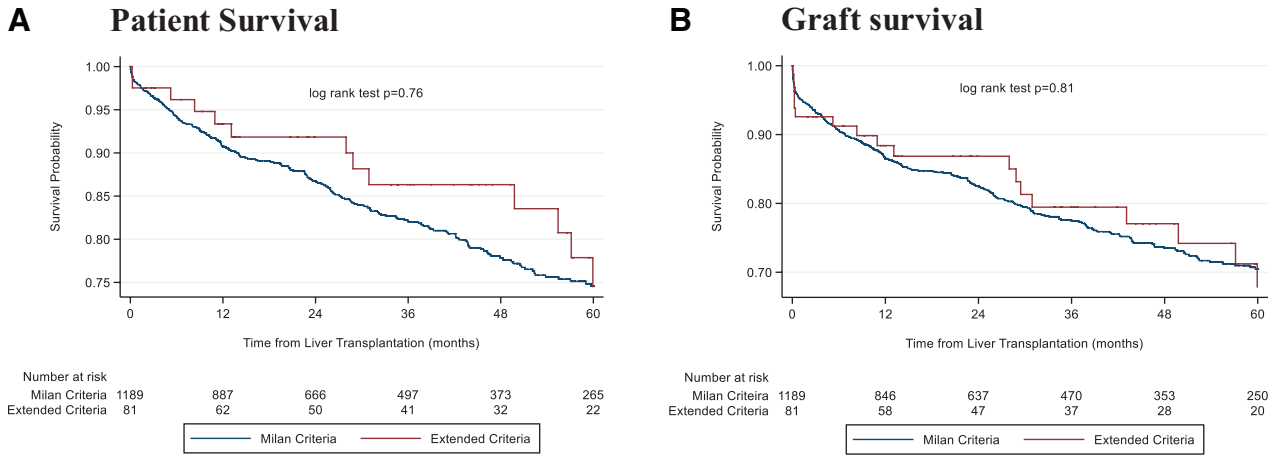

FIGURE 3. Five-year patient and graft survival for hepatocellular carcinoma (HCC) patients stratified by type of selection criteria 2006-2016 (N = 1270).

to HCV status (HCV+ve HR, 1.16; 0.87–1.56, and HCV–ve HR, 0.86; 0.64–1.15; *P* for interaction = 0.10).

In the first 90 days after transplantation, there were no statistically significant differences in the distribution of cause of death between HCC and non-HCC recipients and no patient died from tumor recurrence (recurrence of malignant primary disease; Table 4). In the subsequent posttransplant epochs, tumor recurrence in HCC recipients became a more frequent cause of death accounting for 23 of the 101 deaths (22.7%) between 90 days and

TABLE 2.

Impact of HCC on posttransplant patient survival in 3 separate epochs of follow-up time (N = 4927)

	HCC compared with non-HCC HR (95% CI)			
Posttransplant patient survival	0-3 Months	3-24 Months	24-60 Months	*P* time dependency[a]
Unadjusted analysis	0.88 (0.63–1.23)	2.27 (1.74–2.94)	2.00 (1.50–2.66)	<0.001
Adjusted for recipient characteristics[b]	0.76 (0.53–1.09)	1.99 (1.48–2.66)	1.77 (1.30–2.42)	<0.001
Adjusted for recipient and donor characteristics[b]	0.74 (0.52–1.07)	1.96 (1.46–2.62)	1.74 (1.27–2.31)	<0.001

[a]*P* values represent whether HRs in each epoch of follow-up time differ significantly from each other.
[b]Adjusted for (a) recipient characteristics: sex, ethnicity, HCV status, pretransplant inpatient status, ascites, encephalopathy, pretransplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (kg/m^2), and UKELD and (b) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (kg/m^2), and cold ischemic time.
Tables S1 and S2, SDC, http://links.lww.com/TP/B665 in the supplemental information have HRs and 95% CI for all other donor and recipient characteristics.
BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; UKELD, United Kingdom Model for End-Stage Liver Disease.

TABLE 3.

Impact of HCC on post-transplant graft survival in 3 separate epochs of follow-up time (N = 4927)

	HCC compared to non-HCC HR (95% CI)			
Posttransplant graft survival	0-3 Months	3-24 Months	24-60 Months	*P* time dependency[a]
Unadjusted analysis	0.95 (0.75–1.21)	1.84 (1.46–2.34)	1.82 (1.38–2.39)	<0.001
Adjusted for recipient characteristics[b]	0.89 (0.68–1.17)	1.74 (1.34–2.27)	1.72 (1.28–2.31)	<0.001
Adjusted for recipient and donor characteristics[b]	0.84 (0.65–1.11)	1.67 (1.28–2.17)	1.66 (1.23–2.23)	<0.001

[a]*P* values represent whether HRs in each epoch of follow-up time differ significantly from each other.
[b]Adjusted for (a) recipient characteristics: sex, ethnicity, HCV status, pretransplant inpatient status, ascites, encephalopathy, pretransplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (kg/m^2), and UKELD and (2) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (kg/m^2), and cold ischemic time.
Tables S3 and S4, SDC, http://links.lww.com/TP/B665 in the supplemental information have HRs and 95% CI for all other donor and recipient characteristics.
BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; UKELD, United Kingdom Model for End-Stage Liver Disease.

2 years and 12 of the 77 deaths (15.6%) between 2 and 5 years. When splitting cause of death into 4 epochs, we found that from 90 days onward the number of patients dying from tumor recurrence remained more or less constant (Table S6, SDC, http://links.lww.com/TP/B665).

Of the 35 HCC recipients who died of tumor recurrence, 9 (25.7%) had received a DCD liver compared with 396 of the 1235 other HCC recipients (32.1%; $P = 0.43$) which demonstrates that there is no evidence that the use of DCD livers is linked to an HCC recurrence risk. The proportion of patients who died from malignancies other than tumor recurrence was higher in the HCC recipients (2.9% or 37/1270) than in non-HCC recipients (1.1% or 41/3657), and this difference was most prominent in deaths from nonlymphoid malignancies (Table 4). Overall, recurrence of benign primary disease, which includes HCV, was infrequently reported as a cause of death (Table 4 and see Table S6, SDC, http://links.lww.com/TP/B665), irrespective of HCC status at the time of transplant or epoch of follow-up (Table 4 and see Table S6, SDC, http://links.lww.com/TP/B665).

DISCUSSION

Summary of Results

At the time of transplantation, HCC patients were on average in a better physical condition and had less signs of end-stage liver disease than non-HCC patients, but they received more often suboptimal grafts. We found that the survival of HCC and non-HCC recipients was similar in the first months after transplantation. Then the survival of HCC recipients deteriorated with the rate of mortality and graft failure being at least 50% higher than in non-HCC recipients, with tumor recurrence as the most important explanation. The difference in survival could not be explained by HCC recipients receiving a higher proportion of livers from DCD donors or from donors with other suboptimal characteristics.

Methodological Limitations

The key limitation of our analysis is that we used predefined posttransplant epochs (up to 90 days, between 90 days and 2 years, and between 2 and 5 years) to investigate the time dependency of the impact of HCC on patient and graft survival. This approach assumes that the prognostic impact of HCC on survival is constant within each of these epochs.[21] The advantage of this approach is that the HRs can be estimated using standard Cox regression methods and, more importantly, that the results are relatively easy to interpret. Its disadvantage is that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration is arbitrary.

TABLE 4.

Primary cause of death following liver transplantation for HCC and non-HCC patients in 3 separate epochs of follow-up time (n = 620)

	0-90 days		91 days to 24 months		24 months to 60 months	
Cause of death	**HCC (n = 44)**	**Non-HCC (n = 144)**	**HCC (n = 101)**	**Non-HCC (n = 132)**	**HCC (n = 77)**	**Non-HCC (n = 122)**
Recurrent primary disease—malignant[a]	0% (0)	0% (0)	22.7% (23)	1.5% (2)	15.6% (12)	1.6% (2)
Recurrent primary disease—benign[b]	2.3% (1)	0.0% (0)	1.0% (1)	3.8% (5)	1.3% (1)	2.5% (3)
Malignancy—lymphoproliferative	2.3% (1)	0.0% (0)	3.0% (3)	4.5% (6)	1.3% (1)	4.9% (6)
Malignancy—nonlymphoproliferative	0.0% (0)	0.0% (0)	12.9% (13)	9.1% (12)	24.7% (19)	13.9% (17)
Sepsis	45.5% (20)	42.3% (61)	24.7% (25)	37.1% (49)	22.0% (17)	29.5% (36)
Graft failure	2.3% (1)	4.2% (6)	3.0% (3)	0.8% (1)	1.3% (1)	0.8% (1)
Hemorrhage	4.5% (2)	6.9% (10)	3.0% (3)	1.5% (2)	1.3% (1)	1.6% (2)
Pulmonary failure	2.3% (1)	6.3% (9)	3.9% (4)	9.9% (13)	9.1% (7)	5.8% (7)
Renal failure	0.0% (0)	0.7% (1)	0% (0)	0% (0)	0.0% (0)	0.8% (1)
Cardiac failure	9.1% (4)	9.7% (14)	3.0% (3)	6.1% (8)	1.3% (1)	6.6% (8)
Hepatic failure	2.3% (1)	0.7% (1)	0.0% (0)	1.5% (2)	2.6% (2)	1.6% (2)
Gastrointestinal	0% (0)	0.7% (1)	0.0% (0)	0% (0)	1.3% (1)	1.6% (2)
Infection	4.5% (2)	0.7% (1)	2.0% (2)	0% (0)	0.0% (0)	0.8% (1)
CVA	4.5% (2)	3.5% (5)	0.0% (0)	2.3% (3)	1.3% (1)	2.5% (3)
Other	20.4% (9)	22.2% (32)	10.9% (11)	15.9% (21)	10.4% (8)	10.7% (13)
Unknown	0% (0)	2.1% (3)	9.9% (10)	6.0% (8)	6.5% (5)	14.8% (18)
P[c]	0.38		<0.001		0.03	

[a]Recurrence of malignant disease for patients transplanted for non-HCC indications likely represents recurrence of an intrahepatic malignancy only identified on explant pathology or an error in the recording cause of death.
[b]Includes the recurrence of HCV and the cholestatic liver diseases (PSC and PBC).
[c]*P* value of chi-squared test comparing distribution of causes of death in HCC and non-HCC patients.
HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

In our analysis, we compared HCC patients with a heterogeneous cohort of non-HCC patients. This approach may have masked specific survival patterns of individual primary liver diseases. However, the dichotomy in HCC and non-HCC patients reflects the difference in how HCC and non-HCC patients were selected for transplantation in the United Kingdom. While for most non-HCC patients, the urgency of transplantation was taken from their liver function according to the UKELD score, the urgency for HCC patients came from the need to avoid cancer progression before transplantation.

Comparison With Other Studies

We studied the prognostic impact of HCC on posttransplant survival in 3 distinct epochs, aiming to capture on the one hand that HCC patients are in a better physical condition at the time of transplantation—which may give them better surgical outcomes—but on the other that tumor recurrence may deteriorate survival in the later stages. Already 30 years ago, the importance of analyzing liver transplant outcomes in epochs of follow-up time was recognized, but this statistical approach is very rarely practised.[4,22] Our study is an example of how important it is to analyze posttransplant outcomes in distinct epochs of follow-up time, guided by the understanding of the relevant underlying clinical mechanisms. For example, risk factors for immediate surgical outcomes are predominantly linked to the recipients' physical condition and risk factors for longer-term outcomes to recurrence of the original disease that was the reason for transplantation.

It was expected that the introduction of the Milan criteria would lead to a decrease in recurrence rates in patients transplanted for HCC.[4] However, our study, which reflects the outcomes of modern liver transplantation practice, including a national population-based cohort of patients transplanted between 2008 and 2016, indicates that tumor recurrence remains an important risk factor for survival in the later stages after liver transplantation, which corresponds with earlier reports of posttransplant survival.[1-3]

Despite a formal adoption of expanded HCC selection criteria in 2008, we found that only 6.4% of HCC recipients were selected for transplantation within these expanded criteria and we could not demonstrate differences in posttransplant outcomes compared with those who were selected according to the Milan criteria. Reasons for why only a very small minority of HCC recipients were transplanted beyond the Milan criteria are difficult to explain and we must acknowledge that this analysis does not specifically address this question. However, a tendency for radiological assessment to understage some HCC patients before transplantation may have prohibited the aggressive use of the extended selection criteria, especially when other studies have indicated a linear relationship between tumor burden and posttransplantation survival.[23,24]

Explanation of Results

Our study found that HCC patients were more likely to receive suboptimal donor organs with characteristics previously proven to have poorer posttransplant outcomes.[2] This included donated livers that were either steatotic, abnormal in appearance, or that were from DCD donors. However, our analysis was specifically designed to test the impact of donor characteristics on posttransplant survival, and we observed that additional adjustment for donor characteristics had little effect on the differences in survival between HCC and non-HCC recipients in any of the epochs after transplantation.

The incidence of HCV recurrence after transplantation is also an unlikely explanation for the observed differences in survival. Previous studies have reported that, irrespective of HCC status at the time of transplantation, survival between those with and without HCV is similar up to 5 years after transplantation and worse thereafter.[25,26] In our own analysis, we did not find the effect of HCC on mortality to differ significantly according to whether the patient had a previous diagnosis of HCV nor did we find HCV recurrence to be frequently reported as a cause of death in the first 5 years after transplantation.

Similarly, differences in the incidence of acute rejection do not explain the differences in the survival patterns of HCC and non-HCC recipients. In efforts to reduce the risk of tumor recurrence, HCC recipients can be subjected to more conservative immunosuppression protocols,[27] and therefore, they may be at an increased risk of acute rejection. However, we have found that 1-year readmissions for acute rejection in patients transplanted in the United Kingdom between 2008 and 2016 occurred less frequently in HCC recipients (2.8% or 35/1270) than in non-HCC recipients (3.1% or 112/3657; $P = 0.57$), while acute rejection recorded as a cause of death was not identified at all within the study cohort (London School of Hygiene and Tropical Medicine, unpublished data, 2018).

We identified some differences in the proportion of HCC and non-HCC recipients who died of malignancies other than tumor recurrence. This cause of death, particularly nonlymphoid-related malignancies, were more frequent in HCC recipients and consistent with the existing literature there was a high incidence between 3 months and 2 years after transplantation.[28] However, the differences in the overall number of HCC and non-HCC recipients who died from malignancies other than tumor recurrence were too small to fully explain the differences in survival between the 2 cohorts.

Beyond 90 days, differences in survival are best explained by differences in deaths due to tumor recurrence and this remained so even when we further partitioned the follow-up period to include survival from 90 days to 1 year and from 1 to 2 years. Of the HCC patients who were recorded to have died of tumor recurrence within 1 year, only one was preoperatively staged according to the extended criteria with other early deaths potentially explained by aggressive tumor biology or radiological understaging of the HCC before transplantation.[13] In further analysis, we did not find the use of DCD livers to be associated with an increased risk of death from tumor recurrence.

In the past, HCC patients were found to have 90-day outcomes that were statistically significantly better than non-HCC patients.[5] Our results suggested that 90-day outcomes of HCC patients were better, but the difference with non-HCC patients was not statistically significant. One important explanation for not finding a significant difference is the substantial improvement in posttransplant outcomes in the last 30 years which considerably reduces the statistical power to detect differences.[29] Another explanation is that the impact of recipients' frailty at the time of transplantation has decreased given the improvements in perioperative care and the high dependency care immediately after transplantation.[30]

Implications of Findings

Our results demonstrate that outcomes in patients transplanted for HCC are worse than in those transplanted for non-HCC indications. This is not explained by the fact that we are using more DCD donors in HCC patients or that we are transplanting a significant proportion of patients who, at the time of transplantation, are beyond the Milan criteria. Instead, we must acknowledge that even with the stringent adoption of the Milan criteria in the United Kingdom, we are still selecting for transplantation a significant proportion of patients with HCC who are at risk of tumor recurrence. Therefore, until we can add to our selection criteria new parameters that better predict tumor recurrence, the poorer survival of HCC patients after liver transplantation will remain.

Until recently, many guidelines stipulated that patients with HCC should only receive a liver transplant if their predicted outcomes are comparable to non-HCC patients.[3] However, in the last decade, this has never been the case. This has been recognized by the service providers, and donor liver allocation schemes are now moving toward using criteria based on transplant benefit—in which they aim to maximize the net life years gained from the point of registration on the waiting rather than providing the greatest chance of surviving after transplantation.[31,32] However, the decision to offer HCC patients a liver transplant is further complicated as other treatments, including resection and ablation, have to be considered which is all the more important considering the impact that an increased use of liver transplantation in HCC patients will have on outcomes for non-HCC patients on the waiting list for transplantation given the ongoing donor organ shortage.[1,3]

CONCLUSIONS

Between 2008 and 2016, almost all HCC patients who received a liver transplant in the United Kingdom met the Milan criteria. Nevertheless, 1 in 4 HCC recipients died within 5 years compared with only 1 in 6 non-HCC patients, with tumor recurrence being the most likely explanation for this difference. These differences could not be explained by the increased use of poorer-quality donor organs in HCC patients. Donor allocation schemes based on transplant benefit schemes are likely to accommodate the poor posttransplant survival of HCC patients given their greater net gain in posttransplanted expected life years.

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SUPPLEMENTAL INFORMATION

Table S1: Impact of HCC on post-transplant patient survival in three separate epochs of follow-up time adjusted for recipient characteristics only.

RECIPIENT		Hazard Ratio	Confidence Intervals	P-value
HCC	0-90 days	0.76	0.53 – 1.09	0.14
	90 days – 2 years	1.99	1.48 – 2.66	<0.001
	2 years – 5 years	1.77	1.30 – 2.42	<0.001
Sex	Male	1		
	Female	0.86	0.72 – 1.03	0.10
Recipient ethnicity	White	1		
	Non-White	1.01	0.79 – 1.29	0.92
HCV status	Negative	1		
	Positive	1.38	1.13 – 1.69	0.002
Pre-transplant in patient status	Outpatient	1		
	Inpatient	0.93	0.68 – 1.27	0.65
Ascites	Absence	1		
	Presence	1.10	0.92 – 1.33	0.30
Encephalopathy	Absence	1		
	Presence	1.03	0.85 – 1.25	0.77
Pre-transplant renal support	No	1		
	Yes	0.90	0.61 – 1.34	0.60
Previous abdominal surgery	No	1		
	Yes	1.35	1.07 – 1.69	0.01
Varices	Absence	1		
	Presence	1.18	0.99 – 1.41	0.06
Life style activity	Normal	1		
	Restricted	1.22	0.85 – 1.76	0.28
	Self-care	1.26	0.87 – 1.81	0.22
	Reliant	1.71	1.09 – 2.68	0.02
	Confined	2.51	1.36 – 4.64	0.003
Age (years)	Linear	0.98	0.93 – 1.04	0.56
	Quadratic	1.00	0.99 – 1.00	0.20
BMI, Kg/m2	Linear	0.86	0.78 – 0.97	0.01
	Quadratic	1.00	1.00 – 1.00	0.01
UKELD	Linear	0.86	0.72 – 1.02	0.09
	Quadratic	1.00	0.99 - 1.00	0.1

Table S2: Impact of HCC on post-transplant patient survival in three separate epochs of follow-up time adjusted for recipient and donor characteristics.

RECIPIENT		Hazard Ratio	Confidence Intervals	P-value
HCC	0-90 days	0.74	0.52 – 1.07	0.11
	90 days – 2 years	1.96	1.46 – 2.62	<0.001
	2 years – 5 years	1.74	1.27 – 2.39	<0.001
Sex	Male	1		
	Female	0.91	0.76 – 1.10	0.35
Recipient ethnicity	White	1		
	Non-White	1.3	0.80 – 1.31	0.84
HCV status	Negative	1		
	Positive	1.38	1.13 – 1.69	0.002
Pre-transplant in patient status	Outpatient	1		
	Inpatient	0.94	0.68 – 1.28	0.68
Ascites	Absence	1		
	Presence	1.09	0.91 – 1.31	0.36
Encephalopathy	Absence	1		
	Presence	1.03	0.85 – 1.25	0.75
Pre-transplant renal support	No	1		
	Yes	0.88	0.59 – 1.32	0.53
Previous abdominal surgery	No	1		
	Yes	1.36	1.08 – 1.71	0.008
Varices	Absence	1		
	Presence	1.17	0.98 – 1.40	0.08
Life style activity	Normal	1		
	Restricted	1.16	0.81 – 1.68	0.42
	Self-care	1.20	0.83 – 1.74	0.32
	Reliant	1.62	1.03 – 2.55	0.04
	Confined	2.55	1.33 – 4.72	0.003
Age (years)	Linear	0.98	0.93 – 1.03	0.44
	Quadratic	1.00	0.99 – 1.00	0.15
BMI, Kg/m2	Linear	0.86	0.76 – 0.96	0.007
	Quadratic	1.00	1.00 – 1.00	0.007
UKELD	Linear	0.87	0.73 – 1.03	0.11
	Quadratic	1.00	0.99-1.00	0.12
DONOR				
Sex	Male	1		
	Female	0.92	0.77 – 1.09	0.32
Cause of death	Trauma	1		
	CVA	0.92	0.68 – 1.25	0.59
	Others	0.93	0.68 – 1.28	0.65
Donor Type	DBD	1		
	DCD	1.21	0.99 – 1.48	0.07
ABO Match	Identical	1		
	Compatible	1.01	0.53 – 1.89	0.98
	Incompatible	5.25	1.26 – 21.9	0.02
Graft Type	Whole	1		
	Segmental	1.04	0.73 – 1.47	0.81
Organ appearance	Normal	1		
	Abnormal	1.34	1.09 – 1.65	0.06
Steatosis	Absence	1		
	Presence	0.88	0.73 – 1.06	0.18
Capsular damage	Absence	1		
	Presence	0.90	0.71 – 1.14	0.39
Donor age, years	Linear	1.02	0.99 – 1.05	0.13
	Quadratic	0.99	0.99 – 1.00	0.19
Donor BMI, kg/m^2	Linear	1.11	0.98 – 1.26	0.01
	Quadratic	0.99	0.99 – 1.00	0.12
Cold Ischaemic Time (mins)	Linear	1.00	0.99 – 1.01	0.67
	Quadratic	0.99	0.99 – 1.01	0.08

Table S3: Impact of HCC on post-transplant graft survival in three separate epochs of follow-up time adjusted for recipient characteristics only.

RECIPIENT		Hazard Ratio	Confidence Intervals	P-value
HCC	0-90 days	0.89	0.68 – 1.17	0.41
	90 days – 2 years	1.74	1.34 – 2.27	<0.001
	2 years – 5 years	1.72	1.28 – 2.31	<0.001
Sex	Male	1		
	Female	0.92	0.79 – 1.07	0.28
Recipient ethnicity	White	1		
	Non-White	0.99	0.81 – 1.22	0.93
HCV status	HCV negative	1		
	HCV positive	1.25	1.05 – 1.49	0.001
Pre-transplant in patient status	Outpatient	1		
	Inpatient	0.95	0.73 – 1.23	0.69
Ascites	Absence	1		
	Presence	0.99	0.85 – 1.16	0.91
Encephalopathy	Absence	1		
	Presence	1.01	0.86 – 1.19	0.90
Pre-transplant renal support	No	1		
	Yes	1.02	0.74 – 1.41	0.92
Previous abdominal surgery	No	1		
	Yes	1.29	1.06 – 1.57	0.01
Varices	Absence	1		
	Presence	1.10	0.95 – 1.28	0.20
Life style activity	Normal	1		
	Restricted	1.01	0.75 – 1.36	0.95
	Self-care	1.06	0.79 – 1.42	0.69
	Reliant	1.33	0.92 – 1.94	0.13
	Confined	2.07	1.24 – 3.47	0.006
Age (years)	Linear	0.97	0.93 – 1.01	0.17
	Quadratic	1.00	0.99 – 1.00	0.11
BMI, Kg/m2	Linear	0.92	0.83 – 1.02	0.10
	Quadratic	1.00	0.99 – 1.00	0.09
UKELD	Linear	0.95	0.81 – 1.12	0.54
	Quadratic	1.00	0.99 - 1.00	0.55

Table S4: Impact of HCC on post-transplant graft survival in three separate epochs of follow-up time adjusted for recipient and donor characteristics.

RECIPIENT		Hazard Ratio	Confidence Intervals	P-value
HCC	0-90 days	0.84	0.65 – 1.11	0.22
	90 days – 2 years	1.96	1.46 – 2.62	<0.001
	2 years – 5 years	1.74	1.27 – 2.39	<0.001
Sex	Male	1		
	Female	0.93	0.80 – 1.09	0.39
Recipient ethnicity	White	1		
	Non-White	0.98	0.80 – 1.21	0.85
HCV status	HCV negative	1		
	HCV positive	1.26	1.05 – 1.50	0.01
Pre-transplant in patient status	Outpatient	1		
	Inpatient	0.94	0.72 – 1.23	0.68
Ascites	Absence	1		
	Presence	0.97	0.83 – 1.13	0.68
Encephalopathy	Absence	1		
	Presence	1.01	0.86 – 1.19	0.90
Pre-transplant renal support	No	1		
	Yes	1.00	0.72 – 1.38	0.98
Previous abdominal surgery	No	1		
	Yes	1.36	1.12 – 1.65	0.002
Varices	Absence	1		
	Presence	1.09	0.94 – 1.27	0.27
Life style activity	Normal	1		
	Restricted	0.93	0.69 – 1.25	0.63
	Self-care	1.01	0.75 – 1.36	0.95
	Reliant	1.29	0.89 – 1.88	0.18
	Confined	2.11	1.26 – 3.54	0.005
Age (years)	Linear	0.96	0.93 – 1.00	0.07
	Quadratic	1.00	0.99 – 1.00	0.05
BMI, Kg/m^2	Linear	0.91	0.82 – 1.01	0.07
	Quadratic	1.00	0.99 – 1.00	0.06
UKELD	Linear	0.95	0.81 – 1.11	0.53
	Quadratic	1.00	0.99 – 1.00	0.53
DONOR				
Sex	Male	1		
	Female	0.96	0.83 – 1.11	0.56
Cause of death	Trauma	1		
	CVA	0.90	0.69 – 1.16	0.41
	Others	0.88	0.67 – 1.15	0.36
Donor Type	DBD	1		
	DCD	1.66	1.41 – 1.97	<0.001
ABO Match	Identical	1		
	Compatible	0.98	0.57 – 1.67	0.93
	Incompatible	2.92	0.71 – 12.0	0.14
Graft Type	Whole	1		
	Segmental	1.22	0.92 – 1.63	0.17
Organ appearance	Normal	1		
	Abnormal	1.39	1.17 – 1.66	<0.01
Steatosis	Absence	1		
	Presence	0.85	0.73 – 0.99	0.04
Capsular damage	Absence	1		
	Presence	0.96	0.79 – 1.16	0.65
Donor age, years	Linear	1.02	0.99 – 1.04	0.17
	Quadratic	0.99	0.99 – 1.00	0.41
Donor BMI, kg/m^2	Linear	0.91	0.82 – 1.01	0.07
	Quadratic	1.00	0.99 – 1.00	0.06
Cold Ischaemic Time (mins)	Linear	1.00	0.99 – 1.00	0.22
	Quadratic	0.99	0.99 – 1.00	0.47

5. Results Chapter

Research Paper 3

Title: Time-trends in patient mortality and graft failure of patients receiving a DCD or DBD liver transplantation in the UK & Ireland

The results of this chapter have been presented in the form of the submitted research paper. The supplementary information referred to in the paper is available at the end of the manuscript. At the time of submission of this PhD this research paper is currently under review in the American Journal of Transplantation.

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Primary Supervisor	Professor Jan van der Meulen		

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Stage of publication	**Submitted**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conception of project, literature review, data analysis, interpretation of results and write up of the manuscript.

SECTION E

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TITLE PAGE

Time-trends in patient mortality and graft failure of patients receiving a DCD or DBD liver transplantation in the UK & Ireland.

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ABBREVIATIONS PAGE

BMI, body mass index

CI, Confidence intervals

CIT, cold ischemic time

DBD, donation after brainstem death

DCD, donation after circulatory death

DLI, donor liver index

HAT, hepatic artery thrombosis

HCC, hepatocellular carcinoma

HCV, hepatitis C

HR, hazard ratios

INR, International Normalized Ratio

NHSBT, National Health Service Blood and Transplant

PNF, Primary non-function

UK, United Kingdom

UKELD, United Kingdom Model for End-Stage Liver Disease

UNOS, United Network for Organ Sharing

WIT, Warm ischemic time

ABSTRACT

Despite high waiting list mortalities international concern still exists in the efficacy of livers donated after circulatory death (DCD). We used multinational data from the UK & Ireland to compare mortality and graft loss in recipients of livers donated after circulatory or brainstem death (DBD) across two successive eras. We used Cox regression methods to estimate hazard ratios (HR) that compared the impact of era (2008-2011 and 2012-2016) on post-transplant mortality and graft failure. 1176 DCD recipients and 3749 DBD recipients were included. 3-year patient mortality decreased markedly from 19.6% in era 1 to 10.4% in era 2 (aHR:0.43, 95%CI: 0.30-0.62) for DCD recipients but only decreased from 12.8% to 11.3% (aHR:0.96, 0.78-1.19) in DBD recipients (p for interaction 0.001). No era-specific improvements in 3-year graft failure were observed for DCD (aHR:0.80, 0.61-1.05, p=0.11) or DBD recipients (aHR:0.95, 0.79-1.14, p=0.60). In era 2, there was no difference in mortality between those receiving a DCD or DBD liver (aHR: 0.78, 0.56-1.09, p=0.14). Between 2008 and 2016, mortality more than halved in those who received a DCD liver and is now comparable to those who receive a DBD liver. Countries with high waitlist mortalities should consider increasing the use of DCD livers.

1. INTRODUCTION

Increases in the number of patients who require a liver transplantation in the UK has contributed to a chronic shortage of donors.[1-4] In response, livers donated following circulatory death (DCD) have increasingly been used to address the discrepancy between the number of patients waiting to receive a liver transplant and the number of suitable donor organs available.[2,4]

Early analyses that compared DCD donor livers with livers donated following brainstem death (DBD) described inferior post-transplantation outcomes, especially in the early post-transplantation period.[2, 5-8] Variable periods of warm ischaemia (WIT) during the procurement of DCD donor livers were found to cause irreversible cellular damage and higher rates of post-operative biliary complications, primary non-function (PNF) and hepatic artery thrombosis (HAT).[2, 5-8]

These early and often single centre reports of poorer graft and patient survival contributed to differences internationally in how DCD donors were utilised.[9] In some countries there was a reluctance to maximise their use due to the risk of post-operative complications and graft failure, whilst in other countries - like the UK & Ireland – there was a reliance on DCD donors to provide liver transplantation to patients, and especially HCC patients, before their disease progressed beyond transplantable criteria.[4,10]

The optimal utilisation of grafts from DCD donors is most likely to have been associated with a learning curve.[9] More recent publications from countries outside the UK describe improvements in the use of DCD livers, including improved patient and graft survival and lower rates of biliary complications, PNF and HAT.[11-15] A recent analysis of the UK liver transplant waiting list indicated that patients fair better by accepting an offer of a DCD donor liver rather than waiting for a future offer of a better quality donor liver.[16]

Given that proportionally the UK continues to be the primary proponent in the utilisation of DCD livers it is important to identify whether temporal improvements in patient and graft survival have been observed. Also, with high rates of graft failure reported previously[9], and re-transplantation as the only life-saving option in this event, it is important to investigate whether the rate of re-transplantation has changed over time. Using data from the Standard National Liver Transplant Registry,[17] including all adult patients who received a liver transplantation between 2008 and 2016, we investigated whether there had been era-related changes (2008 to 2011 and 2012 to 2016) in the short and longer term post-transplant mortality for patients who received a DCD or DBD donor liver. In order to understand changes in patient survival we also investigated changes over time in the rate of graft failure, re-transplantation and in the incidence of post-operative complications. Finally, we provide an up-to-date comparison of post-transplant mortality in patients receiving DCD and DBD livers.

2. MATERIALS AND METHODS

2.1 Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains detailed information about all liver transplants carried

out in all eight liver transplant centers in the UK & Ireland.[17] It is managed by NHS Blood and Transplant.[17] This registry was used to identify recipients of a controlled DCD or DBD liver transplant and to capture information on donor and recipient characteristics, and post-transplantation post-operative complications recorded at 3 months, including HAT, biliary tract leak and biliary tract stricture, as well as date and cause of death and graft failure.[17]

2.2 Study Population

All patients aged 18 years or older who had received a first-time elective liver transplant between 1st January 2008 and 31st December 2016 were eligible for inclusion (Figure S1, Supporting information). Recipients were dichotomized into two groups: those transplanted using a DCD liver and those transplanted using a DBD liver. To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multi-visceral, super-urgent, domino or living-related liver transplantations were excluded as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). We also excluded patients whose survival data were missing.

Patients were grouped according to the date of transplantation into two successive eras of transplantation: era 1: 1st January 2008 – 31st December 2011 and era 2: 1st January 2012 – 31st December 2016. The start of the study was chosen to coincide with the introduction into the UK & Ireland in 2008 of donor allocation policies that were based on predicted waiting list mortality.[18]

2.3 Donor and recipient characteristics

Recipients' functional status at the time of transplantation was assessed using a 5-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'.[19] The UKELD score, derived from the International Normalized Ratio (INR), and from the serum bilirubin, sodium and creatinine, was used to score the recipients' severity of the liver disease[18] and values for ethnicity were categorized into white and non-white groups. Changes over time in overall donor quality was measured using the UK Donor Liver Index (DLI), derived from donor age, sex, height, type (DCD donor or not), serum bilirubin, smoking history, and whether the liver was split, with larger values representing poorer donor livers.[20] Cold ischemic time (CIT) was defined as the duration between start of cold perfusion in the donor to start of blood flow through the organ in the recipient.[21] Warm ischemic time (WIT) was separated into agonal and asystolic time-periods.[22] The agonal time was defined as the period between withdrawal of life-sustaining treatment and circulatory arrest and the asystolic time was defined from the time of circulatory death to the time the donor liver was placed in cold storage.[22]

2.4 Donor and recipient selection and organ procurement

All DCD donors included in this analysis were procured under controlled circumstances where potentially life-sustaining treatment was withdrawn after further intervention was deemed futile (Maastricht III), or circulatory death occurred in a DBD donor (Maastricht IV).[2] Criteria for DCD donor selection and post-withdrawal hemodynamic parameters varied among liver transplant center but broadly followed the experience detailed by

Muiesan et al.[23] Administration of heparin or prior dissection of femoral vessels is prohibited by UK law.[2] Death was declared at 5 minutes following cardiac arrest and all UK liver procurement centers used a super-rapid recovery technique, although the type of preservation fluid, bag pressure and the use of simultaneous perfusion techniques varied.[2]

During the study period, DBD and DCD donor liver allocation in the UK & Ireland was organized locally and centers selected recipients according to local criteria. Patients on local waiting lists were prioritized according to the UKELD scoring system that was designed to predict waitlist mortality.[18,24] The scoring systems did not award additional points to patients on the waiting list with HCC.[18,24]

2.5 Statistical analysis

Donor and recipient characteristics, post-operative complications, and cause of death and graft failure were described separately for DCD and DBD recipients. Biliary complications were stratified into those who required treatment for a biliary tract leak or a biliary tract stricture. Biliary complications were reported as complications in their own right and also as a cause of graft failure. Post-operative renal failure was defined as any patient requiring renal replacement therapy. Categorical variables were presented as proportions and continuous variables were presented as means with standard deviations. Patients transplanted for non-HCC indications who were subsequently found to have HCC, according to explant pathology, were analyzed on an intention-to-treat basis.

Kaplan-Meier methods were used to compare patient and graft survival between successive eras of transplantation. Follow-up was censored at 3-years after transplantation or on the last follow-up visit before 7th April 2017, whichever occurred earlier. Graft failure was defined as either re-transplantation or patient death. 3-year follow-up was chosen to reflect the time period in which most complications associated with DCD transplantation would be expected to occur.[2,25]

Multivariable Cox regression models were used to estimate hazard ratios (HRs) that represent the relative differences in post-transplant mortality and graft failure between eras of transplantation. To account for differences in outcomes between hospitals, a categorical variable for transplant center was fitted in each model.[26] To determine whether changes in donor and recipient characteristics had influenced the impact of era on post-transplant outcomes, we initially estimated the HRs without adjustment for recipient or donor characteristics, then with adjustment for recipient characteristics only, and finally with adjustments for both recipient and donor characteristics. Interaction terms were included in the models to investigate whether the effect of era differed according to whether a DCD or DBD liver had been used and also according to whether the effect of era on DCD or DBD liver transplantation differed if the recipient had been transplanted for HCC or non-HCC indications. The significance of all interaction terms was tested using the global Wald test. Re-transplantation rates were calculated with death being considered as a competing risk. Fine and Gray regression was used to estimate adjusted subdistribution hazard ratios to investigate the

differences in re-transplantation rates between era 1 and 2 with adjustment for donor and recipient characteristics.[21]

Three sensitivity analyses were also performed. First, the post-transplantation period was partitioned into two separate epochs of follow-up time and the impact of era on short and longer term mortality and graft failure was assessed.[28,29] The first epoch, up to 1-year after transplantation, was chosen to reflect the occurrence of biliary complications, acute rejection, PNF and re-transplantation and the second epoch from 1 year to 3-years to reflect the longer-term outcomes including the recurrence of primary liver disease.[24] In the second sensitivity analysis, we built a separate multivariable model for DCD donor liver recipients and estimated the HR between eras of transplantation, this time including WIT in the case-mix adjustment as well as all other donor and recipient factors. In the final sensitivity analysis, we additionally adjusted for transplant center volume in the risk models assessing 3-year patient and graft survival. Transplant center annual volumes of DCD and DBD transplants were measured separately. In line with previous studies, transplant center DCD volume was dichotomized into greater or fewer than 20 DCD transplants per year and transplant center DBD volume into greater or fewer than 50 DBD transplants per year.[30]

Missing donor and recipient characteristics were imputed using chained equations creating ten complete datasets.[31] In the imputation procedure, all of the donor and recipient variables used in the case-mix adjustment were used to predict missing values, including the outcome variables.[32] The Cox regression results for each of these datasets were pooled using Rubin's rules.[31] Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A p-value smaller than 0.05 was considered statistically significant.

3.0 RESULTS

3.1 Era-specific changes in donor and recipient characteristics

We included 4925 adult recipients of first elective liver transplants performed between 1st January 2008 and 31st December 2016. Of these recipients, 1176 (23.9%) received a DCD liver and 3749 (76.1%) a DBD liver. The use of DCD livers increased markedly from being used in 16.1% (74/459) of the recipients in 2008 to 30.3% (193/637) in 2016 (Figure 1).

Comparing donor characteristics, we found that recipients of DCD livers were more likely to have male donors, to have received livers with evidence of capsular damage sustained during retrieval, but they were less likely to have received a liver with signs of steatosis and the average CIT was shorter than recipients of DBD livers (Table 1). Only considering DCD recipients, there were no era-related differences in warm ischemic time.

Comparing recipient characteristics, recipients of DCD livers were more likely to have hepatocellular carcinoma (HCC) as the primary indication for the transplantation and to have blood group O (Table 1).

However, they were less likely to be inpatients immediately before the transplantation and to have had previous abdominal surgery. Over time, donor and recipient characteristics remained largely unchanged.

3.2 Era-specific changes in post-transplantation outcomes

Across the two eras of transplantation, a significant improvement in patient mortality was identified in recipients of a DCD donor liver but not in those who received a DBD donor liver. Three-year patient mortality in DCD donor liver recipients decreased from 19.6% (95%CI: 15.9% to 24.1%) in era 1 to 10.4% (95%CI: 7.9% to 13.8%) in era 2 (p<0.001, Figure 2) whilst DBD recipient mortality decreased only from 12.8% (95%CI: 10.3% to 13.6%) to 11.3% (95%CI: 9.7% to 13.1%) (p=0.70). In recipients of DCD donor livers, a non-significant improvement in overall graft failure (defined as failure of graft or death) was observed from 24.6% (95%CI: 20.5% to 29.4%) in era 1 to 21.2% (95%CI: 17.9% to 25.1%) (p=0.17, Figure 3) in era 2. No era-related improvements in graft failure were observed in recipients of a DBD donor liver.

Following case-mix adjustment, the pattern of results remained the same. Comparing era 2 to era 1, post-transplant mortality decreased by 57% (HR 0.43, 95%CI: 0.30-0.62, p<0.001, Table 2) in those who received a DCD donor liver whilst in those who received a DBD donor liver no statistically significant improvements in mortality were observed (HR 0.96, 95%CI: 0.78 to 1.19, p=0.73, Table 2). For graft failure at 3-years, no statistically significant era specific improvements were identified for either DCD (HR 0.80, 95%CI: 0.61 to 1.05, p=0.11) or DBD donor liver recipients (HR 0.95, 95%CI: 0.79 to 1.14, p=0.60, Table 3).

The results presented above demonstrate that 3-year mortality in era 2 was lower in recipients of DCD livers than in recipients of DBD livers but this difference was not statistically significant (adjusted hazard ratio, 0·78 [95%CI, 0·56-1·09, p=0.14]) but 3-year graft loss was increased in recipients of DCD livers (adjusted hazard ratio, 1.71 [95%CI, 1.33-2.18, p<0.001]).

3.3 Era-specific changes in re-transplantation

Considering death as a competing event, we found an increase in the 3-year re-transplantation rate in recipients of DCD livers from 7.3% in era 1 to 11.8% in era 2 (p=0.04) and a decrease in recipients of DBD livers from 4.9% in era 1 to 4.5% in era 2 (p=0.36). However, these changes were not statistically significant with adjustment for donor and recipient characteristics neither in recipients of a DCD liver (adjusted subdistribution hazard ratio, 1.47 [95%CI,0.91-2.36, p=0.12]) nor in recipients of a DBD liver (adjusted subdistribution hazard ratio, 0.88 [95%CI, 0.63-1.23, p=0.45]). Neither was there statistically significant evidence that the changes in the re-transplantation rate over time differed between donation type (p interaction=0.05). We also found that only 2.0% (7/348) of all patients who underwent a re-transplantation received a DCD donor liver as their second donor graft and all of these patients (n=7) had received a DCD donor liver for their first transplant.

3.4 Era-specific changes in post-operative complications

Table 3 shows a decrease in the frequency of post-operative renal failure in recipients of a DCD liver (20.9% to 14.0%, p<0.001) but an increase of this frequency in recipients of a DBD liver (11.5% to 18.2%, p<0.001). Another remarkable change was the increase in portal thrombosis in recipients of a DBD liver from 1.5% in era 1 to 4.2% in era 2 (p<0.001).

3.5 Era-specific changes in causes of death and graft failure, and in re-transplantation

In recipients of a DCD liver, there was a reduction between era 1 and era 2 in the proportion of patients dying within 3 years from sepsis related causes (8.5% (31/363) to 3.1% (25/813), p<0.001, Table S2, Supplementary material), cardiac failure (2.2% (8/363) to 0.2% (2/813), p<0.001) and tumour recurrence (1.9% (7/363) to 0.4% (3/813), p=0.008). In recipients of a DBD liver, there were no such reductions in deaths from these causes, and the only significant improvements were in the proportion of patients dying from recurrence of benign disease (0.5% (8/1 520) to 0.0% (0/2 229), p<0.001) and in those whose deaths were recorded as unknown (0.9% (14/1 520) to 0.2% (5/2 229), p=0.003).

There was little era-specific change in causes of graft failure both for recipients of DCD livers and for recipients of DBD livers, except for a decrease in the frequency of recurrent liver disease – including HCV and cholestatic liver diseases (Table S3, Supporting information).

3.6 Sensitivity analyses

In a sensitivity analysis exploring era-related improvements in distinct epochs of follow-up time, statistically significant era-related improvements in mortality and graft failure from 0 to 1-year were observed for DCD donor liver recipients (HR: 0.32, 95%CI: 0.21 to 0.51 and HR: 0.69, 95%CI: 0.50 – 0.96, respectively, Table S4, Supporting information) but not for DBD donor liver recipients (HR: 0.91, 95%CI: 0.73-1.13 and HR: 0.94, 95%CI: 0.73-1.23). In the epoch of follow-up time from 1 to 3-years no era-related improvements were seen in either cohort (Table S4, Supporting information).

In all multivariable models, adjustment for recipient characteristics, and for both recipient and donor characteristics combined, had only a small impact on the time trends observed in post-transplant mortality or graft failure. This is a result of the recipient and donor characteristics remaining largely stable over time. Similarly, in the second sensitivity analysis, additional adjustment for donor WIT in DCD donor liver recipients had very little impact on the pattern of results (Table S5, Supporting information). In the final sensitivity analysis, additional adjustment for transplant centre volume also had little impact of era on patient mortality (aHR: 0.43, 95%CI: 0.30-0.61) or on graft failure (aHR: 0.95, 95%CI: 0.77-1.18) and transplant centre volume was not found to be an independent risk factor for either outcome (aHR: 1.08, 95%CI: 0.75-1.55, p=0.67 and aHR: 0.97, 95%CI: 0.75 – 1.24, p=0.79). Global Wald tests found that era-related differences in post-transplant mortality or graft failure did not differ according to whether patients were transplanted for HCC or non-HCC indications, within either the

DCD or DBD cohort (patient mortality; p=0.62 and p=0.40 for DCD and DBD cohorts respectively and graft failure; p=0.09 and p=0.59, for DCD and DBD cohorts respectively).

4.0 DISCUSSION

4.1 Summary of results

In the UK & Ireland in the last 9 years, the number of first-time single-organ elective liver transplant recipients who received a DCD liver has continually increased. In the same period, DCD recipients were increasingly more likely to receive a liver that either had evidence of capsular damage or had an appearance documented as abnormal. However, mortality has more than halved for those who received a DCD liver whilst remaining unchanged in recipients of a DBD liver. In particular, there have been significant decreases in DCD recipients who died from septic and cardiac related causes.

4.2 Comparison with other studies

An analysis of the United Network for Organ Sharing (UNOS) database, including 3199 DCD recipients from 2003 to 2014 demonstrated era-related improvements in both patient mortality and graft failure[9] whilst a meta-analysis published in 2014 and representing the results from 24 studies and 24 204 patients identified biliary complications in 26% of DCD recipients compared to 16% of DBD recipients (OR: 2.4, 95%CI: 1.9-3.1; p<0.00001).[9,33] However, we could not find a multinational study that had explicitly investigated temporal trends in donor type specific mortality and graft failure according to epoch of follow-up or that had also described era-related changes in the incidence of post-operative complications, causes of death, causes of graft failure or re-transplantation.

4.3 Explanation of results

Increases in the utilization of DCD donor livers that were observed in our study can be linked to a prolonged period of a relative decline in the rate of DBD liver donation.[34] Recent UK policy documents indicate that during the period of this study, increases in the overall donation rates in the UK & Ireland were almost entirely due to the expansion of DCD programmes.[34] It was acknowledged that compared with many other countries the rate of DBD donation for many years in the UK was 'strikingly' low and attributable to a consistency in the clinical decision-making process that limited or withdrew treatments to patients with non-survivable brain injuries before brainstem death has evolved or can be diagnosed.[34] In fact, in the UK & Ireland it was estimated that one quarter of all patients who fulfilled the pre-conditions of brain-stem death testing did not actually have tests for brainstem death carried out.[34]

In contrast, the proliferation of DCD transplantation in the UK & Ireland is likely a reflection of the number of deaths in intensive care that follow a decision to withdraw life-sustaining treatments that are considered to be of no benefit to the critically ill patient.[35] Therefore, increases in DCD liver donation can at least at an institutional level be attributed to the resolution of legal and ethical obstacles to this form of donation.[35] In this context, DCD donation at a professional level, may also now be viewed as part of the care that a person might wish to receive

at the end of their lives.[35] This perspective toward DCD donation in the UK & Ireland, is reflected in annual reports of liver transplant activity indicating DCD retrieval rates increasing from 178 from 2008 to 2009 to 294 from 2016 to 2017 with the utilization of these livers also increasing from 67% to 74%.[36-37]

We observed massive era-related improvements in patient mortality but only for DCD recipients and only in the first year following transplantation. Potentially important in explaining such a marked reduction in the early post-transplant mortality are reductions in both the proportions of DCD patients who died as a result of sepsis, cardiac failure, and tumor recurrence and the proportion of patients whose post-operative rehabilitation was complicated by renal failure. This most likely indicates a learning curve has been obtained not only in the selection of operative candidates who are able to tolerate the systemic ischemic reperfusion effects of DCD transplantation but also in the peri and post-operative care that they receive.[9]

The era-related improvements in graft survival that were identified were again limited to DCD recipients and again only found to be significant in the first year after transplantation. These improvements are likely attributable to a multitude of factors that may include improvement in surgical and endoscopic techniques (the latter for the post-operative treatment of biliary complications), reductions in overall ischemic times, and a more optimal allocation of DCD donor livers to patients with primary liver diseases – particularly HCC patients - that do better with this type of donation.[5-9]

A failure to demonstrate improved longer term graft survival in either DCD or DBD recipients is more difficult to explain especially as in our analysis we did not demonstrate center specific volume to significantly impact graft failure (or mortality) in either those receiving a DCD or a DBD donor liver. It is possible that an overall deterioration in the quality of donors and the inability for the retrieval of DCD donors to fully mitigate against the deleterious effects of the inevitable WIT – including biliary complications - could have prevented era-related improvements in longer-term graft loss.[5-9,11] However, in this context it should also be noted that even in the first era of the study, rates of graft failure for both DCD and DBD donor cohorts were more than acceptable. Therefore, observed improvements in overall 3-year graft survival were only going to be marginal and most likely inhibited by a deterioration in donor quality that was incompletely captured by the risk adjustment in this analysis.

4.4 Methodological limitations

There are several limitations to our study. First, our adjustment for recipient and donor characteristics may not have fully captured variations in how patients were selected for liver transplantation over the 9 years of the study period. However, given that we adjusted for a wide range of characteristics it is implausible that changes over time in patient selection would explain such large changes in post-transplantation outcomes. Second, the frequency of HAT and biliary complications following transplantation identified in our study may represent an underestimation of their true frequency.[28] These post-transplantation complications, although known to be rare, can be quiescent in their clinical presentation, especially HAT where the rapid development of collateral

circulation can quickly compensate for occlusion of the hepatic artery.[29] However, we note that the frequency of complications that we found is consistent with other studies. [28,31] In the context of biliary complications, we must also acknowledge that our dataset did not allow us to stratify biliary tract strictures according to whether they were either non-anastomotic and more associated with DCD livers or anastomotic and associated also with technical failure.[7-9] Third, we did not have more granular information on cause of death or graft failure recorded as 'other'. This hindered our ability to identify – in more depth – potential causes of era-related changes in post-transplantation outcomes.

4.5 Implications of findings

An increasingly limited potential donor pool, less than optimal DBD donation rates, and increases in the number of patients with HCC who require liver transplantation indicate that the use of DCD donor livers is set to remain.[4,16,33] Therefore, the major implication of this study is for the international transplant community and in particular countries with high waiting list mortalities and low rates of DCD utilisation,[38] especially as mortality following liver transplantation now appears to be comparable for patients receiving DCD and DBD donor livers. However, we must also acknowledge that although the use of DCD livers has dramatically increased the donor pool, approximately 10% of first-time elective DCD liver recipients still require a re-transplantation and the graft used for the re-transplantation has historically come from the limited pool of DBD donors. Yet this may be a situation that is acceptable to both patients and service providers, especially if it improves the prognosis of the primary liver disease that led to the need for transplantation and helps to reduce waiting list mortalities.

5.0 CONCLUSION

Between 2008 and 2016, the number of patients receiving a DCD donor liver graft in the UK & Ireland increased significantly. During the same time-period mortality in these patients more than halved and survival following liver transplantation now appears to be comparable for patients receiving DCD and DBD donor livers. These results are important for countries with high waiting list mortalities and low rates of DCD utilisation.

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THE ROLE OF FUNDING SOURCES

The funder of the study, National Institute for Health Research, had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. DW and JvdM had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

NIHR STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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FIGURES

Figure 1: Time-trends in the utilization of DCD livers (n=4925).

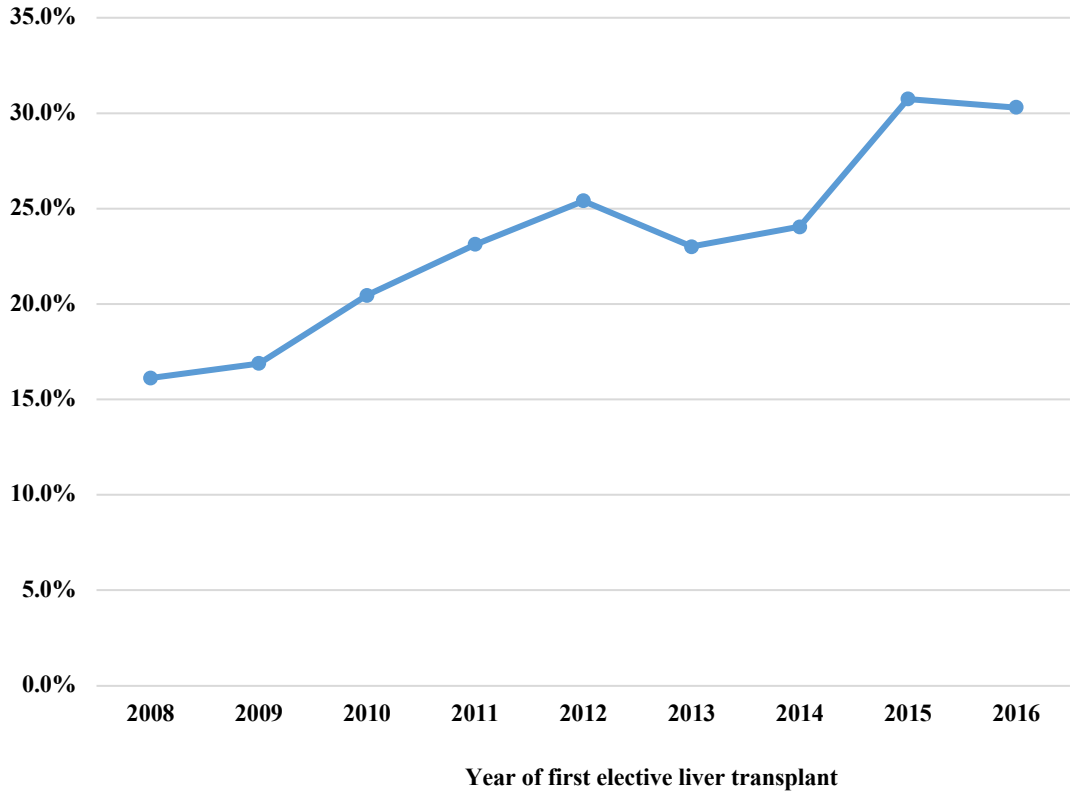
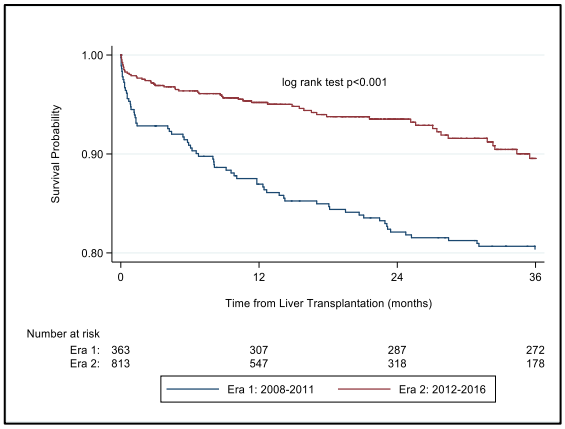


Figure 2: 3-year patient survival across different eras of transplantation (2008-2011 and 2012-2016) in recipients receiving DCD or DBD livers (n=4925).

a. DCD (n=1176)



b. DBD (n=3749)

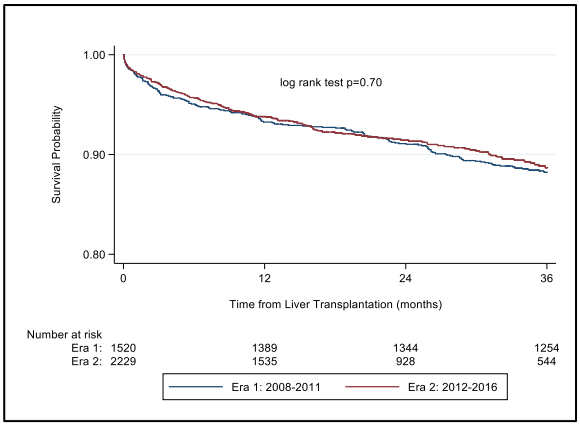
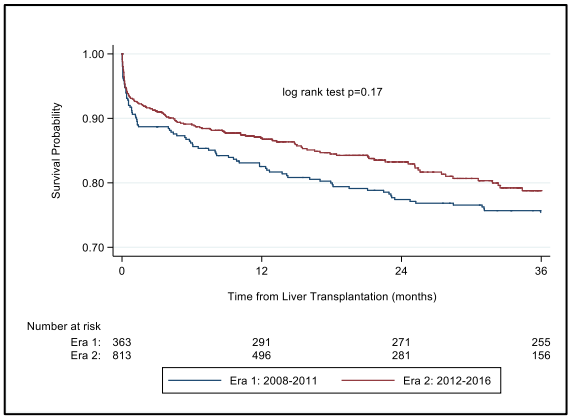
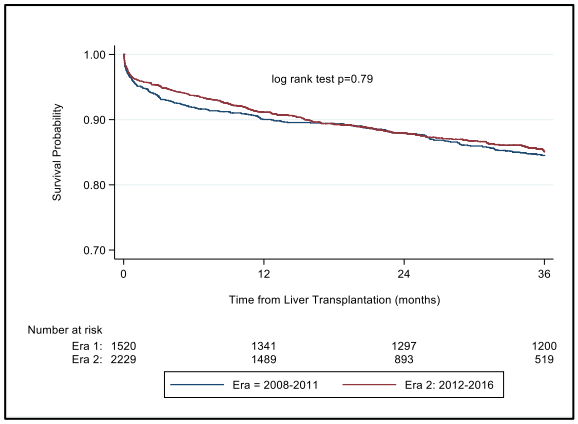


Figure 3: 3-year graft survival across different eras of transplantation (2008-2011 and 2012-2016) in recipients receiving DCD or DBD livers (n=4925).

a. DCD (n=1176)



b. DBD (n=3749)



TABLES

Table 1: Donor and recipient characteristics according to era and stratified by donor type (n=4925).

			ERA OF TRANSPLANTATION		
		Overall 2008-2016	ERA 1: 2008-2011	ERA 2: 2012-2016	Missing values
Number	**DCD recipients**	**1 176**	**363**	**813**	
	DBD recipients	**3 749**	**1 520**	**2 229**	
DONOR CHARACTERISTICS					
Female	DCD	40·3% (474)	42·2% (153)	39·5% (321)	0.0% (0)
	DBD	48·4% (1 813)	49·5% (752)	47·6% (1 061)	0.0% (0)
Age (years)	DCD	48·0 (16·3)	45·0 (15·8)	49·3 (16·4)	0.0% (0)
	DBD	49·6 (16·0)	48·3 (15·6)	50·5 (16·2)	0.0% (0)
BMI (kg/M^2)	DCD	25·5 (4·6)	25·0 (4·7)	25·6 (4·9)	0.2% (2)
	DBD	26.6 (5·0)	25.3 (3·9)	26.8 (5·1)	0.2% (8)
Trauma as cause of death	DCD	10·7% (126)	16·8% (61)	8·0% (65)	0.0% (0)
	DBD	7·2% (270)	8·6% (131)	6·2% (139)	0.0% (0)
Hepatic steatosis	DCD	38·4% (446)	35·5% (128)	39·8% (318)	1·3% (15)
	DBD	47·9% (1 764)	48·9% (728)	47·3% (1 036)	1·8% (69)
Presence of capsular damage	DCD	20·3% (236)	18·3% (66)	21·3% (170)	1·3% (15)
	DBD	12·2% (447)	13·8% (206)	11·0% (241)	2·1% (77)
Abnormal donor liver appearance	DCD	30·7% (296)	35·1% (93)	29·0% (203)	17·9% (211)
	DBD	22·5% (716)	24·7% (310)	21·1% (406)	15·2% (570)
Segmental Graft Type	DCD	0·1% (1)	0·3% (1)	0·0% (0)	0.0% (0)
	DBD	10·7% (402)	11·3% (172)	10·3% (230)	0.0% (0)
CIT (mins)	DCD	438·7 (121·3)	423·8 (107·7)	445·6 (126·6)	8.2% (97)
	DBD	536·2 (160·7)	548·3 (133·6)	527·5 (163·8)	7·9% (296)
Donor Liver Index (DLI)	DCD	1.93 (0.40)	1.89 (0.38)	1.99 (0.40)	3.1% (36)
	DBD	1.16 (0.23)	1.14 (0.23)	1.17 (0.23)	3.7% (139)
WIT (mins) – Agonal phase	DCD	15.3 (7.6)	15.9 (7.8)	15.0 (7.??)	26.2% (308)
	DBD	N/A	N/A	N/A	N/A
WIT (mins) – Asystolic	DCD	11.0 (40.9)	11.8 (4.0)	10.6 (48.7)	7.7% (91)
	DBD	N/A	N/A	N/A	N/A
Abomatch - identical	DCD	97.5% (1 147)	95.6% (347)	98.4% (800)	0.0% (0)
	DBD	98.8% (3 703)	98.9% (1 504)	98.7% (2 199)	0.0% (0)
RECIPIENT CHARACTERISTICS					
Female	DCD	32·7% (383)	31·3% (113)	33·3% (270)	0·4% (5)
	DBD	32·7% (1 218)	34·2% (518)	31·7% (700)	0·7% (25)
Age (Years)	DCD	54·6 (9·8)	54·2 (9·5)	54·9 (9·6)	0.0% (0)
	DBD	52·4 (11·8)	52·1 (11·4)	52·6 (12·1)	0.0% (0)
Non-white ethnicity	DCD	13·0% (153)	16·3% (59)	11·6% (94)	0·1% (1)
	DBD	12·3% (462)	13·7% (208)	11·4% (254)	0·03% (1)
HCC indication for transplant	DCD	31.9% (375)	32.8% (119)	31.5% (256)	0.0% (0)
	DBD	22.1% (830)	23.6% (359)	21.1% (471)	0.0% (0)
BMI (Kg/M^2)	DCD	27.2 (4·9)	26.8 (4·6)	27.4 (5·0)	0.1% (1)
	DBD	27.3 (5·3)	26.9 (5·0)	27.6 (5·4)	0.1% (4)
UKELD***	DCD	53.7 (5·1)	54.1 (5·5)	53.5 (4·9)	1.0% (12)
	DBD	55.0 (5·8)	54.9 (5·9)	55.1 (5·7)	0.7% (28)
Waiting list time (days)	DCD	133.1 (147.0)	113.6 (114.2)	141.9 (158.9)	0.4% (5)
	DBD	157.7 (199.4)	144.0 (162.6)	161.5 (204.6)	0.6% (24)
Blood Group O	DCD	46.5% (545)	47.9% (173)	45.9% (372)	0.4% (5)
	DBD	39.4% (1 469)	39.3% (595)	39.5% (874)	0.6% (24)
Functional status: Self-care****	DCD	42·4% (491)	39·3% (139)	43·7% (352)	1·4% (17)
	DBD	45·9% (1 699)	46·1% (693)	45·8% (1 006)	1·9% (46)
Ascites	DCD	52·0% (608)	49·6% (180)	53·0% (428)	0·5% (6)
	DBD	54·0% (2 018)	52·0% (789)	55·3% (1 229)	0·3% (10)
Previous variceal bleed	DCD	26·4% (306)	30·9% (112)	24·3% (194)	1·3% (15)
	DBD	24·1% (1892)	25·0% (378)	23·4% (514)	1·1% (41)
Encephalopathy	DCD	29·1% (337)	27·4% (99)	29·8% (238)	1·4% (16)
	DBD	27·0% (1 629)	28·9% (435)	32·6% (706)	0·4% (16)
Presence of HCV antibodies	DCD	22·7% (254)	25·4% (87)	21·6% (167)	5·0% (59)
	DBD	19·1% (674)	22·9% (317)	16·7% (357)	5·9% (223)
Inpatient prior to transplant	DCD	9.6% (113)	13.0% (47)	8.1% (66)	0.2% (2)
	DBD	14.8% (554)	15.8% (240)	14.1% (314)	0.1% (4)
Renal support prior to transplant	DCD	4.6% (54)	5.5% (20)	4.2% (34)	0.2% (3)
	DBD	4.8% (180)	3.6% (54)	5.7% (126)	0.2% (12)
Previous abdominal surgery	DCD	7.3% (85)	9.7% (35)	6.2% (50)	0.3% (4)
	DBD	13.3% (497)	14.1% (214)	12.7% (283)	0.3% (11)
Re-transplantation rate (within 3-years)	DCD	9.1% (108)	7.2% (26)	10.1% (82)	0.0% (0)
	DBD	4.2% (157)	4.9% (74)	3.7% (83)	0.0% (0)

**Liver donated following circulatory death.*
***Includes donor factors; DCD, segmental graft, height, age, smoking status and bilirubin*
****United Kingdom Model for End-stage Liver Disease.*
*****3rd level of 5-point scale assessing patient's pre-transplantation functional status*

Table 2: The effect of era on 3-year post-transplant mortality in patients receiving a DCD (n=1176) or DBD (n=3749) donor liver.

	ERA OF TRANSPLANTATION		
STATUS OF CASE-MIX ADJUSTMENT	**ERA 1: 2008-2011**	**ERA 2: 2012-2016**	**P-value for the effect of era**
	Hazard ratio		
DCD PATIENTS			
Unadjusted	**1**	0·45 (0·32-0·64)	<0.001
Adjusted for recipient characteristics only*	**1**	0.44 (0.31–0.62)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0.43 (0.30-0.62)	<0.001
DBD PATIENTS			
Unadjusted	**1**	0.94 (0.76-1.16)	0.57
Adjusted for recipient characteristics only*	**1**	0.96 (0.78-1.18)	0.70
Adjusted for recipient and donor characteristics**	**1**	0.96 (0.78-1.19)	0.73

** Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery and transplant unit*

***Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, and cold ischemic time*

Table 3: The effect of era on 3-year graft failure in patients receiving a DCD (n=1176) or DBD (n=3749) donor liver.

	ERA OF TRANSPLANTATION		
STATUS OF CASE-MIX ADJUSTMENT	**ERA 1: 2008-2011**	**ERA 2: 2012-2016**	**P-value for the effect of era**
	Hazard ratio		
DCD PATIENTS			
Unadjusted	**1**	0·83 (0·63-1·09)	0.18
Adjusted for recipient characteristics only*	**1**	0.82 (0.62-1.08)	0.15
Adjusted for recipient and donor characteristics**	**1**	0.80 (0.61-1.05)	0.11
DBD PATIENTS			
Unadjusted	**1**	0.93 (0.78-1.11)	0.57
Adjusted for recipient characteristics only*	**1**	0.95 (0.79-1.14)	0.56
Adjusted for recipient and donor characteristics**	**1**	0.95 (0.79-1.14)	0.60

***** *Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery and transplant unit.*

***Adjusted for recipient characteristics listed above <u>and</u> donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, and cold ischemic time.*

Table 4: Post-operative complications reported at 3 months and stratified by donor type (n=4925).

			Era of transplantation		
		Overall 2008-2016	**Era 1: 2008-2011**	**Era 2: 2012-2016**	**p-value for the effect of era**
Number	**DCD recipients**	**1 176**	**363**	**813**	
	DBD recipients	**3 749**	**1 520**	**2 229**	
BILIARY COMPLICATIONS					
Biliary Tract Leak	DCD	5.8% (68)	4.7% (17)	6.3% (51)	0.31
	DBD	5.3% (199)	4.9% (75)	5.6% (124)	0.42
Biliary Tract Stricture	DCD	6.3% (74)	5.0% (18)	6.9% (56)	0.24
	DBD	4.4% (163)	3.8% (57)	4.8% (106)	0.16
VASCULAR COMPLICATIONS					
Hepatic artery thrombosis	DCD	3.9% (46)	5.0% (18)	3.4% (28)	0.24
	DBD	2.8% (106)	3.3% (50)	2.5% (56)	0.17
Portal vein thrombosis	DCD	3.2% (38)	3.3% (12)	3.2% (26)	0.93
	DBD	3.1% (116)	1.5% (22)	4.2% (94)	<0.001
IVC occlusion	DCD	1.2% (14)	1.1% (4)	1.2% (10)	0.85
	DBD	1.0% (37)	1.3% (19)	0.8% (18)	0.18
Hemorrhage	DCD	7.1% (84)	7.2% (26)	7.1% (58)	0.99
	DBD	6.5% (243)	7.6% (115)	5.7% (128)	0.04
INFECTION					
Sepsis**	DCD	37.1% (436)	33.6% (122)	38.6% (314)	0.26
	DBD	36.8% (1 381)	34.6% (526)	37.4% (855)	0.11
RENAL FAILURE					
Renal Failure	DCD	19.1% (224)	20.9% (76)	14.0% (312)	<0.001
	DBD	13.0% (487)	11.5% (175)	18.2% (148)	<0.001

*Includes sepsis from bacterial, fungal and viral infections.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

1. Figure S1: Flow chart detailing selection of study population (2008-2016).

2. Table S1: A comparison of patient mortality and graft failure between DCD (n=813) and DBD livers (n=2 229) in era 2 (2012-2016).

3. Table S2: The impact of era of transplantation on the post-transplantation outcomes in first 1-year and from 1-year to 3 years in DCD (n= 1 176) and DBD recipients (n=3 749).

4. Table S3: The effect of era on 3-year post-transplant mortality and graft failure in patients receiving a DCD liver (n=1 176) and including warm ischemic time (WIT) in the case mix-adjustment.

5. Table S4: Cause of death following liver transplantation stratified by donor type (n=4 925).

6. Table S5: Cause of graft failure following liver transplantation stratified by donor type (n=4 925).

SUPPORTING INFORMATION

Figure S1: Flow chart detailing selection of study population (2008-2016).

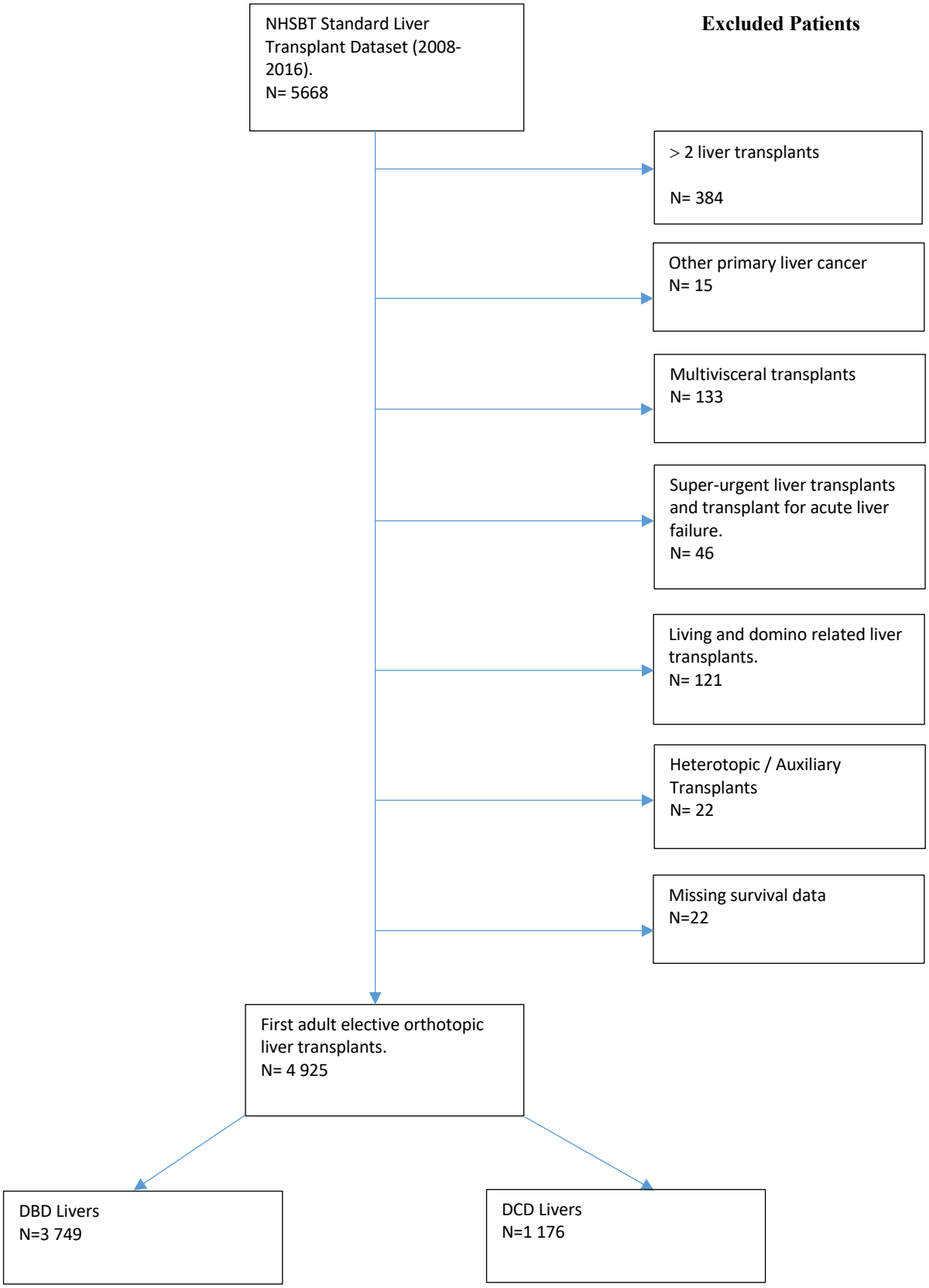


Table S1: A comparison of patient mortality and graft failure between DCD (n=813) and DBD livers (n=2229) in era 2 (2012-2016).

	DCD compared to DBD Hazard ratio (95%CI)			
STAUTS OF CASE-MIX ADJUSTMENT	**Post-transplant patient mortality**	**P-value**	**Post-transplant graft failure**	**P-value**
Unadjusted analysis	0·85 (0.62-1.14)	0.28	1·52 (1·24-1·89)	<0.001
Adjusted for recipient characteristics*	0.79 (0.58-1.08)	0.14	1·59 (1·28-2·00)	<0.001
Adjusted for recipient and donor characteristics**	0·78 (0·56-1·09)	0.14	1.71 (1·33-2·18)	<0.001

***** *Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M²), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery and transplant unit.*

***Adjusted for recipient characteristics listed above <u>and</u> donor characteristics: sex, age, BMI (Kg/m²), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, and cold ischemic time.*

Table S2: Cause of death following liver transplantation stratified by donor type (n=4925).

Cause of Death	Overall		Era 1: 2008-2011		Era 2: 2012-2016	
	DCD (n=1176)	**DBD (n=3749)**	**DCD (n=363)**	**DBD (n=1 520)**	**DCD (n=813)**	**DBD (n=2229)**
	126 deaths	**363 deaths**	**70 deaths**	**177 deaths**	**56 deaths**	**186 deaths**
Recurrence of disease – malignant*[1]	0.9% (10)	0.6% (25)	1.9% (7)	0.9% (14)	0.4% (3)	0.5% (11)
Recurrence of disease – benign*[2]	0.1% (1)	0.2% (8)	0.3% (1)	0.5% (8)	0.0% (0)	0.0% (0)
Malignancy – other*[3]	0.8% (9)	1.1% (41)	1.1% (4)	1.2% (18)	0.6% (5)	1.0% (23)
Sepsis	4.8% (56)	3.5% (131)	8.5% (31)	4.1% (63)	3.1% (25)	3.1% (68)
Graft Dysfunction*[4]	0.3% (3)	0.2% (9)	0.6% (2)	0.6% (1)	0.1% (1)	0.4% (8)
Haemorrhage	0.5% (6)	0.4% (14)	1.1% (4)	0.1% (6)	0.2% (2)	0.4% (8)
Pulmonary failure	0.6% (7)	0.7% (25)	1.1% (4)	0.7% (11)	0.4% (3)	0.6% (14)
Renal failure	0.1% (1)	0.0% (0)	0.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Cardiac failure	0.9% (10)	0.6% (21)	2.2% (8)	0.5% (8)	0.2% (2)	0.6% (13)
Gastrointestinal failure	0.2% (2)	0.1% (5)	0.3% (1)	0.1% (1)	0.2% (2)	0.2% (4)
CVA	0.0% (0)	0.3% (10)	0.0% (0)	0.3% (4)	0.0% (0)	0.3% (6)
Other*[5]	1.2% (14)	1.5% (55)	0.8% (3)	8.0% (29)	1.4% (11)	1.2% (26)
Unknown	0.6% (7)	0.5% (19)	1.1% (4)	0.9% (14)	0.4% (3)	0.2% (5)

*[1] *Recurrence of malignant disease for patients transplanted for non-HCC indications likely represents recurrence of a intrahepatic malignancy only identified on explant pathology or an error in the recording cause of death*
*[2] *Includes the recurrence of HCV and the cholestatic liver diseases (PSC & PBC).*
*[3] *Includes both lymphoid and non-lymphoid malignant disease.*
*[4] *Includes uraemia caused by graft failure*
*[5] *Specified only as 'other cause of death' in Standard National Liver Transplant Registry.*

Table S3: Cause of graft failure following liver transplantation stratified by donor type (n=4 925).

Cause of Graft Failure	Overall 2008 - 2016		Era 1: 2008 - 2011		Era 2: 2012 - 2016	
	DCD (n=1176)	**DBD (n=3 749)**	**DCD (n=363)**	**DBD (n=1520)**	**DCD (n=813)**	**DBD (n=2 29)**
	201 failures	**440 failures**	**86 failures**	**219 failures**	**115 failures**	**221 failures**
Acute rejection	0.0% (0)	0.2% (7)	0.0% (0)	0.1% (2)	0.0% (0)	0.2% (5)
Chronic rejection	0.8% (9)	0.7% (26)	1.4% (5)	0.9% (13)	0.5% (4)	0.6% (13)
PNF	3.4% (40)	1.1% (40)	3.0% (11)	1.3% (19)	3.6% (29)	0.9% (21)
Acute vascular Occlusion	2.0% (24)	1.3% (49)	2.2% (8)	1.5% (23)	2.0% (16)	1.2% (26)
Vascular Occlusion	0.3% (3)	0.6% (22)	0.3% (1)	0.6% (9)	0.2% (2)	0.6% (13)
Non-thrombotic infarction	0.3% (4)	0.2% (8)	0.3% (1)	0.2% (3)	0.4% (3)	0.2% (5)
Ductopenic rejection	0.0% (0)	0.1% (2)	0.0% (0)	0.1% (2)	0.0% (0)	0.0% (0)
Recurrent disease*[1]	1.7% (20)	1.2% (45)	4.1% (15)	1.9% (29)	0.6% (5)	0.7% (16)
Biliary Complications	2.5% (29)	0.4% (15)	1.7% (6)	0.2% (3)	2.8% (23)	0.5% (12)
Graft still functioning at death	3.1% (36)	3.5% (133)	5.0% (18)	4.4% (67)	1.2% (18)	3.0% (66)
Other *	2.6% (30)	2.0% (76)	4.4% (16)	2.3% (35)	1.7% (14)	1.8% (41)
Unknown	0.5% (6)	0.5% (17)	1.3% (5)	0.9% (14)	0.1% (1)	0.1% (3)

**[1] Includes the recurrence of HCV and the cholestatic liver diseases (PSC & PBC).*

**[2] Specified only as 'other cause of graft failure' in Standard National Liver Transplant Registry.*

Table S4: The impact of era of transplantation on the post-transplantation outcomes in first 1-year and from 1-year to 3 years in DCD (n= 1176) and DBD recipients (n=3749).

	TIME PERIOD AFTER TRANSPLANTATION	
Patient mortality	**First 1-year**	**From 1-year to 3-years**
DCD recipients		
Era 1:	1	1
Era 2:	0.32 (0.21 - 0.51)	0.57 (0.31 – 1.06)
DBD recipients		
Era 1:	1	1
Era 2:	0.94 (0.73 – 1.23)	1.03 (0.72 – 1.47)
Graft failure		
DCD recipients		
Era 1:	1	1
Era 2:	0.69 (0.50 – 0.96)	0.94 (0.55 – 1.62)
DBD recipients		
Era 1:	1	1
Era 2:	0.91 (0.73 – 1.13)	1.13 (0.81 – 1.57)

***** *Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery, transplant unit, and donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, and cold ischemic time.*

Table S5: The effect of era on 3-year post-transplant mortality and graft failure in patients receiving a DCD liver (n=1 176) and including warm ischemic time (WIT) in the case mix-adjustment.

	ERA OF TRANSPLANTATION		
STATUS OF CASE-MIX ADJUSTMENT	**ERA 1: 2008-2011**	**ERA 2: 2012-2016**	**P-value for the effect of era**
	Hazard ratio		
PATIENT MORTALITY			
Unadjusted	**1**	0·44 (0·31-0·64)	<0.001
Adjusted for recipient characteristics only*	**1**	0.40 (0.28-0.58)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0.39 (0.27-0.57)	<0.001
GRAFT FAILURE			
Unadjusted	**1**	0.80 (0.61-1.06)	0.12
Adjusted for recipient characteristics only*	**1**	0.76 (0.58-1.01)	0.06
Adjusted for recipient and donor characteristics**	**1**	0.75 (0.56-1.00)	0.05

***** *Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery and transplant unit.*

****Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischemic time and, warm ischemic time*

6. Results Chapter

Research Paper 4

Title: Assessing the Time-Dependent Impact of Performance Status on Outcomes After Liver Transplantation

The results of this chapter have been presented in the form of a published paper. The supplementary information referred to in the paper is available at the end of the manuscript.

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Surname/Family Name	Wallace		
Thesis Title	Liver transplantation as a treatment for patients with hepatocellular carcinoma: a study using electronic health care data		
Primary Supervisor	Professor Jan van der Meulen		

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HEPATOLOGY

HEPATOLOGY, VOL. 72, NO. 4, 2020

Assessing the Time-Dependent Impact of Performance Status on Outcomes After Liver Transplantation

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BACKGROUND AND AIMS: Identifying how the prognostic impact of performance status (PS) differs according to indication, era, and time period ("epoch") after liver transplantation (LT) could have implications for selection and treatment of patients on the waitlist. We used national data from the United Kingdom and Ireland to assess impact of PS on mortality separately for HCC and non-HCC recipients.

APPROACH AND RESULTS: We assessed pre-LT PS using the 5-point modified Eastern Cooperative Oncology Group scale and used Cox regression methods to estimate hazard ratios (HRs) that compared posttransplantation mortality in different epochs of follow-up (0-90 days and 90 days to 1 year) and in different eras of transplantation (1995-2005 and 2006-2016). 2107 HCC and 10,693 non-HCC patients were included. One-year survival decreased with worsening PS in non-HCC recipients where 1-year survival was 91.9% (95% confidence interval [CI], 88.3-94.4) in those able to carry out normal activity (PS1) compared to 78.7% (95% CI, 76.7-80.5) in those completely reliant on care (PS5). For HCC patients, these estimates were 89.9% (95% CI, 85.4-93.2) and 83.1% (95% CI, 61.0-93.3), respectively. Reduction in survival in non-HCC patients with poorer PS was in the first 90 days after transplant, with no major effect observed between 90 days and 1 year. Adjustment for donor and recipient characteristics did not change the findings. Comparing era, post-LT mortality improved for HCC (adjusted HR, 0.55; 95% CI, 0.40-0.74) and non-HCC recipients (0.48; 95% CI, 0.42-0.55), but this did not differ according to PS score (P = 0.39 and 0.61, respectively).

CONCLUSIONS: Impact on mortality of the recipient's pretransplant PS is principally limited to the first 3 months after LT. Over time, mortality has improved for both HCC and non-HCC recipients and across the full range of PS. (Hepatology 2020;72:1341-1352).

Patients with cirrhosis with chronic liver disease (CLD) may develop multiple complications that impact upon their functional or performance status (PS)—the ability to perform activities of daily living.[1-3] This deterioration in condition reflects the development of a "frail" state, with contribution from many of the clinical sequelae of liver cirrhosis, including ascites, encephalopathy, sarcopenia, and hepatocellular carcinoma (HCC).[1,4]

Measurements of PS are designed to capture a global assessment of health status as opposed to identifying the specific effects of particular organ dysfunction.[3,5-7] A variety of metrics are available to quantify

Abbreviations: CI, confidence interval; CLD, chronic liver disease; DCD, donation after cardiac death; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; IRQ, interquartile range; KM, Kaplan-Meier; LT, liver transplantation; NHSBT, National Health Service Blood and Transplant; PS, performance status; UKELD, United Kingdom Model for End-Stage Liver Disease.

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The funder of the study, National Institute for Health Research, had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. D.W. and J.v.d.M. had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

PS, and a subjective, but reproducible, one of these is through recording of PS scores—patient-reported or clinician-recorded assessments of patients' ability to care for themselves.[3] In multiple epidemiological analyses, ratings of overall health status have been found to be powerful predictors of subsequent mortality, with the suggestion that computation of perceived health captures information beyond that identified through specific measurements of end-organ function.[7,8]

In patients on the transplant waitlist, impaired PS has been shown to have important adverse effects on quality of life as well as survival.[5,6,9] In patients who have received a liver transplant (LT), the impact of pretransplant PS on posttransplant survival is less well described. One commonly used PS score shown to have a strong association with mortality in nontransplanted patients with CLD is the Eastern Cooperative Oncology Group (ECOG) scale.[10] The first published analysis of the impact of impaired PS on post-LT survival followed analysis of the UK liver transplant registry and found impaired PS to be a strong and independent risk factor on posttransplant mortality.[3] However, this study used data from almost two decades ago and may not represent the current outcomes of LT.[3] Furthermore, it only explored survival up to 90 days after transplantation, and the longer-term impact of impaired PS on mortality remains relatively unknown.

Since that report, major advances in perioperative care and immunosuppressive strategies[11] have occurred, which may have altered the prognostic impact of impaired PS scores on posttransplant mortality. Determining how the association between PS scores and posttransplant mortality has changed over time and how it changes according to different posttransplantation time periods ("epochs") could have important implications in the selection and counseling of patients and for initiation of interventions on the waitlist and in the postoperative period. Similarly, in the past decade, the number of recipients with hepatocellular carcinoma (HCC) has increased,[11] yet the specific impact of PS on posttransplant mortality in this select group of patients also remains unknown.[12] This has the potential to be very different because, at the time of transplantation, HCC recipients are often in a better physical condition with fewer manifestations of end-stage liver disease than patients without HCC, but with advanced CLD, who have deteriorating liver function and its resulting complications.[11]

Given the increasing appreciation of the clinical impact of frailty on the outcome of transplantation in patients with CLD, we investigated the impact of PS on posttransplant mortality, separately for recipients with and without HCC. Using data from the Standard National Liver Transplant Registry,[13] including all adult patients who had an LT between 1995 and 2016 in the United Kingdom and Ireland, the impact of PS on patient mortality was estimated in the short and longer term and according to era of transplantation.

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Patients and Methods

STANDARD NATIONAL LIVER TRANSPLANT REGISTRY

The Standard National Liver Transplant Registry contains detailed information about all LTs carried out since 1984 in the eight LT centers in the United Kingdom and Ireland.[13] The data set is currently managed by National Health Service Blood and Transplant (NHSBT),[13] and regular checks indicate that the data are consistently >93% complete and accurate and results from several studies confirm the validity of the data set.[3] The use of national data for the purpose of the research described in this paper was approved by the NHS Health Research Authority's Confidentiality Advisory Group (17/CAG/0025) and Research Ethics Committee (17/LO/0231).

STUDY POPULATION

All adults (aged ≥18 years) who received a first LT between January 1, 1995 and December 31, 2016 were eligible for inclusion (Fig. 1). To select a sample of LT recipients that was representative of clinical practice, recipients who underwent multivisceral transplants or superurgent transplants and those who required intensive therapy unit (ITU) support (ventilation and/or dialysis) before transplantation were included. Those whose survival data were missing and those in which a PS score was not recorded before their transplant were excluded. Recipients were categorized into two groups: patients transplanted with HCC mentioned in any of three diagnosis fields available in the Standard National Liver Transplant Registry (HCC patients) and patients transplanted with other liver disease diagnoses (non-HCC patients).[13] Patients transplanted for non-HCC indications who were subsequently found to have HCC on explant pathology were analyzed on an intention-to-treat basis and remained in the non-HCC cohort.[11]

A modified version of the ECOG scale was used to measure recipients' PS on a 5-point scale (Table 1), ranging from "able to carry out normal activity without restriction'" (PS1) to "completely reliant on nursing/medical care" (PS5).[3,10] Measurements of PS were assessed by clinicians either at the time of transplantation or at the most recent clinic before surgery. Self-reports of functional ability were included in the assessment of patients' PS.[3,13]

Severity of recipients' liver disease was assessed using the United Kingdom Model for End-Stage Liver Disease (UKELD) score.[14] Cold ischemic time was defined as the duration between start of cold perfusion in the donor to start of blood flow through the organ in the recipient.[15] All livers that were donated after cardiac death (DCD) were procured under controlled circumstances where cardiac arrest either followed the planned withdrawal of life-sustaining treatments (Maastricht III) or occurred in a patient who was brain dead (Maastricht IV).[16] Ethnic background was categorized into white and nonwhite groups.

STATISTICAL ANALYSIS

Donor and recipient characteristics and cause of death were described separately for HCC and non-HCC recipients and according to the 5-point ECOG scale. Categorical variables are presented as proportions and continuous variables presented as medians with interquartile ranges (IQRs). In accord with recent Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, we did not apply significance tests to the patient characteristics included in descriptive tables.[17]

Kaplan-Meier (KM) methods were used to compare patient survival between successive levels of PS score, separately for HCC and non-HCC patients. Follow-up was censored at 1 year after transplantation or on the last follow-up visit before December 31, 2016, whichever occurred earlier. Patients alive at their last follow-up visit were considered to be censored observations.

Multivariable Cox regression models were used to estimate difference in posttransplant mortality across the different levels of PS, separately for HCC and non-HCC recipients, adjusting for all donor and recipient characteristics in Table 2. Interaction terms were included in the Cox models to determine whether prognostic impact of PS varied according to time period ("epoch")[18] after transplantation and according to era of transplantation. Epochs of 0-90 days and 90 days to 1-year posttransplant were chosen to reflect impact of PS during the immediate postoperative period and its impact on longer-term survival, respectively. Partitioning eras of transplantations between 1995 and 2005 and 2006 and 2016 was chosen to capture the introduction of urgency-based allocation policies in 2006 and the transplantation of

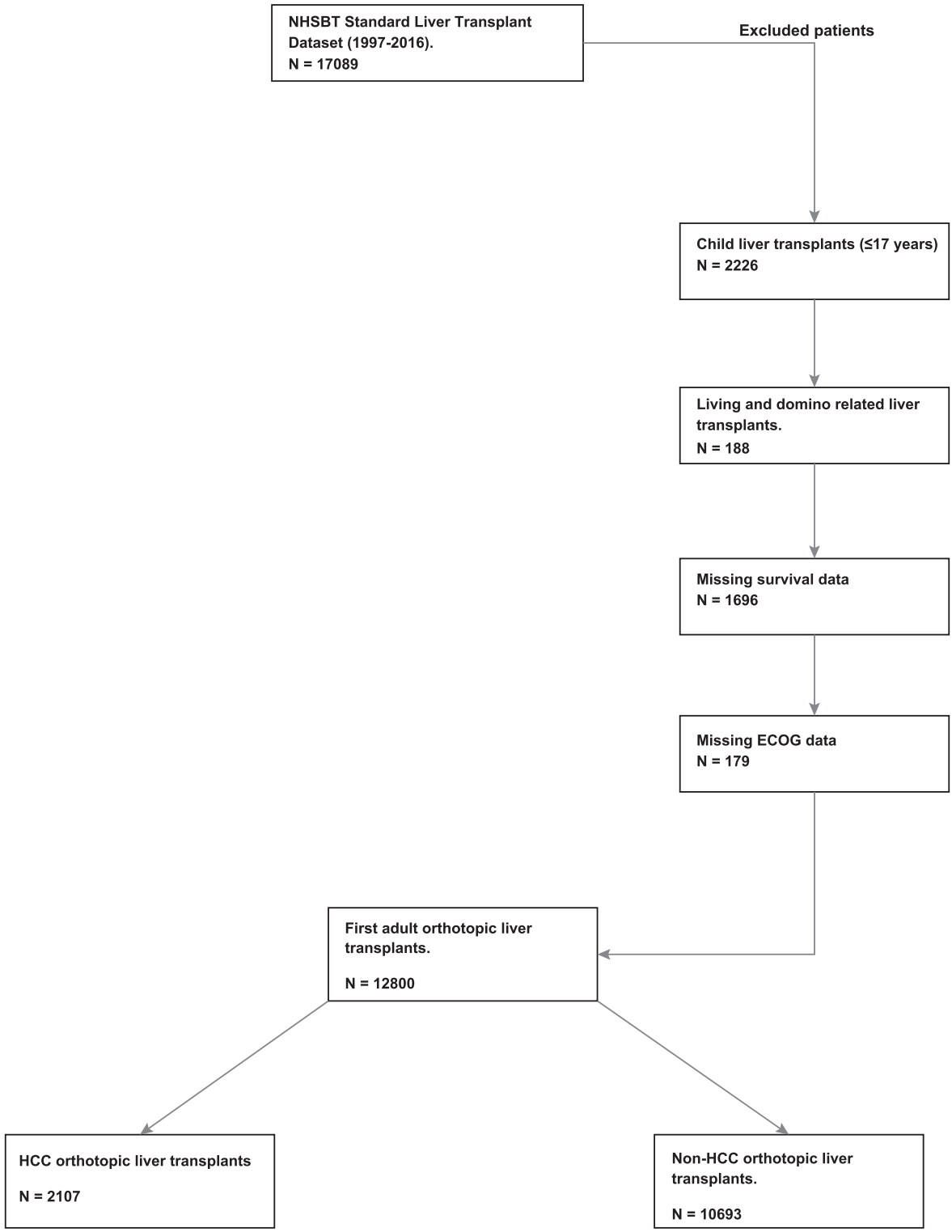


FIG. 1. Flow chart presenting selection of study population (January 1, 1995 to December 31, 2016).

patients with more severe liver disease.[19] In the Cox models that were used to test the time-dependent effect of PS, "self-care" (PS3) was used as the reference value given that it was the largest group.[3] Statistical significance of the interaction terms in each model was tested using the global Wald test.

TABLE 1. Modified ECOG PS

PS Score	Description
1	Able to carry out normal activity without restriction
2	Only restricted in physically strenuous activity
3	Can move freely. Capable of self-care. Unable to do any form of work
4	Only capable of limited self-care. Confined mostly to bed or chair
5	Completely reliant on nursing/medical care

To assess the influence that liver disease severity had on the prognostic impact of PS, adjusted hazard ratios (HRs) for the effect of PS on posttransplant mortality were estimated with and without adjustment for: UKELD, ascites, varices, and encephalopathy (with all other donor and recipient characteristics included in both models). All risk adjustment included adjusting for differences across levels of the ECOG scale in those who received a multiorgan or superurgent transplantation, those who had been transplanted in the presence of acute liver failure and or cirrhosis, and those who required preoperative ITU support.

Three sensitivity analyses were performed. First, effect of PS on mortality was assessed having collapsed HCC and non-HCC patients with the worst PS scores (PS score of 4 or 5) into a single group, because of small numbers of HCC patients in these two groups. Second, effect of PS of mortality was compared between Cox models that did and did not adjust for multivisceral transplants, superurgent transplants, and those who required ITU support before transplantation. Third, additional adjustment for tumor characteristics were applied to the Cox model that assessed impact of PS on mortality for HCC patients, allowing us to specifically assess how tumor burden influenced the association between PS and posttransplant mortality. Included in this model were measurements of maximum tumor diameter, total tumor diameter, number of tumors, and alpha-fetoprotein levels (ng/mL).

Missing donor and recipient characteristics were imputed with multiple imputation using chained equations, creating 10 complete data sets.[20] In the imputation procedure, all donor and recipient variables in the regression analyses were used to predict missing values, including the outcome variables.[20] HRs for each of these data sets were pooled using Rubin's rules.[20] Stata software (V15; StataCorp LP, College Station, TX) was used for all statistical analyses.

Results

PATIENT CHARACTERISTICS

A total of 12,800 adult LTs were recorded as performed between 1995 and 2016, of which 2,107 were for HCC recipients and 10,693 for non-HCC recipients (Table 2). The number of HCC recipients increased from 29 in 1995 to 130 in 2016. PS was poorer for non-HCC patients, with almost one-third of non-HCC patients having PS4 or 5 compared to only 1 in 15 for HCC patients. Those recipients who had poorer PS scores also had more severe liver disease (as captured by UKELD) and were more likely to have encephalopathy. They were also more frequently required to be inpatients or to require renal support before their transplant. HCC recipients were more likely to be male, older, and they also more often received grafts that were DCD or grafts in which the appearance had been documented as "abnormal."

KM SURVIVAL ANALYSIS

KM survival curves showed that impaired PS was associated with poorer patient survival in non-HCC patients (log rank, $P < 0.001$; Fig. 2), but not in HCC recipients (log rank, $P = 0.17$). For non-HCC patients, the difference in survival between recipients with PS1 and 5 appeared most marked in the first months after transplantation, resulting in a 1-year patient survival of 91.9% (95% confidence interval [CI], 88.3-94.4) and 78.7% (95% CI, 76.7-80.5), respectively.

MULTIVARIABLE COX REGRESSION

Risk adjustment did not change these findings (Fig. 3; Supporting Tables S1 and S2). In a multivariable Cox model comparing impact of PS scores in the different epochs of follow-up, survival of non-HCC patients was progressively worse with poorer PS scores (Fig. 3; Supporting Table S1), with evidence of a larger effect in the first 3 months' posttransplant (P for interaction between PS and epoch, <0.001). In the first 90 days following transplantation, mortality of non-HCC recipients with PS score of 5 was almost double that of recipients with PS3 (HR, 1.89; 95% CI, 1.42-2.61). There was no statistical evidence of any further effect of PS score on survival from 90 days

TABLE 2. Donor and Recipient Characteristics According to PS (n = 12,800)

		Modified ECOG Status					
		ECOG 1	ECOG 2	ECOG 3	ECOG 4	ECOG 5	
	HCC recipients	247	830	891	115	24	
No.	Non-HCC recipients	330	2,208	4,933	1,486	1,736	Missing Values
Donor characteristics							
Female sex	HCC	43.3% (106)	41.5% (344)	41.6% (369)	50.4% (58)	54.2% (13)	0.2% (5)
	Non-HCC	45.3% (149)	49.2% (1,086)	46.4% (2,288)	48.9% (727)	49.8% (865)	0.1% (10)
Age (years)	HCC	49 (37-60)	49 (36-60)	49 (37-58)	51 (34-61)	52 (37-57)	0.0% (0)
	Non-HCC	46 (31-56)	48 (35-59)	47 (34-57)	48 (36-57)	46 (33-56)	0.0% (0)
BMI (kg/m^2)	HCC	25 (22-28)	26 (23-28)	25 (23-28)	26 (23-29)	26 (25-27)	3.8% (80)
	Non-HCC	25 (22-28)	25 (23-28)	25 (23-28)	25 (23-28)	25 (22-27)	6.6% (705)
Trauma as cause of death	HCC	13.4% (33)	14.2% (118)	14.3% (127)	10.4% (12)	8.3% (2)	0.0% (0)
	Non-HCC	16.1% (53)	13.0% (286)	15.8% (777)	16.1% (239)	16.8% (292)	0.0% (0)
DCD donor	HCC	15.0% (37)	24.5% (203)	15.3% (136)	16.5% (19)	16.7% (4)	0.0% (0)
	Non-HCC	6.4% (21)	15.9% (352)	8.9% (440)	6.1% (90)	1.7% (29)	0.0% (0)
Abnormal organ appearance	HCC	18.9% (46)	24.3% (159)	25.8% (215)	21.0% (21)	22.7% (5)	12.0% (253)
	Non-HCC	11.5% (37)	20.1% (367)	19.9% (927)	19.1% (257)	15.2% (236)	9.2% (983)
Segmental graft type	HCC	5.3% (13)	5.9% (49)	4.8% (43)	2.6% (3)	4.2% (1)	0.0% (0)
	Non-HCC	8.5% (28)	8.3% (184)	6.5% (322)	4.9% (73)	4.7% (81)	0.0% (0)
Cold ischemic tine (min)	HCC	556 (435-671)	514 (410-655)	522 (421-660)	600 (442-716)	485 (394-620)	7.1% (149)
	Non-HCC	565 (453-701)	558 (439-697)	587 (457-720)	589 (466-719)	554 (441-679)	5.8% (619)
Recipient characteristics							
Female sex	HCC	15.0% (37)	20.6% (171)	18.5% (165)	25.2% (29)	25.0% (6)	0.0% (0)
	Non-HCC	43.3% (143)	40.5% (894)	40.3% (1 987)	42.7% (635)	58.8% (1,020)	0.9% (1)
Age (years)	HCC	58 (53-63)	58 (52-63)	58 (52-63)	57 (52-61)	59 (50-62)	0.0% (0)
	Non-HCC	50 (40-58)	52 (43-59)	53 (45-59)	53 (44-59)	40 (29-52)	0.0% (0)
BMI (kg/m^2)	HCC	25 (22-28)	26 (23-28)	25 (23-28)	26 (23-29)	26 (25-27)	3.8% (80)
	Non-HCC	25 (22-28)	25 (23-28)	25 (23-28)	25 (23-28)	25 (22-27)	6.6% (705)
Nonwhite ethnicity	HCC	13.4% (33)	17.5% (145)	18.0% (160)	14.8% (17)	20.8% (5)	0.1% (1)
	Non-HCC	9.2% (30)	9.9% (219)	12.3% (606)	14.0% (208)	14.3% (247)	0.1% (9)
Liver-only transplant	HCC	100% (247)	99.4% (825)	99.6% (887)	99.1% (114)	100% (24)	0.0% (0)
	Non-HCC	98.2% (324)	98.4% (2 172)	97.7% (4 821)	97.6% (1 450)	99.4% (1 725)	0.0% (0)
Elective transplant	HCC	100% (247)	100% (830)	100% (891)	100% (115)	95.8% (23)	0.0% (0)
	Non-HCC	93.0% (307)	99.6% (2 199)	99.6% (4 911)	89.9% (1,336)	23.0% (399)	0.0% (0)
Encephalopathy	HCC	3.4% (8)	10.5% (86)	10.9% (97)	34.8% (40)	73.9% (17)	1.1% (24)
	Non-HCC	14.6% (46)	21.6% (474)	24.8% (1,218)	50.1% (756)	89.6% (1,537)	0.8% (90)
Previous abdominal surgery	HCC	20.7% (50)	12.7% (105)	13.5% (120)	19.3% (22)	8.3% (2)	0.6% (12)
	Non-HCC	16.5% (54)	14.3% (315)	16.2% (795)	15.0% (221)	9.3% (160)	0.4% (42)
Ventilatory support	HCC	0.4% (1)	0.1% (1)	0.0% (0)	0.0% (0)	12.5% (3)	0.1% (1)
	Non-HCC	4.6% (15)	0.3% (6)	0.2% (12)	1.9% (28)	61.0% (1 057)	0.1% (8)
Renal support	HCC	9.3% (23)	3.4% (28)	3.5% (31)	9.6% (11)	20.8% (5)	0.2% (5)
	Non-HCC	10.0% (33)	5.1% (113)	5.2% (253)	9.9% (146)	50.6% (874)	0.4% (41)
Inpatient before transplant	HCC	2.0% (5)	1.6% (13)	4.4% (39)	41.7% (48)	87.5% (21)	0.0% (0)
	Non-HCC	10.6% (35)	4.0% (88)	8.1% (400)	60.2% (894)	97.4% (1,690)	0.02% (3)
UKELD	HCC	49 (46-52)	50 (48-53)	51 (48-55)	56 (51-60)	61 (56-63)	3.0% (64)
	Non-HCC	54 (51-57)	54 (51-58)	55 (52-59)	58 (55-63)	61 (57-67)	19.3% (2,065)

Abbreviation: BMI, body mass index.

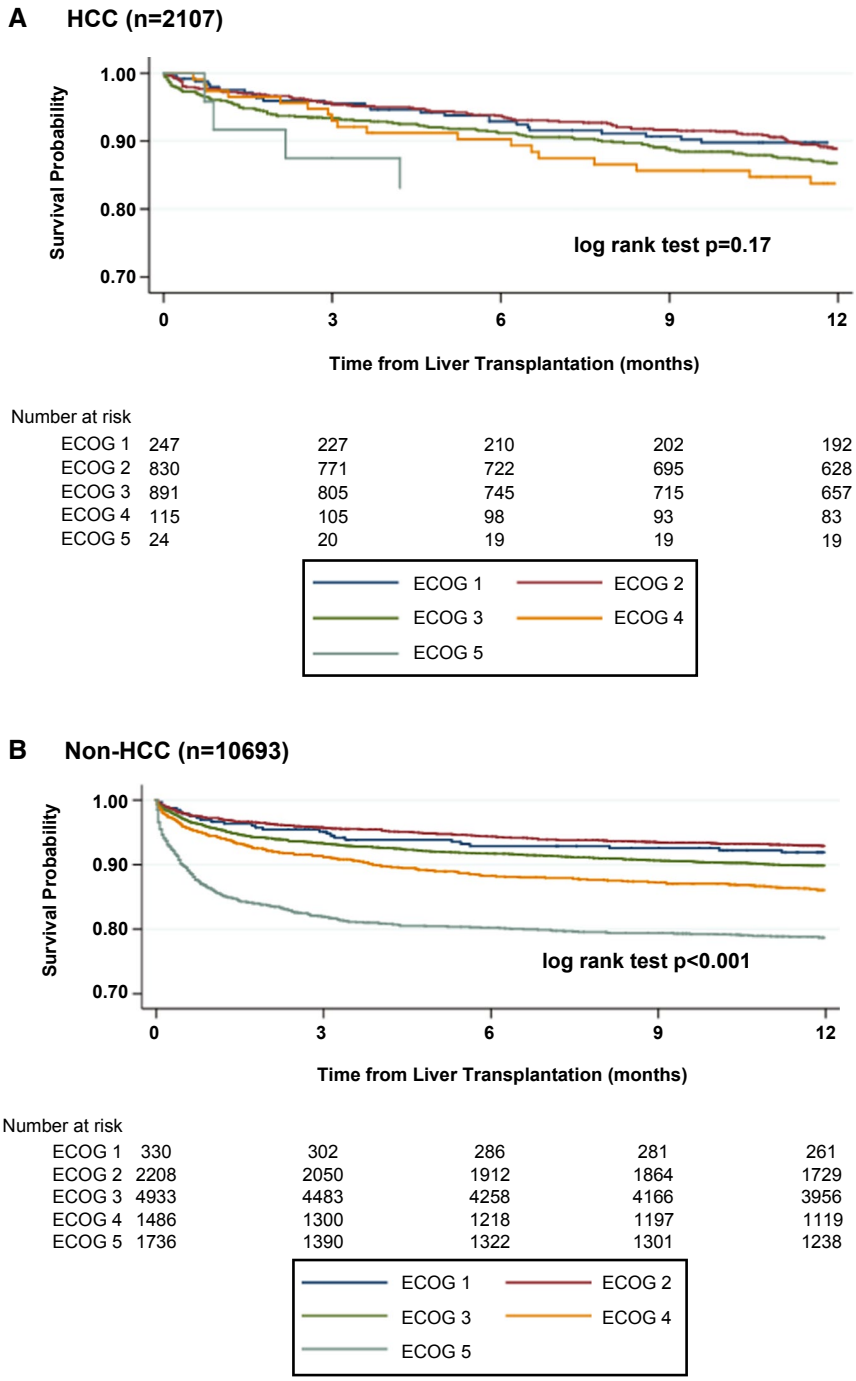
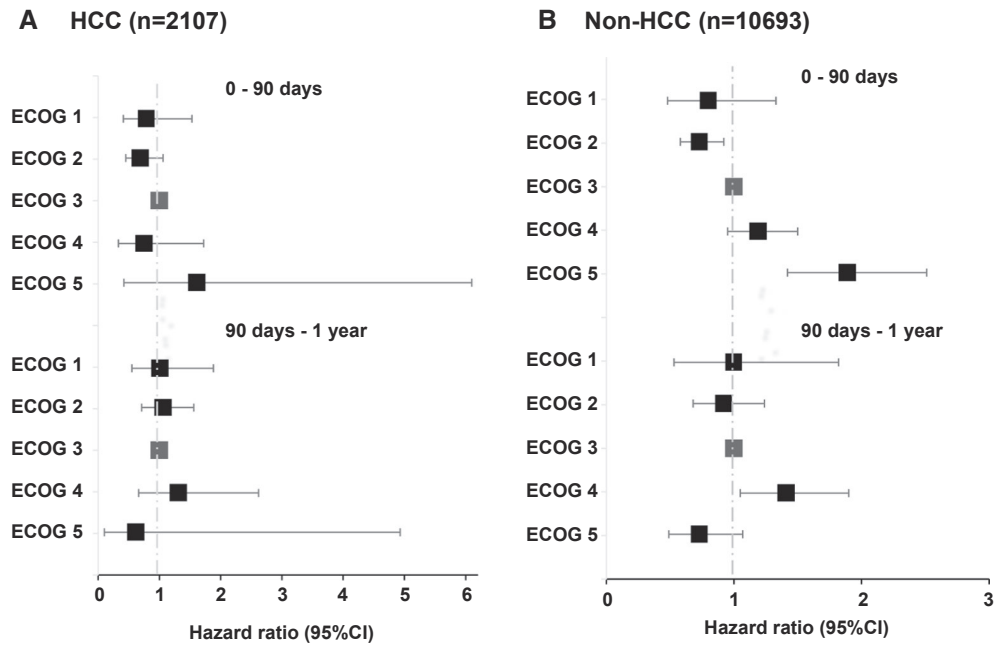


FIG. 2. Impact of PS on posttransplant survival for HCC (A) and non-HCC (B) patients (n = 12,800).

to 1 year in non-HCC recipients overall, although an increased mortality was observed in those with PS4 compared to those with PS3 (HR, 1.41; 95% CI, 1.05-1.90). No effect of PS score on survival was found in HCC recipients, either in the first 3 months or from 3 months to 1 year posttransplant (*P* for interaction between PS and epoch = 0.44; Fig. 3; Supporting Table S2). Adjustment for measures of liver disease severity had little impact on these comparisons (Supporting Tables S1 and S2).

In the multivariable Cox model that compared impact of PS over different eras of transplantation,



*ECOG 3 (blue plot) indicates reference value of 1.
**Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m²), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M²), ascites, varices, encephalopathy, cirrhosis, previous abdominal surgery, abomatch, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, urgency of transplantation, acute liver failure, transplant type (liver only, liver & kidney, liver 7 other), era of transplantation.

FIG. 3. Adjusted impact of PS on patient survival in two separate epochs of follow-up time in HCC (A) and non-HCC (B) patients (n = 12,800). Abbreviations: BMI, body mass index; HCV, hepatitis C virus.

improvements in overall mortality were observed in both HCC and non-HCC cohorts (Table 3). However, there was no evidence that improvements in survival over time differed between those with different PS scores, and this was the same for both HCC and non-HCC recipients (*P* for interaction between era and PS = 0.39 and 0.61, respectively). In the sensitivity analyses, the effect of combining those with the worst PS scores into one stratum had no impact on the analysis that assessed the impact of PS in different epochs or the analysis that assessed PS according to era (Supporting Table S3 and footnote of Table 3, respectively). Similarly, there was no difference in the pattern of results when comparing HRs of the Cox models that had or had not adjusted for multivisceral transplants, superurgent transplants, or pretransplantation ITU support (Supporting Tables S1 and S2-S4) or in the Cox model that for HCC patients had adjusted for tumor characteristics (Supporting Tables S2 and S5). However, progressively poorer performance status was associated with recipients more frequently dying from sepsis in both HCC and non-HCC recipients (Supporting Table S6).

Discussion

SUMMARY OF RESULTS

At the time of transplantation, almost 1 in 3 non-HCC patients were either confined to a bed or chair (PS4) or completely reliant on care (PS5), compared to 1 in 15 HCC patients. PS at the time of transplantation was found to be independently associated with posttransplantation mortality, but only in non-HCC recipients and principally within the first 3 months following transplantation. Improvements in posttransplant mortality of HCC and non-HCC recipients over time appear to have occurred equally across all levels of PS.

COMPARISON WITH OTHER STUDIES

Few studies have examined the association between PS scores before transplantation and subsequent mortality. A national study in the United Kingdom and Ireland, published 16 years ago and using PS scores based on the ECOG scale taken

TABLE 3. Effect of Era on Posttransplant Mortality of HCC (n = 2,107) and Non-HCC Recipients (n = 10,693) in the First Year After LT and According to PS

	Overall	Modified ECOG Score					*P* Value for Interaction[†]
		ECOG 1	ECOG 2	ECOG 3	ECOG 4	ECOG 5	
HCC							
Era 1: 1995-2005	1	1	1	1	1	1	0.39
Era 2: 2006-2016*	0.55 (0.40-0.74)	0.51 (0.22-1.17)	0.77 (0.47-1.26)	0.43 (0.29-0.66)	0.39 (0.15-1.03)	Not available[‡]	
Non-HCC							
Era 1: 1995-2005	1	1	1	1	1	1	0.61
Era 2: 2006-2016*	0.48 (0.42-0.55)	0.70 (0.32-1.51)	0.51 (0.37-0.72)	0.44 (0.35-0.54)	0.54 (0.41-0.73)	0.48 (0.38-0.60)	

*Adjusted for donor characteristics: donor sex, donor age, donor BMI (kg/m^2), cause of death, donor type (DCD, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischemic time, and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (kg/m^2), ascites, varices, encephalopathy, cirrhosis, previous abdominal surgery, abomatch, HCV status, UKELD, pretransplant inpatient status, pretransplant renal support, pretransplant ventilatory support, urgency of transplantation, acute liver failure, transplant type (liver only, liver and kidney, and liver and other), and era of transplantation.
[†]Wald test to determine whether the HRs for era differ significantly by ECOG.
[‡]ECOG 4 and 5 combined for HCC patients to create combined era effect HR 0.51 (95% CI, 0.22–1.17).
Abbreviations: BMI, body mass index; HCV, hepatitis C virus.

from the same data set as in this analysis, observed a similar pattern of results as described in our study.[3] They found that recipients who were completely reliant on care (PS5) before transplantation were significantly more likely to die within 90 days of their transplant than those capable of self-care (PS3). A more recent U.S. study, including 50,417 transplants identified in the United Network of Organ Sharing database between 2006 and 2016, also found pretransplant measurements of PS (using the Karnofsky Score) to be independent predictors of posttransplant survival.[7]

However, to date no analysis has estimated the impact of PS on mortality separately for HCC and non-HCC patients or specifically investigated how that impact has changed according to epoch of follow-up or era of transplantation.

EXPLANATION OF RESULTS

There are several possible explanations for the association between pretransplantation PS and shorter-term posttransplant mortality in non-HCC recipients. It could be that PS scores are a more inclusive and accurate measure of a patient's health status than more specific measurements of organ dysfunction and some of the clinical sequelae of CLD, such as sarcopenia or undernutrition.[3] PS scores may also better reflect behavior that influences the short-term outcome of transplantation.[3] For example, those with the poorer PS on the transplant waitlist are more likely to suffer from prolonged periods of immobilization, reduced physical activity, and an increased risk of perioperative death.[1,2] Finally, the limited association of PS on mortality beyond the early posttransplant period may reflect the relatively rapid reversal of the clinical sequelae of severe liver dysfunction that follows restoration of liver function by transplantation, as opposed to other extrahepatic chronic conditions that are not corrected and persist beyond the immediate posttransplant period and impact survival later.

In HCC recipients, there was no evidence of an association of PS and mortality. In the United Kingdom, HCC patients listed for transplantation tend to have more preserved liver function, fewer complications of end-stage liver disease, and low tumor burdens. This means that very few HCC patients have a significantly impaired PS at the time of transplantation, making it difficult to detect PS-specific

differences in posttransplant mortality even if they do exist. Therefore, although our results suggest that PS has less of an association with posttransplant mortality in HCC patients, a larger sample of waitlist patients with PS scores of 4 or 5 who have HCC would be needed to confirm this.

It is likely that improvements over time in posttransplant mortality reflect the effect of multiple interventions,[11] especially given that for HCC and non-HCC patients, these improvements were not found to differ according to PS score. Previous analysis by this research group has shown that, irrespective of PS, increased survival of both HCC and non-HCC recipients has largely been driven by a decreased rate of early postoperative death.[11] Advances in surgical technique, perioperative care, and, more specifically, in the prevention of sepsis-related complications are likely to be responsible for these improvements.[11,21]

METHODOLOGICAL LIMITATIONS

A first limitation is that the PS scores that were used in this study were reported by clinicians in the eight participating transplant centers. Although less prone to interobserver error than the more complex measurements of PS, agreement between clinicians' scoring of the ECOG status of patients has varied between a coefficient of 0.91 in some studies to as low as 0.50 in others.[22,23] If we assume in our analysis that a level of disagreement—somewhere between these two coefficients—occurred to the same extent in patients who survived and in those who died, the true effect of pretransplant PS on posttransplant mortality may have been larger than that observed in our study.[3]

Second, clinicians who were recording PS scores at the time of transplantation were not blinded to the other known risk factors of posttransplant mortality, including those measures of severe liver dysfunction.[3] This could have contributed to the observed association between PS and these risk factors. However, the association between PS scores and posttransplant mortality remained even after extensive adjustment for pretransplant factors, making it unlikely that a lack of blinding fully explains our findings.[3]

Finally, the small number of HCC patients who were reported to have the most severely impaired PS scores may have precluded the detection of significant differences in posttransplant mortality, especially in those patients who were reported to have a PS score of 4 or 5. However, when those with the worst PS score were collapsed into one stratum and a four-level modified ECOG scale was used, no difference in the association of PS and posttransplant mortality was observed in either HCC or non-HCC recipients.

CLINICAL AND METHODOLOGICAL IMPLICATIONS

Our observations in a national cohort of LT recipients in the United Kingdom and Ireland suggest that considering the PS of patients before transplantation, in addition to other conventional risk factors, improves the ability to predict posttransplant survival. These are important findings that are relevant to the assessment of the suitability of potential LT candidates in daily clinical practice. Also, despite an increasing reliance on complex prognostic models to predict outcome, these findings emphasize that asking patients traditional questions about their general health and well-being is still an important part of their clinical assessment that can help determine their suitability for transplantation and their risk of mortality after it.

The chief importance of the association between pretransplantation PS and posttransplant mortality lies in the potential for its modification through pretransplant and posttransplant interventions. These may encompass medical optimization, exercise therapies, and nutritional and psychological support. However, if interventions to address functional impairment are considered, we must acknowledge that the subjective nature of PS scores means that they may be best used as screening tools that can be used in a "frailty toolkit" alongside other more objective measures of PS.[24] In this utility, they could also be used to identify patients before transplantation who may benefit from targeted prehabilitative interventions[2,24] or patients following transplantation who are most vulnerable to early postoperative death. This is even more important now that it is known that beyond the first few months after transplantation, even those with the most impaired PS before their operation can have similar outcomes to those who had a much better PS score.

PS scores therefore help to identify those patients at greater risk of a poor posttransplant outcome, but do not definitively identify patients whose PS should

preclude them from receiving an LT. To aid in the selection of patients for LT, further research is needed to identify whether the characteristics of patients with PS5, which are associated with a poorer outcome, are potentially modifiable with prehabilitative interventions. It must also be established whether the postoperative implications of poor PS score in patients hospitalized before their transplant are the same as those who have a poor PS score but remain outpatients.

Finally, this study re-established the importance of analyzing posttransplant outcomes in distinct epochs of follow-up time.[18] By testing the prognostic impact of PS scores in different time periods, the relative impact of functional status on posttransplant outcomes could be quantified for HCC and non-HCC recipients.[18] This method of time-dependent analysis reintroduces, after decades, an exemplar of statistical modeling that is likely to be informative for a wider range of questions about determinants of outcomes after LT.[18]

Considering PS scores before transplantation, in addition to other conventional risk factors, improves the ability to predict posttransplant survival. Measurements of PS, while subjective, are still important initial tools in assessing the suitability of patients for transplantation and for identifying those patients who may benefit from targeted preoperative interventions that could improve their PS and subsequent posttransplant mortality.

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Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31124/suppinfo.

Table S1: The impact of performance status on post-transplant mortality in two separate epochs of follow-up time in non-HCC patients (n=10 693).

	Time-period after transplantation (Epoch)		
Patient Mortality	**Unadjusted**	**Adjusted for donor and recipient factors excluding measures of liver disease severity***	**Adjusted for all donor and recipient factors including measures of liver disease severity****
0 to 90 days			
ECOG 1:	0.72 (0.44 – 1.19)	0.77 (0.47 – 1.28)	0·80 (0·48 - 1·33)
ECOG 2:	0.63 (0.50 – 0.79)	0.73 (0.58 – 0.92)	0·73 (0·58 - 0·92)
ECOG 3:	**1**	**1**	**1**
ECOG 4:	1.32 (1.08 – 1.62)	1.24 (0.98 – 1.55)	1·19 (0·95 - 1·50)
ECOG 5:	2.91 (2.49 – 3.40)	2.02 (1.52 – 2.67)	1·89 (1·42 - 2·51)
90 days to 1-year			
ECOG 1:	0.91 (0.48 – 1.72)	0.96 (0.51 – 1.82)	1·00 (0·53 - 1·82)
ECOG 2:	0.79 (0.58 – 1.27)	0.91 (0.68 – 1.23)	0·92 (0·68 - 1·24)
ECOG 3:	**1**	**1**	**1**
ECOG 4:	1.53 (1.16 – 2.02)	1.47 (1.09 – 1.97)	1·41 (1·05 - 1·90)
ECOG 5:	1.08 (0.80 – 1.47)	0.78 (0.53 – 1.14)	0·73 (0·49 - 1·07)
P for interaction between ECOG and Epoch***	<0.001	<0.001	<0.001

***Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), cirrhosis, previous abdominal surgery, abomatch, HCV status, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, urgency of transplantation, transplant type (liver only, liver & kidney, liver & other), era of transplantation.*

***Adjusted for donor and recipient factors listed above but also including ascites, varices, encephalopathy UKELD*

**** Wald test to determine whether the hazard ratios from 0 to 90 days and from 90 days to 1-year differ significantly from each other.*

Table S2: The impact of performance status on post-transplant mortality in two separate epochs of follow-up time in HCC patients (n=2 107).

	Time-period after transplantation (Epoch)		
Patient Mortality	**Unadjusted**	**Adjusted for donor and recipient factors excluding measures of liver disease severity***	**Adjusted for all donor and recipient factors including measures of liver disease severity****
0 to 90 days			
ECOG 1:	0.66 (0.35 – 1.26)	0.76 (0.40 – 1.46)	0·79 (0·41 - 1·53)
ECOG 2:	0.64 (0.43 – 0.97)	0.67 (0.44 – 1.03)	0·69 (0·45 - 1·06)
ECOG 3:	**1**	**1**	**1**
ECOG 4:	0.90 (0.41 – 1.97)	0.77 (0.34 – 1.74)	0·75 (0·33 - 1·72)
ECOG 5:	1.90 (0.60 – 6.06)	1.56 (0.42 – 5.79)	1·61 (0·42 - 6·10)
90 days to 1-year			
ECOG 1:	0.86 (0.47 – 1.58)	0.98 (0.53 – 1.80)	1·01 (0·55 - 1·88)
ECOG 2:	0.99 (0.68 – 1.48)	1.03 (0.70 – 1.52)	1·06 (0·71 - 1·56)
ECOG 3:	**1**	**1**	**1**
ECOG 4:	1.59 (0.83 – 3.05)	1.34 (0.67 – 2.67)	1·31 (0·66 - 2·62)
ECOG 5:	0.71 (0.10 – 5.18)	0.59 (0.10 – 4.70)	0·62 (0·10 - 4·93)
P for interaction between ECOG and Epoch***	0.41	0.44	0.44

**Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), cirrhosis, previous abdominal surgery, abomatch, HCV status, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, urgency of transplantation, transplant type (liver only, liver & kidney, liver & other), era of transplantation.*

***Adjusted for donor and recipient factors listed above but also including ascites, varices, encephalopathy UKELD*

**** Wald test to determine whether the hazard ratios from 0 to 90 days and from 90 days to 1-year differ significantly from each other.*

Table S3: The impact of performance status on post-transplant mortality in two separate epochs of follow-up time in HCC (n=2 107) and non-HCC recipients (n=10 693) and using a 4-point ECOG scale.

	Time-period after transplantation (Epoch)		
Patient mortality	**0 to 90 days**	**90 days to 1-year**	**P for interaction between ECOG and Epoch****
HCC Recipients*			
ECOG 1:	0·78 (0·41 - 1·51)	1·00 (0·54 - 1·85)	
ECOG 2:	0·69 (0·45 - 1·05)	1·05 (0·71 - 1·55)	
ECOG 3:	**1**	**1**	
ECOG 4/5:	0·88 (0·43 - 1·83)	1·18 (0·60 - 2·35)	0.53
Non-HCC Recipients*			
ECOG 1:	0·77 (0·47 - 1·28)	0·96 (0·51 - 1·83)	
ECOG 2:	0·73 (0·58 - 0·92)	0·92 (0·68 - 1·24)	
ECOG 3:	**1**	**1**	
ECOG 4/5:	1·41 (1·21 - 1·82)	0·93 (0·71 - 1·22)	<0.001

*****_Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, previous abdominal surgery, abomatch, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, urgency of transplantation, transplant type (liver only, liver & kidney, liver & other), era of transplantation._
**Wald test to determine whether the hazard ratios from 0 to 90 days and from 90 days to 1-year differ significantly from each other.

Table S4: The impact of performance status on post-transplant mortality in two separate epochs of follow-up time in HCC (n=2 107) and non-HCC recipients (n=10 693) excluding adjustment for multivisceral or super-urgent transplant or patients requiring pre-operative ITU support.

	Time-period after transplantation (Epoch)		
Patient mortality	**0 to 90 days**	**90 days to 1-year**	**P for interaction between ECOG and Epoch****
HCC Recipients*			
ECOG 1:	0·75 (0·39 - 1·44)	0·97 (0·52 - 1·79)	
ECOG 2:	0·68 (0·45 - 1·04)	1·05 (0·71 - 1·55)	
ECOG 3:	**1**	**1**	
ECOG 4:	0·73 (0·32 - 1·67)	1·29 (0·65 - 2·59)	0.53
ECOG 5:	1.40 (0.39 - 4.99)	0.51 (0.10 – 3.96)	
Non-HCC Recipients*			
ECOG 1:	0·80 (0·48 - 1·33)	0·99 (0·53 - 1·90)	
ECOG 2:	0·73 (0·58 - 0·92)	0·92 (0·68 - 1·24)	
ECOG 3:	**1**	**1**	
ECOG 4:	1·19 (0·95 - 1·50)	1·41 (1·05 - 1·90)	
ECOG 5:	1.89 (1.42 – 2.51)	0.73 (0.49 – 1.07)	<0.001

***** *Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, previous abdominal surgery, abomatch, HCV status, UKELD, pre-transplant inpatient status.*

***Wald test to determine whether the hazard ratios from 0 to 90 days and from 90 days to 1-year differ significantly from each other.*

Table S5: The impact performance status on post-transplant mortality in two separate epochs of follow-up time in HCC recipients (n=1 211) and adjusted additionally for tumour characteristics (2008-2016).

Patient mortality	Time-period after transplantation (Epoch)		P for interaction between ECOG and Epoch**
	0 to 90 days	90 days to 1-year	
HCC Recipients*			
ECOG 1:	1·01 (0·39 - 2·66)	1·08 (0·44 - 2·65)	
ECOG 2:	0·80 (0·41 - 1·58)	1·10 (0·61 - 2·00)	
ECOG 3:	**1**	**1**	
ECOG 4:	0·70 (0·08 - 5·81)	1·24 (0·26 - 5·93)	
ECOG 5:	4.81 (0.63 – 35.4)	2.91 (0.26 – 31.2)	0.92

***Adjusted for donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time and recipient characteristics: recipient sex, recipient age, recipient ethnicity, recipient BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, previous abdominal surgery, abomatch, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, urgency of transplantation, transplant type (liver only, liver & kidney, liver & other), era of transplantation.*
and, tumour characteristics max tumour diameter, total tumour diameter, no of tumours, AFP
***Wald test to determine whether the hazard ratios from 0 to 90 days and from 90 days to 1-year differ significantly from each other.*
**** ECOG 4 and 5 combined; 0 to 90 days HR: 1.33 (95%CI; 0.32 – 5.63), and 90 days to 1-year HR: 1.29 (95%C1: 0.32-5.20).*

7. Results Chapter

Research Paper 5

Title: The Impact of Performance Status on Length of Hospital Stay and Clinical Complications Following Liver Transplantation

The results of this chapter have been presented in the form of a published paper. The supplementary information referred to in the paper is available at the end of the manuscript.

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Primary Supervisor	Professor Jan van der Meulen		

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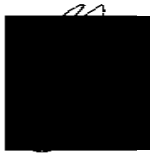
Supervisor Signature	
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The Impact of Performance Status on Length of Hospital Stay and Clinical Complications Following Liver Transplantation

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Background. Impaired pretransplant performance status (PS) is associated with chronic liver disease (CLD). We studied its impact on hospital length of stay (LOS), complications, and readmissions in the first year after liver transplantation. **Method.** The Standard National Liver Transplant Registry was linked to a hospital administrative dataset, and all first-time liver transplant recipients with CLD aged ≥18 years in England were identified. A modified 3-level Eastern Cooperative Oncology Group score was used to assess PS. Linear- and logistic-fixed effect regression models were used to estimate the effect of specific posttransplant complications and readmissions in the first year after transplantation. **Results.** Six thousand nine hundred sixty-eight recipients were included. Impaired PS was associated with an increased LOS in the initial posttransplant period (comparing ECOG 1–3, adjusted difference 7.2 d; 95% confidence [CI], 4.8-9.6; $P<0.001$) and in time spent on the ITU (adjusted difference 1.2 d; 95% CI, 0.4-2.0; $P<0.001$). There was no significant association between ECOG status and total LOS of later admissions (adjusted difference, 2.5 d; 95% CI, –0.4-5.5; $P=0.23$). Those with a poorer ECOG status had an increased incidence of renal failure (odds ratio, 1.5; 95% CI, 1.1-2.0; $P=0.004$) and infection (odds ratio, 1.2; 95% CI, 1.1-1.4; $P=0.02$) but not an increased incidence of readmission (odds ratio, 1.2; 95% CI, 0.9-1.5; $P=0.13$). **Conclusion.** In liver transplant recipients with CLD, impaired pretransplant PS is associated with prolonged LOS in the immediate posttransplant period but not with LOS of later admissions in the first year after transplantation. Impaired PS increased the risk of renal failure and infection.

(*Transplantation* 2020;00: 00–00).

INTRODUCTION

Identifying modifiable factors that predict longer hospital admissions and posttransplant complications has major potential clinical utility.[1-6] First, it may help clinicians counsel their patients on what might be experienced in the postoperative period. Second, it can assist service providers plan hospital resource use and optimize resource utilization.[1-6] Third, it could facilitate the introduction of interventions on the waiting list that may serve to reduce morbidity and length of stay (LOS) following transplantation.

To date, studies that have reported LOS following liver transplantation have largely been restricted to small cohorts of patients from single center.[2-6] These have

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D.W. did conception of project, literature review, data analysis, interpretation of results, and write up of the article. T.E.C. and K.W. did conception of the project, data analysis, interpretation of results, and write up of the article. A.S., A.G., I.R., C.C., and N.H. in interpretation of results and write up of the article. J.v.d.M. and W.B. did conception of project, literature review, interpretation of results, and write up of the article. All authors have given final approval for this article to be submitted to Transplantation.

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tended to focus on the association of hospital stay with specific markers of organ dysfunction or graft quality.[3-6] However, including only clinical measures of organ function may obfuscate other risk factors that have an impact on the postoperative course.[7,8] There is now an increasing appreciation of the global decline in physical health seen in patients with advanced CLD.[9,10] This decline includes changes in multiple organ systems and in both the development of liver-specific complications including ascites and encephalopathy and global loss of muscle bulk and function, although the development of sarcopenia.[9,10] Together, these pathological changes result in progressive frailty and impaired functional status, which has major impacts upon quality of life and nontransplanted survival.[9,10]

Measurements of overall health status capture information beyond that identified through specific measurements of end-organ function.[2,7,8] Impaired performance status (PS) is now well established as an independent risk factor for posttransplant mortality.[7,8] Given the increasing appreciation of the clinical impact of impaired PS on posttransplant outcomes, it is possible that PS will also be a predictor of posttransplant LOS.

Only 1 single-center study from the United States, including 598 recipients of a liver transplant between 2009 and 2014, has identified an association between PS and hospital LOS,[2] and none has explored the association of using a national cohort of liver transplant recipients. While in the last decade, the number of recipients with hepatocellular carcinoma (HCC) has increased significantly,[11] the difference in how PS affects hospital resource use in HCC and non-HCC patients has not been assessed. This is potentially important as at the time of transplantation HCC recipients are often in a better physical condition and have fewer manifestations of end-stage liver disease than non-HCC patients.[11]

We carried out a cohort study to assess the impact of PS on length of hospital stay, readmissions, and specific-key posttransplant complications in the first year after transplantation. We distinguished LOS immediately after transplantation and total LOS of later admissions. We used national data from the United Kingdom Standard National Liver Transplant Registry, including all patients who underwent a liver transplantation in England in the period from 1997 to 2015, linked at patient level with administrative data from all hospital admissions in the English National Health Services (NHS).

MATERIAL AND METHODS

Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains detailed information about all liver transplants performed in the 6 liver transplant centers in England.[12] This registry was used to identify recipients of a liver transplant from 1997 to 2015 and to capture information on the date of transplant and on donor and recipient characteristics, the number of days ventilated or in ITU, the incidence of specific posttransplant complications of infection or need for renal replacement therapy, and readmissions within the first year after transplantation.[12]

Hospital Episodes Statistics database

The Hospital Episodes Statistics database is an administrative dataset capturing records of all admissions to English NHS hospitals.[13] Each HES record can contain up to 20 diagnoses using codes based on the 10th revision of the International Classification of Disease, up to 24 operations and procedures using codes from the Office of Population, Census and Surveys Classification of Surgical Operations and Procedures (OPCS-4) and information on length of hospital stay based on the dates of admission and discharge.[13] The linked HES records from 1997 to 2016 also provided information on comorbidities and the patients' socioeconomic status based on the Index of Multiple Deprivation, grouped according to national quintiles.[13]

Study Population

All patients (aged 17 y or older) who had received a first liver transplant between January 1, 1997, and December 31, 2015, were eligible for inclusion (Figure 1). To include F1
a cohort of liver transplant recipients that were representative of clinical practice, recipients who underwent multivisceral transplants and those who required ITU support before transplantation were included. We excluded those whose survival data were missing and those in which a PS score was not recorded before their transplant. Recipients were also categorized into 2 groups: patients transplanted with HCC mentioned in any of the 3 diagnosis fields available in the Standard National Liver Transplant Registry (HCC patients) and patients transplanted with other liver disease diagnoses (non-HCC patients).[12]

A modified version of the Eastern Cooperative Oncology Group (ECOG) was used to measure recipients' PS.[14] ECOG scores were stratified into 3 groups: ECOG 1 (normal or minimally restricted level of activity), ECOG 2 (able to self-care), and ECOG 3 (confined to bed or chair or completely reliant on medical care). ECOG scores were assessed by clinicians either at the time of transplantation or at the most recent clinic before surgery. Included in the assessment of a patient's PS were their own reports of their functional ability.[7,8] The severity of recipients' liver disease was assessed using the UK model for end-stage liver disease (UKELD) score.[15] Ethnic background was categorized into white and nonwhite groups.

LOS in the initial postoperative period was calculated from the date of transplant to the date of discharge.[1] LOS of any later admission was calculated from the date of admission to the date of discharge. LOS following the initial postoperative admission was defined as the sum of LOS of every admission in any NHS hospital in England with an admission date within 1 year from the date of transplant.[1] This included days spent in hospital during nontransplant-related admissions.[1] Posttransplant infections were categorized into those causing infection due to bacterial or viral causes. Posttransplant renal failure was defined as those patients requiring renal replacement therapy. These complications were captured in the national dataset up to 12 months following initial transplantation. Readmissions considered only those related to transplant-specific complications and were dichotomized according to those who had 1 or more readmissions within the first year of their operation.

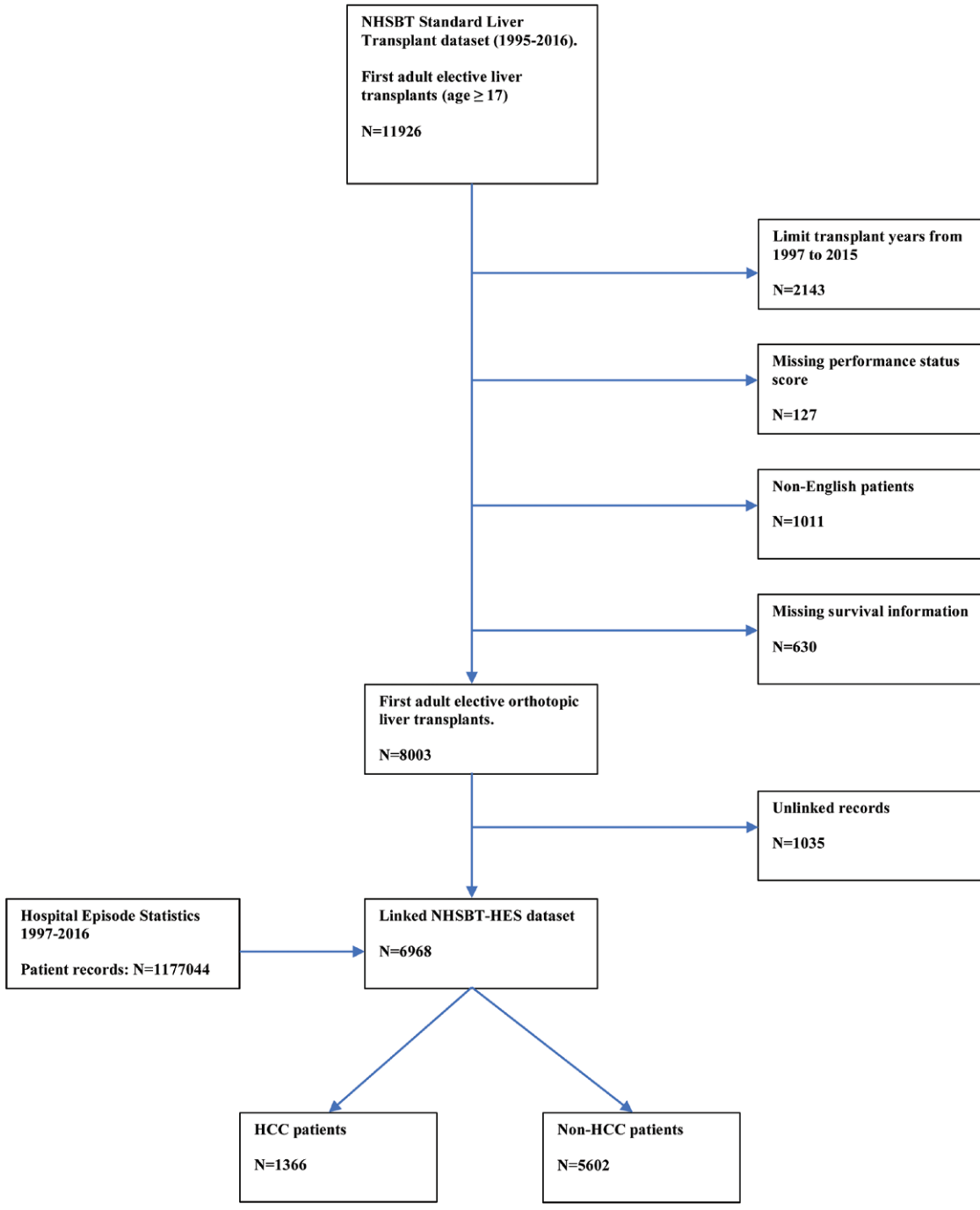

FIGURE 1. Flow chart presenting selection of study population.

Statistical Analysis

Donor and recipient characteristics, comorbidities, LOS, posttransplant complications, and readmissions were described and stratified according to the modified 3-level ECOG scale. Categorical variables were presented as proportions and continuous variables including were presented as means with SD. In accordance with recent Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, we did not apply significance tests to the patient characteristics included in descriptive tables.[16]

Separate multivariable fixed effects regression models were used to estimate the independent effect of PS on each outcome. Linear regression models were used to provide the adjusted mean differences in LOS by PS, and logistic regression models were used to estimate the adjusted odds ratios for posttransplant complications and readmissions by PS. To account for differences in outcomes between hospitals, a categorical variable for transplant center was fitted in each model.[1] ECOG 1 was used as the reference value. In the analysis, LOS, specific posttransplant complications, and readmissions were considered for all patients including those who died within the first year following their transplant. A global Wald test was used in the separate multivariable models to test whether the adjusted mean differences in LOS or the incidence of complications and readmissions differed significantly between levels of

ECOG status (*P* for overall association). To determine whether the prognostic impact of ECOG status varied according to HCC or non-HCC indications, models were also fitted on HCC and non-HCC patients together with interaction terms (*P* for interaction) between ECOG and HCC status. The statistical significance of these interaction terms in each model was again tested using a global Wald test. To account for patients who died early after transplantation, a sensitivity analysis was performed that included only patients who survived to 1 year.

In all models, risk adjustment included the recipient and donor characteristics (in Table 1) and comorbidities (Table S1, SDC, http://links.lww.com/TP/C27). Missing donor and recipient characteristics were imputed using chained equations creating ten complete datasets.[17] In the imputation procedure, all available donor and recipient variables were used to predict missing values, including the outcome variables.[18] The regression coefficients across the datasets were pooled using Rubin's rules.[17]

Stata V15 (StataCorp, College Station, TX) was used for all statistical analyses. Health Research Authority (HRA) Confidentiality Advisory Group (17/CAG/0025) approval and Research Ethical Committee (REC reference 17/LO/0231) approval was obtained for this study.

RESULTS

Donor and Recipient Characteristics

A total of 6968 adult liver transplants were included in the study (Table 1). At the time of transplantation, recipients with the poorest PS scores had more severe liver disease (as captured by UKELD) and were more likely to have been encephalopathic. They were also more frequently required to be inpatients or require renal support before transplantation. The presence of comorbidity was infrequently found in recipients (Table S1, SDC, http://links.lww.com/TP/C27).

Length of Stay

Hospital LOS in the immediate postoperative period was twice as long in those recipients with ECOG 3, who were severely restricted or almost completely reliant on care, as compared with those with ECOG 1 who had a relatively normal level of functional activity (mean LOS of ECOG 1 and 3; 19.8 d and 41.4 d, respectively; Table 2).

At 1 year, the overall difference in mean LOS following the initial postoperative admission to 1 year was less marked with 22.4 days in those with an ECOG status of 1 compared with 28.5 days in ECOG 3. Stratifying for indication of transplantation, there were increases in LOS for both HCC (comparing ECOG 1 to ECOG 3; 22.8–24.6 d) and non-HCC recipients (ECOG 1 to ECOG 3; 22.2–28.8 d).

Following risk adjustment, impaired ECOG status remained associated with an increase in LOS in the initial postoperative period (comparing ECOG 3 to ECOG 1: adjusted difference; 7.2 d; 95% CI, 4.8-9.6), *P* for overall association <0.001, Table S2, SDC, http://links.lww.com/TP/C27; Figure 2) and associated with LOS in the ITU (comparing ECOG 3 to ECOG 1; 1.2 d; 95% CI, 0.4-2.0;

TABLE 1.

Donor and recipient characteristics according to performance status

	ECOG status			
	ECOG 1	ECOG 2	ECOG 3	
Number	2207	3721	1040	Missing values
Donor characteristics				
Female sex	46.7% (1032)	46.2% (1718)	49.1% (511)	0.1% (1)
Donor age	47.2 (16.1)	46.0 (15.3)	46.5 (15.3)	0.1% (1)
BMI in kg/m^2	26.0 (4.6)	26.1 (4.8)	26.5 (4.0)	3.0% (209)
Trauma as cause of death	12.3% (80)	14.2% (90)	6.0% (5)	0.0% (0)
DCD donor	18.9% (418)	11.5% (426)	8.7% (91)	0.01% (1)
Segmental graft type	10.0% (220)	7.5% (279)	6.4% (67)	0.0% (0)
Cold ischemic time in min	548.5 (180.7)	567.7 (182.6)	577.2 (180.7)	5.7% (400)
Recipient characteristics				
Female sex	34.4% (759)	35.9% (1337)	37.4% (389)	0.0% (0)
Age in y	51.4 (11.6)	52.3 (10.7)	50.7 (11.9)	0.0% (0)
HCC indication for transplantation	29.4% (650)	17.0% (633)	8.0% (83)	0.0% (0)
BMI in kg/m^2	26.5 (4.8)	26.8 (5.0)	26.7 (5.3)	3.3% (228)
Liver only transplant	99.6% (2177)	98.0% (3645)	97.6% (1016)	0.0% (0)
Nonwhite ethnicity	13.0% (288)	12.9% (478)	12.3% (128)	0.0% (0)
Ascites	37.4% (823)	55.1% (2049)	74.1% (771)	0.2% (12)
Previous variceal bleed	25.1% (552)	31.4% (1161)	35.8% (369)	0.5% (38)
Previous abdominal surgery	12.1% (267)	14.4% (533)	15.9% (165)	0.2% (13)
Encephalopathy	17.2% (379)	22.4% (833)	52.1% (539)	0.2% (13)
Requiring ventilation	0.1% (2)	0.2% (8)	3.9% (41)	0.1% (4)
Requiring renal support	3.7% (82)	4.3% (158)	13.4% (139)	0.1% (9)
Inpatient before transplant	1.5% (10)	3.6% (23)	48.2% (40)	0.03% (2)
UKELD	53.3 (5.2)	54.4 (5.2)	58.8 (6.5)	2.7% (185)
Era of transplant 2007–2015	66.9% (1478)	52.2% (1904)	54.5% (567)	0.0% (0)

TABLE 2.

Mean length of hospital stay and incidence of postoperative complications and readmissions stratified by performance status

	ECOG Status		
	1998–2015		
Length of stay	**ECOG 1 n = 2207**	**ECOG 2 n = 3721**	**ECOG 3 n = 1040**
Initial los	19.8 (21.3)	22.8 (23.6)	41.4 (41.9)
LOS on ITU	3.4 (5.7)	4.9 (9.8)	5.9 (10.2)
LOS following the intial postoperative period at 1-y	22.2 (33.0)	22.7 (33.3)	28.8 (38.8)
Postoperative complications			
Infection	31.4%	43.3%	45.0%
Renal failure	10.8%	14.5%	21.3%
Readmissions	30.9%	39.3%	38.5%

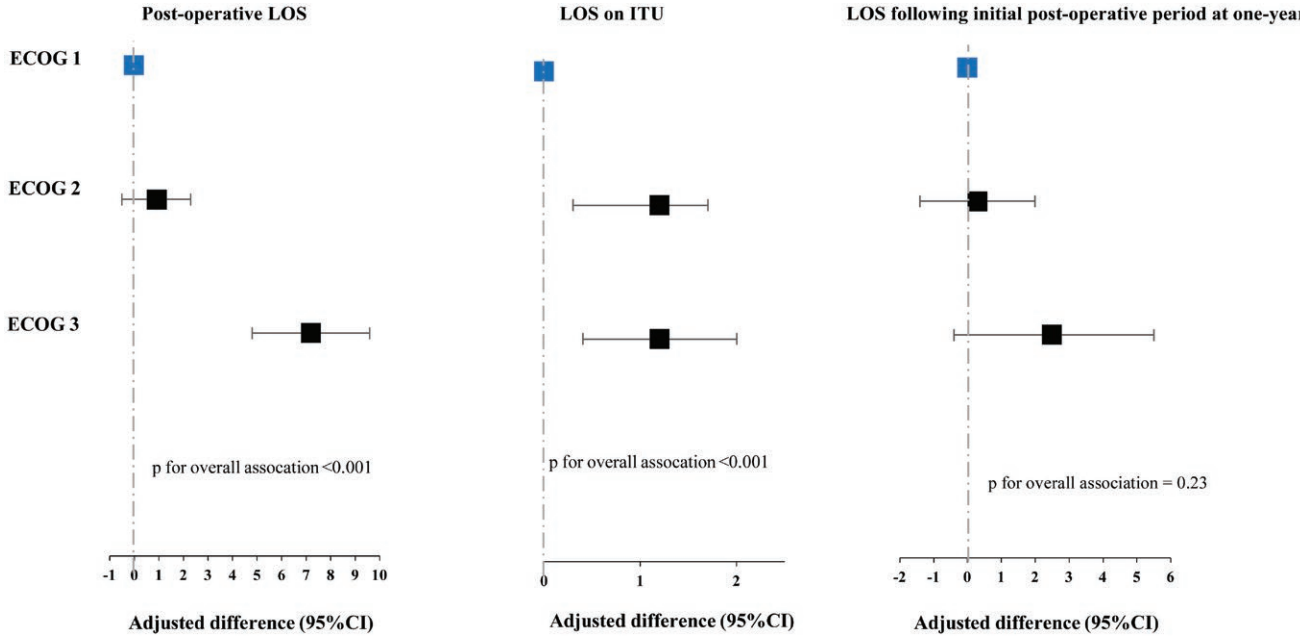

FIGURE 2. Impact of performance status on mean length of hospital stay adjusted for donor and recipient factors.

P for overall association <0.001). However, following the initial postoperative admission to 1 year, no independent association was found between ECOG status and LOS (*P* for overall association = 0.23; Table S3, SDC, http://links.lww.com/TP/C27; Figure 2). The impact of ECOG status on any of the LOS metrics did not differ according to HCC status (*P* for interaction >0.05).

Posttransplant Complications and Readmissions

In the descriptive analysis, incremental increases in the incidence of specific posttransplant complications of infections and renal failure and intransplant-related readmissions were observed in recipients with the poorer ECOG scores (Table 2). For example, the proportion of those developing posttransplant infection increased from 31.4% in those with ECOG 1 to 45.0% in those with an ECOG status 3. Increases in the incidence of posttransplant renal failure were also seen, with 10.8% of with an ECOG score of 1 observed to have renal failure compared with 21.3% in those with ECOG 3. The proportion of recipients requiring 1 or more readmissions also increased from 30.9% in those who were most active at the time of transplantation (ECOG 1) to 38.5% in those most reliant or dependent on care (ECOG 3).

Following risk adjustment, associations remained between ECOG status and renal failure (comparing ECOG 3 with 1; OR, 1.5; 95% CI, 1.1-2.0; *P* for overall association = 0.02; Figure 3). For posttransplant infection, the largest difference was between ECOG 2 and ECOG 1 (OR, 1.2; 95% CI, 1.1-1.4; *P* for overall association = 0.004). No association between ECOG status and readmissions was identified (*P* for overall association = 0.13) nor did the effect of ECOG status on posttransplant complications differ according to HCC status (*P* for interaction >0.05).

Sensitivity Analyses

In sensitivity analysis that included only those recipients who survived to 1 year, no major changes in the association of ECOG status and LOS metrics or posttransplant renal failure, infections, or readmissions were observed.

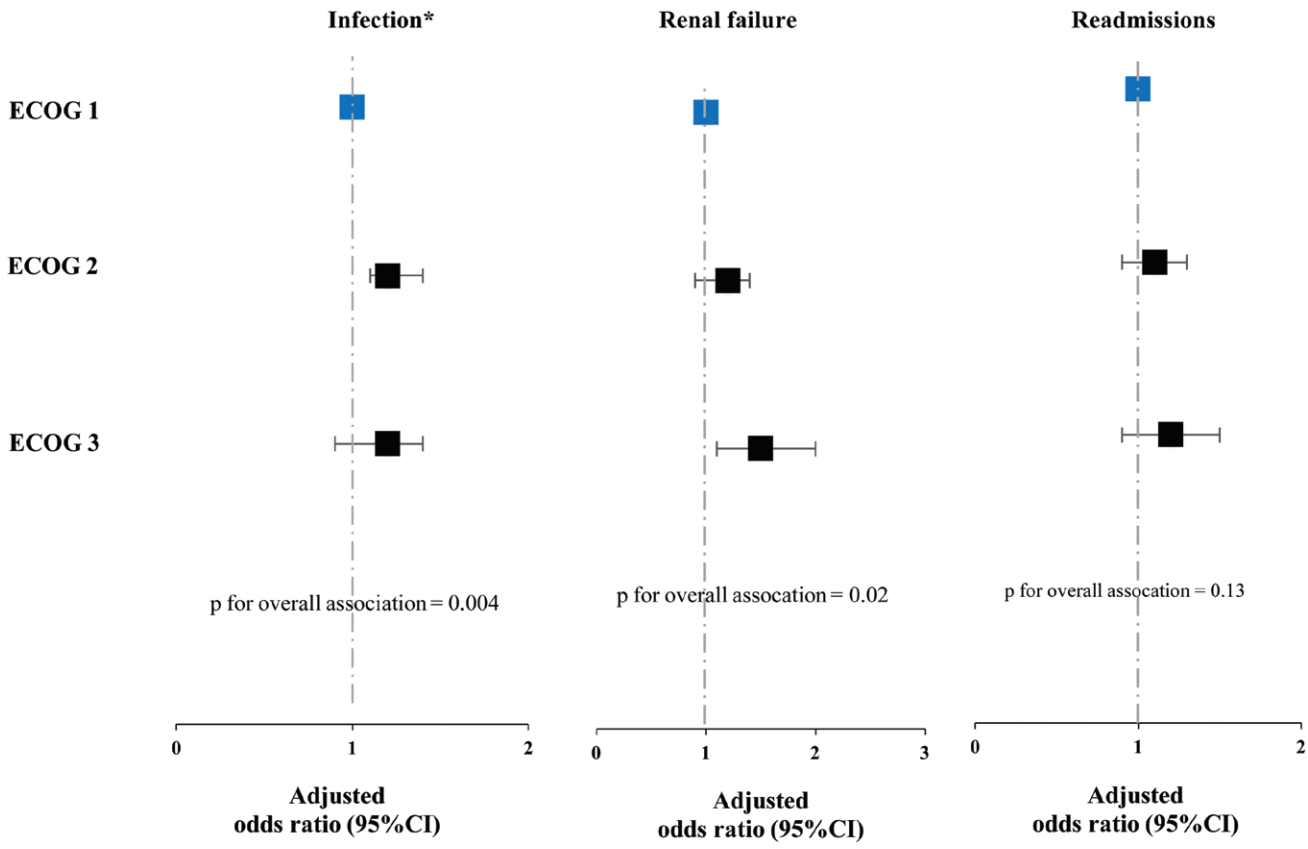

FIGURE 3. Impact of performance status on postoperative complications and readmission adjusted for donor and recipient factors.

DISCUSSION

Summary of Results

In multivariable models that included measures of liver disease severity and other donor and recipient characteristics, ECOG scores taken at the time of transplantation were associated with an increased LOS in the initial posttransplant hospital admission. Impaired ECOG status at the time of transplantation was also associated with an increased incidence of specific major posttransplant complications. However, after the initial posttransplant admission, no significant association between impaired pretransplant ECOG status and LOS was identified.

Methodological Limitations

A first limitation is that the ECOG scores reported by clinicians in the 6 participating transplant centers are prone to interobserver error.[19,20] In previous analyses, coefficients that have measured the level of agreement between clinicians scoring ECOG score have varied between 0.50 and 0.91.[19,20] If we assume in our analysis that a level of disagreement—somewhere between these 2 coefficients—occurred to the same extent, then the true effect of ECOG on LOS may have been larger to that observed in our study.[7] Second, clinicians who were recording ECOG scores at the time of transplantation were not blinded to the other known risk factors of prolonged hospital stay and posttransplant complications, including those measures of severe liver dysfunction and other comorbidity.[7,8] This could have contributed to the observed association between ECOG scores and these risk factors. However, the association between the ECOG scores and posttransplant LOS remained even after extensive adjustment for pretransplant factors making it unlikely that a lack of blinding fully explains our findings.[7] Third, to select a sample of patients that was truly reflective of national practice, we included all patients who received a liver transplant during the study period. This meant those who died early after their liver transplantation would shorten the average LOS and reduce the overall rate of complications. However, in a sensitivity analyses that excluded patients who did not survive to 1 year, the significance of the association of ECOG and LOS metrics did not change for any metric of LOS or for either of the specific posttransplant complications. It is also important to note that we considered only 2 specific posttransplant complications. Both impact significantly on patient and graft survival and on posttransplant LOS, but other complications including impaired early graft function or biliary leaks may be also be affected by ECOG status.

Finally, we recognize the importance to understand how the underlying conditions that the determine the preoperative PS are related to posttransplant infection and renal complications. However, when estimating the impact of preoperative PS on posttransplant outcomes, we did include comorbidity—as defined by the RCS Charlson score—and the presence of other recipient characteristics including the requirement of preoperative renal failure.

Comparison With Other Studies

To date, the association of ECOG status with LOS and posttransplant complications has not been explored in a national cohort of LT recipients. One study, including

598 patients from a single center in the United States, used the Karnofsky score[2] to group patients into 3 strata of functional ability and identified impaired PS at the time of transplantation to be associated with a prolonged posttransplant LOS.[2] However, the small sample size is taken from only 1 transplant center, the lack of adjustment for risk factors that have previously been proven to be predictive of prolonged posttransplant LOS, and a focus on LOS only in the immediate postoperative period limit the generalizability of these results.

In the same cohort of liver transplant patients, we have already demonstrated that pretransplant PS affects posttransplant mortality and principally within the first 3 months.[21] This is in line with findings reported in the current article that pretransplant PS is associated with prolonged LOS in the immediate posttransplant period but not with LOS of later admissions. This further confirms that a poor PS at the time of transplantation has a short-term rather than a long-term impact on posttransplant outcomes.

Explanation of Results

The association between pretransplant functional status and postoperative LOS may arise from a number of contributory factors. ECOG scores are considered a more inclusive assessment of patient health and most probably encompass factors predictive of prolonged LOS that are not captured in the clinical measurements of end-organ function that are adjusted for in this analysis.[2,7,21] These factors are likely to range from the more physiological such as measures of sarcopenia—shown in other studies to be independently predictive of postoperative LOS[22]—to the more psychosocial including the extent to which functional status scores reflect an assessment of the individual resources and support network a patient has available to be able to cope with undergoing major abdominal surgery.[7]

It is also possible that assessments of PS also reflect patient behaviors that are known to influence the recovery period following liver transplantation.[7,8] Those with poorer PS at the time of transplantation are known to experience prolonged periods of immobilization[23] making them more predisposed to a cascade of events after surgery that includes increased susceptibility to complications,[22] impaired postoperative recovery,[22] extended initial hospital stay,[1] and increased risk of readmissions.[24,25] In the context of posttransplant complications, the immunoparesis and declining physiological reserve seen in those who are frail will also expose them to an increased risk of posttransplant infection and renal failure—and these complications will also make later readmission more likely.

Beyond the initial posttransplant stay, there was no indication that ECOG status had an impact on hospital resource use. In studies that have focused on posttransplant survival, there is evidence that PS only affects mortality in the first few months following transplantation.[8,21] It is likely that the effect of PS on posttransplant mortality, and LOS is influenced by a relatively rapid reversal of the clinical sequelae of severe liver dysfunction that follows restoration of liver function by transplantation. Once this restoration occurs, a reversal in PS[8] and its impact of hospital resource use would be expected.

Clinical Implications

Our findings, the first in a complete national cohort of liver transplant recipients, have a number of clinical implications. First, considering the PS of patients before transplantation, in addition to other conventional risk factors, can help in the assessment, selection, and counseling of patients who are potentially eligible for transplantation.[1,2] In particular, the ability to estimate LOS and the risk of key complications can help inform patients and their relatives about what to expect in the initial postoperative period and following discharge from hospital.[1,2] Second, metrics that can be used to identify those at risk of prolonged postoperative stay can also be used to target those on the transplant waitlist who may benefit from intensive pre or postoperative multidisciplinary led rehabilitation regimes that could serve to decrease postoperative LOS, reduce the incidence of frailty-induced posttransplant complications, and potentially improve posttransplant survival. Third, a better understanding of the impact of impaired PS on LOS and resource use will help to quantify the consequences of proposed selection policies that include offering LT to severely ill cirrhotic patients who are hospitalized—a subgroup where mortality outcomes now appear favorable, but morbidity is little understood.[26,27] The observed association of PS with healthcare utilization also has implications for other future practices and policies.[1,2] For example, the assessment of factors that guide healthcare-related expenditure, including LOS, is particularly relevant in an era of constrained resource.[2] Economic evaluations that have suggested those with the most severe liver dysfunction and worst PS increase the healthcare expenditure by 40% within the first posttransplant year.[2]

CONCLUSION

Frailty, reflected in impaired PS is significantly associated with both an increase in LOS in the immediate posttransplant period and in the frequency of major complications following liver transplantation. The use of assessment of preoperative functional status to predict posttransplant complications and LOS could be useful to counsel patients before surgery and to guide waitlist interventions.

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SUPPLEMENTAL INFORMATION

Table S1: Comorbidity in HCC (n=1 366) and non-HCC patients (n=5 602) according to performance status.

		Performance status		
		PS 1	**PS 2**	**PS 3**
Number	**HCC recipients**	**650**	**633**	**83**
	Non-HCC recipients	**1 557**	**3 088**	**957**
Myocardial Infarction	HCC	0.6% (4)	0·5% (3)	1.2% (1)
	Non-HCC	0.5% (8)	0·7% (21)	1.2% (11)
Peripheral vascular disease	HCC	1.5% (10)	1.4% (9)	2.4% (2)
	Non-HCC	1.0% (16)	1.7% (53)	1.2% (11)
Cerebrovascular disease	HCC	0.3% (2)	0.8% (5)	1.2% (1)
	Non-HCC	0.6% (10)	0.8 (26)	0.8% (8)
Congestive cardiac failure	HCC	1.1% (7)	1·1% (7)	2.4% (2)
	Non-HCC	1.1% (17)	1·3% (41)	1.7% (16)
Chronic pulmonary disease	HCC	6.5% (42)	5.2% (33)	9.6% (8)
	Non-HCC	5.0% (78)	6.6% (203)	8.0% (77)
Chronic renal disease	HCC	4.2% (27)	4.9% (31)	8.4% (7)
	Non-HCC	7.4% (115)	8.4% (259)	8.7% (83)
Rheumatological disease	HCC	0.5% (3)	0·8% (5)	0.0% (0)
	Non-HCC	1.8% (28)	1·3% (40)	1.0% (10)
Dementia	HCC	0.3% (2)	0·6% (4)	1.2% (1)
	Non-HCC	2.2% (34)	2·8% (87)	2.6% (26)
Non-hepatic malignancy	HCC	4.9% (32)	3·8% (24)	1.2% (1)
	Non-HCC	0.3% (4)	0·3% (9)	0.8% (6)
Hemi and paraplegia	HCC	0.0% (0)	0.2% (0)	0.0% (0)
	Non-HCC	0.1% (1)	0.2% (5)	0.3% (3)
Atherosclerosis	HCC	2.5% (16)	2.7% (17)	4.8% (4)
	Non-HCC	2.2% (34)	3.2% (99)	3.0% (29)

Table S2: Comparison of recipients and donor characteristics in linked and unlinked NHSBT records.

LINKAGE		Unlinked (n=1 033) HCC=193 / Non-HCC=842			Linked (n=6 968) HCC=1 366 / Non-HCC=5 602		
		Performance status			Performance status		
		PS 1	PS 2	PS 3	PS 1	PS 2	PS 3
DONOR CHARACTERISTCS							
Female Sex	HCC	42.1% (40)	36.5% (31)	66.7% (8)	42.8% (278)	41·8% (264)	49.4% (41)
	Non-HCC	50.2% (119)	47.4% (210)	43.8% (70)	48.4% (754)	47·1% (1 454)	49.1% (470)
Age (years)	HCC	48 (15.8)	48.8 (13.5)	48.7 (16.3)	48.2 (16.2)	46.8 (15·6)	47.4 (17.1)
	Non-HCC	46.3 (16.5)	45.3 (16.0)	46.1 (16.6)	46.8 (16.0)	45.8 (15·3)	46.4 (15.1)
BMI (Kg/M²)	HCC	25.7 (4.5)	26.4 (4.6)	24.9 (3.1)	26.0 (4.6)	26.1 (4·8)	26.5 (4.0)
	Non-HCC	25.4 (5.0)	25.8 (5.0)	26.0 (4.7)	25.6 (4.6)	25.9 (4·9)	25.6 (4.2)
Trauma as cause of death	HCC	17.9% (17)	9.4% (8)	0.0% (0)	12.3% (80)	14·2% (90)	6.0% (5)
	Non-HCC	11.8% (28)	14.2% (63)	14.4% (23)	11.4% (178)	13·6% (421)	14.5% (139)
DCD donor	HCC	20.0% (19)	8.2% (7)	16.7% (2)	24.6% (160)	16·6% (105)	20.5% (17)
	Non-HCC	15.2% (36)	3.4% (15)	5.6% (9)	16.6% (258)	10·4% (321)	7.7% (74)
Steatosis	HCC	56.5% (39)	52.2% (36)	62.5% (5)	45.4% (271)	43·1% (251)	43.1% (31)
	Non-HCC	43.4% (75)	48.2% (171)	46.0% (51)	44.1% (594)	40·4% (1 079)	43.2% (351)
Presence of capsular damage	HCC	7.3% (5)	9.0% (6)	0.0% (0)	14.0% (83)	15·0% (87)	15.3% (11)
	Non-HCC	9.8% *17)	15.8% (55)	17.1% (19)	12.8% (171)	14·1% (374)	11.0% (89)
Abnormal organ appearance	HCC	29.7% (19)	36.4% (28)	37.5% (3)	27.9% (141)	27·5% (161)	26.0% (19)
	Non-HCC	26.5% (41)	37.9% (152)	44.1% (56)	22.4% (282)	22·2% (638)	21.2% (179)
Segmental Graft type	HCC	8.4% (8)	7.1% (6)	0.0% (0)	7.7% (50)	6·0% (38)	3.6% (3)
	Non-HCC	16.0% (38)	11.3% (50)	11.3% (18)	10.9% (170)	7·8% (241)	6.7% (64)
Cold Ischaemic Time (mins)	HCC	533.1 (223.5)	602.0 (176.0)	640.8 (149.6)	527.1 (181.4)	534.1 (174.5)	569.7 (187.6)
	Non-HCC	544.3 (229.3)	619.6 (208.7)	606.5 (212.5)	557.2 (179.7)	574.6 (183.5)	577.9 (180.2)
RECIPIENT CHARACTERISTICS							
Age (years)	HCC	57.2 (8.3)	55.5 (8.1)	56.0 (9.1)	56.4 (8.1)	56.8 (8.2)	56.0 (9.0)
	Non-HCC	47.7 (13.0)	50.8 (10.4)	49.7 (11.6)	49.3 (12.2)	51.4 (11.0)	50.2 (12.0)
BMI (Kg/M²)	HCC	27.6 (4.0)	27.0 (3.9)	24.3 (3.0)	27.3 (4.5)	27.6 (4.6)	27.1 (5.2)
	Non-HCC	26.0 (5.1)	27.1 (5.2)	25.5 (4.9)	26.1 (4.9)	26.6 (5.1)	26.7 (5.4)
Liver transplant only	HCC	100% (95)	100% (85)	100% (12)	99.5% (647)	99.5% (630)	99.8% (82)
	Non-HCC	99.6% (236)	99.6% (441)	98.8% (158)	98.1% (1 530)	97.6% (3 015)	97.5% (934)
Non-white ethnicity	HCC	28.4% (27)	36.9% (31)	25.0% (3)	19.7% (128)	19.4% (123)	16.9% (14)
	Non-HCC	32.6% (77)	36.8% (163)	46.3% (74)	10.3% (160)	11.5% (355)	11.9% (114)
Ascites	HCC	25.3% (24)	45.9% (39)	83.3% (10)	20.0% (130)	35.2% (223)	71.2% (59)
	Non-HCC	43.5% (103)	67.7% (299)	88.8% (142)	44.6% (693)	59.2% (1 826)	74.3% (712)
Previous variceal bleed	HCC	83.2% (16)	20.0% (17)	25.0% (3)	13.5% (87)	21.8% (137)	36.1% (30)
	Non-HCC	23.7% (56)	29.1% (129)	40.0% (64)	30.0% (465)	33.3% (1 024)	35.7% (339)
Previous abdominal surgery	HCC	12.8% (12)	21.2% (18)	25.0% (3)	10.3% (67)	11.9% (75)	16.9% (14)
	Non-HCC	18.2% (43)	13.0% (57)	18.8% (30)	12.9% (200)	14.9% (458)	15.8% (151)
Encephalopathy	HCC	12.6% (12)	7.1% (6)	33.3% (4)	7.5% (49)	11.5% (73)	47.0% (39)
	Non-HCC	18.6% (44)	23.8% (105)	53.2% (84)	21.2% (330)	24.6% (760)	52.5% (500)
Requiring ventilation	HCC	0.0% (0)	0.0% (0)	8.3% (1)	0.0% (0)	0.0% (0)	2.4% (2)
	Non-HCC	0.4% (1)	0.0% (0)	8.8% (14)	0.1% (2)	0.3% (8)	4.1% (39)
Requiring renal support	HCC	3.2% (3)	3.5% (3)	16.7% (2)	2.3% (15)	3.3% (21)	13.3% (11)
	Non-HCC	4.2% (10)	3.6% (16)	18.1% (29)	4.3% (67)	4.4% (137)	13.4% (128)
Inpatient prior to transplant	HCC	3.2% (3)	4.7% (4)	66.7% (8)	1.5% (10)	3.6% (23)	48.2% (40)
	Non-HCC	4.2% (10)	8.1% (36)	65.6% (105)	3.0% (46)	6.9% (214)	65.1% (624)
HCV antibodies	HCC	51.1% (45)	68.4% (54)	33.3% (4)	45.5% (274)	44.2% (266)	32.9% (25)
	Non-HCC	21.9% (47)	33.0% (133)	32.2% (48)	12.2% (169)	14.9% (436)	14.5% (126)
UKELD	HCC	51.1 (4.6)	52.3 (5.2)	58.6 (9.6)	50.4 (4.4)	51.4 (5.1)	56.1 (6.8)
	Non-HCC	54.3 (6.2)	55.1 (5.1)	59.4 (6.4)	54.5 (5.1)	55.0 (5.0)	59.0 (6.4)
Era of transplant 2007-2015	HCC	46.3% (44)	31.8% (27)	33.3% (4)	73.7% (479)	62.2% (394)	66.3% (55)
	Non-HCC	51.% (121)	27.8% (123)	30.6% (49)	64.1% (999)	48.9% (1 510)	53.4% (512)

Table S3: The effect of performance status on mean length of hospital stay (days) in HCC (n=1 366) and non-HCC recipients (n=5 602) adjusted for recipient and donor characteristics.

HOSPITAL STAY	Unadjusted length of stay (mean no of days)			Length of stay adjusted for donor and recipient characteristics and comorbidity*		
	HCC (mean no of days 95%CI)	Non-HCC (mean no of days 95%CI)	P-value for interaction**	HCC (mean no of days 95%CI)	Non-HCC (mean no of days 95%CI)	P-value for interaction**
POST-OPERATIVE LOS						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	3.0 (0.9 – 5.2)	2.4 (0.7 – 4.1)		1.3 (-0.8 – 3.5)	0.6 (-1.1 – 2.3)	
PS 3	21.2 (16.8 – 25.7)	20.8 (18.5 – 23.0)	0.93	10.5 (5.2 – 15.7)	6.6 (3.9 – 9.3)	0.63
LOS ON VENTILATION						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	1.2 (0.5 – 1.9)	1.0 (0.6 – 1.4)		0.9 (0.2 – 1.6)	0.8 (0.4 - 1.3)	
PS 3	0.9 (-0.5 – 2.4)	1.5 (0.9 – 2.1)	0.67	0.5 (-1.3 – 2.2)	0.7 (0.02 - 1.4)	0.53
LOS ON ITU						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	1.2 (0.4 – 1.9)	1.5 (1.0 – 2.1)		0.9 (0.1 – 1.7)	1.3 (0.7 – 1.9)	
PS 3	0.7 (-0.8 – 2.3)	2.5 (1.8 – 3.3)	0.26	-0.2 (-2.1 – 1.7)	1.3 (0.4 – 2.2)	0.20
LOS AT 1-YEAR						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	-0.3 (-4.6 – 4.1)	0.9 (-0.9 – 2.8)		-1.0 (-5.5 – 3.5)	0.5 (-1.3 – 2.4)	
PS 3	3.4 (-5.7 – 12.5)	5.4 (2.9 – 7.8)	0.80	2.1 (-8.8 – 13.3)	2.4 (-0.6 – 5.4)	0.90

**Adjusted for a) recipient characteristics: sex, age, ethnicity, socioeconomic status, BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, previous abdominal surgery, transplant type (liver only, liver & kidney, liver & other), transplant centre and era of transplantation b) donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time, and c) Comorbidity; diabetes, myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure, chronic pulmonary disease, chronic renal disease, rheumatological disease, dementia, non-hepatic malignancy, hemi and paraplegia and atherosclerosis.*

***P-value for interaction between LOS and HCC status (HCC vs non-HCC).*

Table S4: The effect of performance status on post-operative complications and readmissions in HCC (n=1 366) and non-HCC recipients (n=5 602), adjusted for recipient and donor characteristics.

COMPLICATIONS / READMISSION	Unadjusted			Adjusted for donor and recipient characteristics and comorbidity*		
	HCC (OR 95%CI)	Non-HCC (OR 95% CI)	P-value for interaction**	HCC (OR 95%CI)	Non-HCC (OR 95%CI)	P-value for interaction**
INFECTION						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.5 (1.2 – 1.8)	1.7 (1.5 – 1.9)	0.30	1.1 (0.8-1.4)	1.3 (1.1-1.5)	0.38
PS 3	2.0 (1.3 – 3.2)	1.7 (1.5 – 2.1)		1.5 (0.8-2.9)	1.1 (0.9-1.4)	
RENAL FAILURE						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.3 (0.9 – 1.8)	1.4 (1.2 – 1.7)	0.56	1.2 (0.8 – 1.7)	1.2 (0.9 – 1.5)	0.56
PS 3	1.6 (0.8 – 3.0)	2.3 (1.8 – 2.8)		1.2 (0.5 – 2.8)	1.5 (1.1 – 2.0)	
READMISSIONS						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.2 (0.9 – 1.5)	1.5 (1.4 – 1.8)	0.08	1.0 (0.7 – 1.3)	1.2 (1.0 – 1.4)	0.22
PS 3	1.5 (0.9 – 2.4)	1.4 (1.2 – 1.7)		1.5 (0.8 – 2.8)	1.2 (0.9 – 1.5)	

**Adjusted for a) recipient characteristics: sex, age, ethnicity, socioeconomic status, BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, previous abdominal surgery, transplant type (liver only, liver & kidney, liver & other), transplant centre and era of transplantation b) donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time, and c) Comorbidity; diabetes, myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure, chronic pulmonary disease, chronic renal disease, rheumatological disease, dementia, non-hepatic malignancy, hemi and paraplegia and atherosclerosis.*

***P-value for interaction between LOS and HCC status (HCC vs non-HCC).*

Table S5: Sensitivity analysis comparing the effect of performance status on mean length of hospital stay (days) in HCC (n=1 366) and non-HCC recipients (n=5 602) who did or did not survive to 1-year following transplantation.

	Length of stay in all patients			Length of stay <u>in only patients who survived to 1-year.</u>		
HOSPITAL STAY	**HCC (mean no of days +/- SD)**	**Non-HCC (mean no of days +/- SD)**	**P-value for interaction****	**HCC (mean no of days 95%CI)**	**Non-HCC (mean no of days 95%CI)**	**P-value for interaction****
POST-OPERATIVE LOS						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	1.3 (-0.8 – 3.5)	0.6 (-1.1 – 2.3)		0.6 (-1.5 – 2.7)	0.6 (-0.9 – 2.3)	
PS 3	10.5 (5.2 – 15.7)	6.6 (3.9 – 9.3)	0.63	7.7 (2.6 – 12.7)	6.7 (4.0 – 9.4)	0.82
LOS ON VENTILATION						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	0.9 (0.2 – 1.6)	0.8 (0.4 - 1.3)		0.3 (-0.1 – 0.8)	0.5 (0.2 - 0.8)	
PS 3	0.5 (-1.3 – 2.2)	0.7 (0.02 - 1.4)	0.53	0.6 (-0.4 – 1.7)	0.8 (0.3 - 1.3)	0.88
LOS ON ITU						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	0.9 (0.1 – 1.7)	1.3 (0.7 – 1.9)		0.5 (-0.1 – 1.2)	0.7 (0.3 – 1.2)	
PS 3	-0.2 (-2.1 – 1.7)	1.3 (0.4 – 2.2)	0.20	-0.3 (-1.8 – 1.2)	1.1 (0.3 – 1.8)	0.18
LOS AT 1-YEAR						
PS 1	**Reference**	**Reference**		**Reference**	**Reference**	
PS 2	-1.0 (-5.5 – 3.5)	0.5 (-1.3 – 2.4)		-0.6 (-5.5 – 4.3)	1.0 (-0.8 – 2.9)	
PS 3	2.1 (-8.8 – 13.3)	2.4 (-0.6 – 5.4)	0.90	0.2 (-11.7 – 12.1)	3.1 (0.1 – 6.2)	0.65

**Adjusted for a) recipient characteristics: sex, age, ethnicity, socioeconomic status, BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, previous abdominal surgery, transplant type (liver only, liver & kidney, liver & other), transplant centre and era of transplantation b) donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time, and c) Comorbidity; diabetes, myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure, chronic pulmonary disease, chronic renal disease, rheumatological disease, dementia, non-hepatic malignancy, hemi and paraplegia and atherosclerosis.*

***P-value for interaction between LOS and HCC status (HCC vs non-HCC).*

Table S6: Sensitivity analysis comparing the effect of performance status on post-operative complications and readmissions in HCC (n=1 366) and non-HCC recipients (n=5 602) who did or did not survive to 1-year following transplantation.

COMPLICATIONS / READMISSIONS	Post-operative complications and readmission in all patients			Post-operative complications and readmission <u>in only patients who survived to 1-year.</u>		
	HCC (OR 95%CI)	Non-HCC (OR 95%CI)	P-value for interaction**	HCC (OR 95%CI)	Non-HCC (OR 95%CI)	P-value for interaction**
INFECTION						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.1 (0.8-1.4)	1.3 (1.1-1.5)		1.0 (0.8 – 1.4)	1.3 (1.1 – 1.5)	
PS 3	1.5 (0.8-2.9)	1.1 (0.9-1.4)	0.38	1.1 (0.6 – 2.2)	1.2 (0.9 – 1.5)	0.27
RENAL FAILURE						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.2 (0.8 – 1.7)	1.2 (0.9 – 1.5)		1.1 (0.7 – 1.7)	1.3 (1.0 - 1.6)	
PS 3	1.2 (0.5 – 2.8)	1.5 (1.1 – 2.0)	0.56	0.9 (0.3 – 2.5)	1.5 (1.1 - 2.2)	0.30
READMISSIONS						
PS 1	**1**	**1**		**1**	**1**	
PS 2	1.0 (0.7 – 1.3)	1.2 (1.0 – 1.4)		1.0 (0.7 – 1.3)	1.2 (1.1 – 1.4)	
PS 3	1.5 (0.8 – 2.8)	1.2 (0.9 – 1.5)	0.22	1.5 (0.8 – 3.1)	1.2 (0.9 – 1.6)	0.10

**Adjusted for a) recipient characteristics: sex, age, ethnicity, socioeconomic status, BMI (Kg/M^2), ascites, varices, encephalopathy, cirrhosis, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, pre-transplant ventilatory support, previous abdominal surgery, transplant type (liver only, liver & kidney, liver & other), transplant centre and era of transplantation b) donor characteristics: donor sex, donor age, donor BMI (Kg/m^2), cause of death, donor type (donation after cardiac death, donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time, and c) Comorbidity; diabetes, myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure, chronic pulmonary disease, chronic renal disease, rheumatological disease, dementia, non-hepatic malignancy, hemi and paraplegia and atherosclerosis.*

***P-value for interaction between LOS and HCC status (HCC vs non-HCC).*

8. Results Chapter

Research Paper 6

Title: Liver transplantation outcomes after transarterial chemotherapy for hepatocellular carcinoma

The results of this chapter have been presented in the form of a published paper. The supplementary information referred to in the paper is available at the end of the manuscript.

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SECTION A – Student Details

Student ID Number	1605002	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Wallace		
Thesis Title	Liver transplantation as a treatment for patients with hepatocellular carcinoma: a study using electronic health care data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Transplantation		
When was the work published?	28th March 2020		
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SECTION E

Student Signature	[redacted]
Date	04/01/2021

Supervisor Signature	[redacted]
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Original article

Liver transplantation outcomes after transarterial chemotherapy for hepatocellular carcinoma

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Background: **Transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) awaiting liver transplantation is widespread, although evidence that it improves outcomes is lacking and there exist concerns about morbidity. The impact of TACE on outcomes after transplantation was evaluated in this study.**

Methods: **Patients with HCC who had liver transplantation in the UK were identified, and stratified according to whether they received TACE between 2006 and 2016. Cox regression methods were used to estimate hazard ratios (HRs) for death and graft failure after transplantation adjusted for donor and recipient characteristics.**

Results: **In total, 385 of 968 patients (39·8 per cent) received TACE. Five-year patient survival after transplantation was similar in those who had or had not received TACE: 75·2 (95 per cent c.i. 68·8 to 80·5) and 75·0 (70·5 to 78·8) per cent respectively. After adjustment for donor and recipient characteristics, there were no differences in mortality (HR 0·96, 95 per cent c.i. 0·67 to 1·38; $P = 0·821$) or graft failure (HR 1·01, 0·73 to 1·40; $P = 0·964$). The number of TACE treatments (2 or more *versus* 1: HR 0·97, 0·61 to 1·55; $P = 0·903$) or the time of death after transplantation (within or after 90 days; $P = 0·291$) did not alter the outcome. The incidence of hepatic artery thrombosis was low in those who had or had not received TACE (1·3 and 2·4 per cent respectively; $P = 0·235$).**

Conclusion: **TACE delivered to patients with HCC before liver transplant did not affect complications, patient death or graft failure after transplantation.**

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Introduction

In many countries, the number of patients with hepatocellular carcinoma (HCC) who are candidates for a liver transplant has increased significantly[1]. This has put pressure on liver transplant waiting lists, with many listed patients in danger of having to wait longer to receive a transplant, especially in countries where there is a chronic donor shortage[1,2]. In response, more patients with HCC on the liver transplant waiting list are now receiving transarterial chemoembolization (TACE) to minimize tumour growth and prevent disease progressing beyond transplantable criteria[1].

TACE, a form of locoregional therapy (LRT), is an angiographic procedure that involves the local administration of chemotherapeutic agents into the hepatic artery followed by embolization of the arterial branch(es) supplying the targeted HCC nodules[3]. The procedure can induce decompensation of cirrhotic liver and can also cause damage to the inner lining or intima of the hepatic artery, potentially increasing the risk of hepatic artery thrombosis (HAT)[3–5]. A recent systematic review[5], representing 1122 patients from 14 retrospective studies, found that TACE increased the overall risk of hepatic artery complications after liver transplantation.

So far, there is no evidence that the use of TACE in patients with HCC waiting for transplantation has an impact on post-transplant survival. Analyses of the US Multicenter HCC Transplant Consortium (UMHTC) database, including 3601 transplantations carried out between 2002 and 2013, and the European Liver Transplant Registry (ELTR), including 4978 transplantations between 1990 and 2016, found no statistically significant effect of TACE[6,7]. However, both the US and European studies represent a selected group of patients; the UMHTC database included data from only 20 of the 144 registered liver transplant centres in the USA, whereas the ELTR contained information on LRT for only one-fifth of all patients with HCC who were liver transplant recipients in Europe[6,7]. In addition, the frequency of use of TACE was relatively high, with 79 per cent of the US patients and 72 per cent of the European patients receiving TACE before transplantation.

Since 2017, formal allocation policies in the UK have recommended the use of TACE and other LRTs in all patients with HCC who are predicted to wait 6 months or more for a liver transplant[8]. The impact of TACE on survival after transplantation is likely to depend on the specific patient selection and organ allocation policies being followed in a particular country[1]. Until 2018, the selection of patients with HCC for transplantation in the UK mainly followed the Milan criteria, which define the maximum number and size of tumours in the liver, and donor organs were being allocated to patients on the waiting list according to a modified Model for End-stage Liver Disease score[9]. In 2018, a national selection and allocation policy[10] was introduced in the UK that also takes account of the primary liver disease and α-fetoprotein levels, and number and size of tumours in patients with HCC.

A study of the impact of TACE on outcomes in patients undergoing liver transplantation for HCC was carried out using data from the Standard National Liver Transplant Registry (2006–2016), linked to administrative data from all hospital admissions in the English National Health Service (NHS), to compare post-transplant complications, mortality and graft failure in patients who did or did not receive TACE before liver transplantation.

Methods

Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains information on all liver transplants carried out in all six liver transplant centres in England. It is managed by National Health Service Blood and Transplant (NHSBT)[11]. This registry was used to identify patients with HCC who received a liver transplant, and to capture information on donor and recipient characteristics, including tumour characteristics at the time of registration on the waiting list, outcomes (HAT, biliary tract leak and biliary tract stricture) within 3 months after transplantation, and date and cause of death[11].

Hospital Episode Statistics database

The HES database is an administrative data set capturing records of all admissions to English NHS hospitals[8]. Each HES record can contain up to 20 diagnoses using codes based on ICD-10, and up to 24 operations and procedures using OPCS-4 codes[12]. The linked HES records provided information on patients who received TACE (OPCS-4 codes J101, J103, J108 and J109), and on the patients' socioeconomic status according to the area-based Index of Multiple Deprivation grouped in national quintiles.

Linkage of national data sets

HES records were linked to patient records from the Standard National Liver Transplant Registry at patient level using the following identifiers: NHS number (the unique patient identifier used in the NHS), sex, date of birth and postcode. The data linkage was performed by NHS Digital, which used a hierarchical deterministic linkage approach following a stepwise approach with increasingly less strict matching criteria[12,13]. A previous validation study of records from the Standard Liver Transplant Registry linked to HES following this approach has shown that 99·3 per cent of linked HES records have at least one diagnosis code relevant to an indication for liver transplantation[13].

Study population

All patients aged 16 years or older with HCC who received a liver transplant between 1 January 2006 and 31 December 2016 were eligible for inclusion. The diagnosis of HCC for each patient was identified from the three diagnostic fields available in the Standard National Liver Transplant Registry. To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multivisceral, super-urgent, domino or living-related liver transplantation were excluded, as well as those who received a liver transplant for other indications including those with acute liver failure. Patients whose survival data were missing were also excluded (*Fig. S1*, supporting information), as were listed patients who received LRTs other than TACE and those who received TACE in addition to other LRTs.

Table 1 Donor and recipient characteristics of 968 patients undergoing liver transplantation for hepatocellular carcinoma stratified by use of transarterial chemoembolization

	TACE ($n = 385$)	No TACE ($n = 583$)	Missing values	P†
Donor				
Age (years)*	49·2(16·3)	48·2(15·7)	0	0·324‡
Sex ratio (F : M)	159 : 226	239 : 344	0	0·952
BMI (kg/m^2)*	26·4(4·6)	26·6(5·2)	3	0·677‡
Cause of death: trauma	38 (9·9)	61 (10·5)	0	0·962
Donor type: DCD	110 (28·6)	186 (31·9)	0	0·272
ABO match: identical	378 (98·2)	574 (98·5)	0	0·476
Graft type: segmental	24 (6·2)	34 (5·8)	0	0·791
Organ appearance: abnormal	85 (28·0)	171 (35·0)	176	0·041
Steatosis	182 (47·9)	265 (46·0)	12	0·575
Capsular damage	58 (15·3)	87 (15·1)	13	0·932
Cold ischaemia time (min)*	504(165)	503(163)	80	0·938‡
Recipient				
Age (years)*	58·1(7·3)	56·8(8·5)	0	0·012‡
Sex ratio (F : M)	64 : 321	116 : 467	0	0·206
BMI (kg/m^2)*	28·2(4·6)	27·9(4·9)	3	0·461‡
Ethnicity: non-white	78 (20·3)	94 (16·1)	0	0·104
IMD quintile: most deprived	45 (12·0)	102 (19·7)	81	0·003
Tumour characteristics				
Maximum tumour size > 3 cm	37 (11·1)	39 (9·5)	227	0·475
Total tumour diameter > 5 cm	9 (2·7)	7 (1·7)	227	0·352
> 1 nodule	115 (33·4)	131 (31·7)	211	0·628
Radiological evidence of vascular invasion	10 (3·0)	11 (2·8)	232	0·911
AFP (ng/ml)*	86(295)	88(338)	279	0·931‡
Blood group			0	0·156
A	155 (40·3)	278 (47·7)		
AB	20 (5·2)	28 (4·8)		
B	44 (11·4)	62 (10·6)		
0	166 (43·1)	215 (36·9)		
Era of transplantation			0	< 0·001
2006–2010	139 (36·1)	328 (56·3)		
2011–2016	246 (63·9)	255 (43·7)		
HCV-positive	180 (49·6)	201 (37·3)	66	< 0·001
Diabetes	111 (31·8)	156 (31·1)	112	0·937
Cirrhosis	362 (94·0)	533 (91·4)	0	0·132
Inpatient before transplantation	10 (2·6)	42 (7·2)	0	0·002
Renal support before transplantation	10 (2·6)	27 (4·7)	3	0·117
Previous abdominal surgery	19 (4·9)	38 (6·5)	2	0·303
Ascites	71 (18·4)	238 (41·0)	2	< 0·001
Encephalopathy	30 (7·9)	120 (20·6)	4	< 0·001
Varices	45 (11·7)	138 (23·7)	9	< 0·001
Functional status: restricted	179 (47·2)	227 (39·5)	14	< 0·001
Creatinine (μmol/l)*	80·9(28·5)	86·5(29·9)	0	0·461‡
UKELD score*	49·7(4·0)	52·4(5·4)	13	< 0·001‡
Time on waiting list (days)*	157(155)	100·0(117)	0	< 0·001‡

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). TACE, transarterial chemoembolization; DCD, donation after cardiac death; IMD, Index of Multiple Deprivation; AFP, α-fetoprotein; HCV, hepatitis C virus; UKELD, UK Model for End-Stage Liver Disease. †χ^2 test, except ‡t test.

Table 2 Postoperative complications recorded at 3 months

	No. of patients with complication								
	TACE *versus* no TACE ($n = 968$)			No. of TACE treatments ($n = 385$)			Interval from TACE to transplantation (months) ($n = 385$)		
	TACE	No TACE	*P**	1	≥2	*P**	≤3	>3	*P**
Hepatic artery thrombosis	5 (1·3)	14 (2·4)	0·235	4 (1·8)	1 (0·6)	0·299	2 (1·6)	3 (1·2)	0·692
Biliary tract stricture	18 (4·7)	21 (3·6)	0·425	10 (4·6)	8 (4·8)	0·912	6 (4·9)	12 (4·6)	0·885
Biliary tract leak	22 (5·7)	25 (4·3)	0·337	13 (5·9)	9 (5·4)	0·839	8 (6·6)	14 (5·3)	0·632

Values in parentheses are percentages. TACE, transarterial chemoembolization. *χ^2 test.

Recipients' lifestyle activity was assessed using a five-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'[14]. The UK Model for End-Stage Liver Disease was used to score the severity of the disease[15]. Waiting list time was calculated from the date of registration on the waiting list to the date of transplantation. Ethnicity was classified into white and non-white groups. Complications after transplantation were recorded at 3 months, and included HAT, biliary tract leak and biliary tract stricture. The TACE treatments were administered according to protocols described previously[16]. Selection of patients with HCC for TACE as a bridging therapy was based on the decisions of centre-specific multidisciplinary team meetings. There was no information in the Standard National Liver Transplant Registry on explant pathology.

Statistical analysis

Donor and recipient characteristics, postoperative complications, and cause of death and graft failure were compared between recipients who received TACE and those who did not. Differences between groups were analysed using χ^2 tests for categorical variables and *t* tests for continuous variables. Tumour characteristics at the time of registration on the waiting list that are predictive of post-transplant survival were also compared between TACE and no-TACE cohorts, including: size of largest nodule, total number of tumours, total tumour diameter, radiological evidence of vascular invasion and maximum α-fetoprotein level before transplantation[16]. Published service evaluations by NHSBT indicated that only a maximum of eight patients underwent transplantation after tumour downstaging, and none before 2015[17].

The Kaplan–Meier method and log rank test were used to compare patient and graft survival, and *Z* tests to analyse differences in complication rates, after liver transplantation in recipients who did or did not receive TACE. Follow-up data, including those on mortality, graft failure and postoperative complications, were available until 14 April 2017. Patients with a functioning graft or alive at the last follow-up visit were censored. Graft loss was defined by either retransplantation, or patient death.

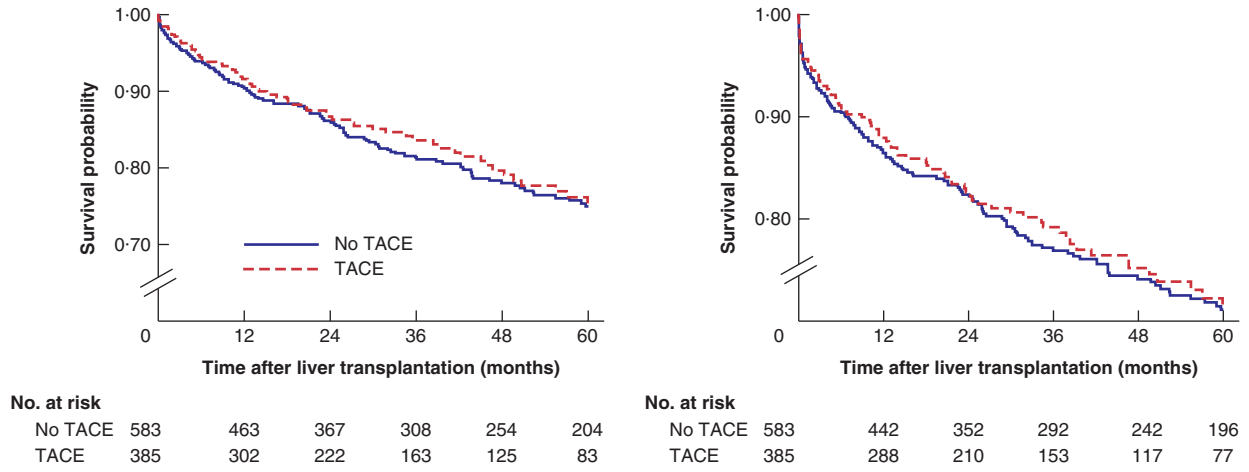
Multivariable Cox regression was used to examine the prognostic impact of TACE on patient and graft survival in the first 5 years after transplantation. Hazard ratios (HRs) comparing outcomes after liver transplantation in recipients who did or did not receive TACE were estimated, with and without adjustment for donor and recipient characteristics. Interaction terms were included in the Cox regression model to assess whether the prognostic impact of TACE varied according to time after transplantation (within *versus* after 90 days) or according to donor type (donation after cardiac death (DCD) *versus* donation after brain death (DBD)). A period of 90 days after transplantation was chosen as death in this period is likely to reflect the occurrence of surgical complications, whereas death between 90 days and 5 years is more likely to reflect tumour recurrence, which is an indicator of the curative success of cancer treatment[18]. The significance of the interaction terms was examined using the Wald test. All recipient and donor factors included in the regression models were chosen because they were thought to be clinically plausible risk factors for post-transplant outcomes[19]. Missing patient and donor characteristics were imputed using chained equations creating ten complete data sets[20]. The Cox regression results for each of these data sets were pooled using Rubin's rules[20].

$P < 0{\cdot}050$ was considered significant for each statistical analysis. Stata® version 15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

Results

A total 1204 patients with HCC who were recipients of a liver transplant were identified, of whom 1122 (93·2 per cent) had at least one matched patient record in HES. Each linked HES record was explored to identify patients on the

Fig. 1 Five-year patient and graft survival stratified by transarterial chemoembolization status, 2006–2016



a Patient and **b** graft survival. TACE, transarterial chemoembolization. **a** $P = 0{\cdot}661$, **b** $P = 0{\cdot}602$ (log rank test).

Table 3 Impact of transarterial chemoembolization on 5-year patient and graft survival (968 patients)

	Hazard ratio	
	Patient survival	Graft survival
Unadjusted analysis	0·93 (0·69, 1·27)	0·95 (0·72, 1·25)
Adjusted for recipient characteristics only*	0·93 (0·66, 1·31)	0·96 (0·70, 1·48)
Adjusted for recipient and donor characteristics*	0·96 (0·67, 1·38)	1·01 (0·73, 1·40)

Hazard ratios with 95 per cent confidence intervals are shown for transarterial chemoembolization (TACE) *versus* no TACE. *Recipient characteristics adjusted for: age, sex, BMI, ethnicity, socioeconomic status, maximum tumour size, total tumour diameter, number of tumours, α-fetoprotein level, vascular invasion, diabetes, hepatitis C virus status, inpatient status before transplant, presence of cirrhosis, ascites, encephalopathy, renal support before transplant, previous abdominal surgery, presence of varices, functional status, UK Model for End-Stage Liver Disease score, time on waiting list and era of transplantation. Donor characteristics adjusted for: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI, cold ischaemia time.

transplant waiting list who had undergone TACE before liver transplantation. Listed patients who had received LRTs other than TACE were excluded, as were those who had received TACE in addition to other LRTs (*Fig. S1*, supporting information).

A total of 968 patients with HCC who underwent liver transplantation between 2006 and 2016 were included in the study, of whom 385 (39·8 per cent) received TACE before transplantation and 583 (60·2 per cent) did not. One hundred and sixty-six patients (17·1 per cent) had more than one TACE treatment. The use of TACE as a bridging therapy increased from 29·8 per cent (139 of 467) between 2006 and 2010 to 49·1 per cent (246 of 501) between 2011 and 2016. At the time of registration on the waiting list, patients who received TACE were more likely to have tumour characteristics predictive of poorer outcomes, but these differences were not statistically significant (*Table 1*). Patients receiving TACE were also more physically active, had better liver function, and were less likely to show signs of end-stage liver disease. The mean time on the waiting list for liver transplantation was 157 days among patients who received TACE and 100 days in those who did not have TACE. The median interval from TACE to transplantation was 154 (i.q.r. 72–278) days, and 62·3 per cent of these patients (240 of 385) had TACE before being registered on the waiting list. There were only small differences between the characteristics of patients whose transplant records could and those whose records could not be linked to HES records (*Table S1*, supporting information).

There were no significant differences between the TACE and no-TACE groups at 3 months in the occurrence of HAT (1·3 per cent (5 of 385) and 2·4 per cent (14 of 583) respectively; $P = 0{\cdot}235$), biliary tract stricture (4·7 per cent (18 of 385) and 3·6 per cent (21 of 583); $P = 0{\cdot}425$) or biliary tract leak (5·7 per cent (22 of 385) and 4·3 per cent (25 of 583); $P = 0{\cdot}337$) (*Table 2*).

Table 4 Cause of death after liver transplantation for patients with hepatocellular carcinoma in two separate epochs of follow-up and stratified by use of pre-transplant transarterial chemoembolization

	Overall			0–90 days			90 days to 60 months		
	TACE (*n* = 65)	No TACE (*n* = 115)	*P*§	TACE (*n* = 13)	No TACE (*n* = 25)	*P*§	TACE (*n* = 52)	No TACE (*n* = 90)	*P*§
Recurrence of disease – malignant	16 (25)	15 (13·0)	0·101	0 (0)	0 (0)	–	16 (31)	15 (17)	0·121
Malignancy – other*	9 (14)	23 (20·0)	0·383	0 (0)	1 (4)	0·474	9 (17)	22 (24)	0·423
Graft failure	1 (2)	2 (1·7)	0·921	0 (0)	1 (4)	0·474	1 (2)	1 (1)	0·697
Sepsis	18 (28)	34 (29·6)	0·843	8 (62)	13 (52)	0·765	10 (19)	21 (23)	0·646
Single organ failure†	6 (9)	16 (13·9)	0·412	1 (8)	3 (12)	0·710	5 (10)	13 (14)	0·461
Haemorrhage	0 (0)	5 (4·3)	0·095	0 (0)	4 (16)	0·159	0 (0)	1 (1)	0·448
Stroke	1 (2)	1 (0·9)	0·685	0 (0)	1 (4)	0·474	1 (2)	0 (0)	0·191
Other‡	11 (17)	11 (9·6)	0·204	4 (31)	2 (8)	0·129	7 (13)	9 (10)	< 0·001
Unknown	3 (5)	8 (7·0)	0·552	0 (0)	0 (0)	–	3 (6)	8 (9)	0·534

Values in parentheses are percentages. *Includes both lymphoid and non-lymphoid malignant disease. †Includes death from pulmonary, renal, cardiac, hepatic and gastrointestinal failure. ‡Other includes benign recurrence of disease. TACE, transarterial chemoembolization. §χ^2 test.

Table 5 Cause of graft failure after liver transplantation for patients with hepatocellular carcinoma in two separate epochs of follow-up and stratified by use of pre-transplant transarterial chemoembolization

	Overall			0–90 days			90 days to 60 months		
	TACE (*n* = 75)	No TACE (*n* = 137)	*P*†	TACE (*n* = 24)	No TACE (*n* = 43)	*P*†	TACE (*n* = 51)	No TACE (*n* = 94)	*P*†
Acute rejection	1 (1)	0 (0)	0·178	1 (4)	0 (0)	0·186	0 (0)	0 (0)	–
Chronic rejection	2 (3)	6 (4·4)	0·546	0 (0)	1 (2)	0·457	2 (4)	5 (5)	0·720
Primary graft non-function	9 (12)	12 (8·8)	0·496	9 (38)	12 (28)	0·561	0 (0)	0 (0)	–
Acute vascular occlusion	4 (5)	6 (4·4)	0·765	2 (8)	6 (14)	0·543	2 (4)	0 (0)	0·058
Vascular occlusion	0 (0)	2 (1·5)	0·297	0 (0)	0 (0)	–	0 (0)	2 (2)	0·299
Non-thrombotic infarction	1 (1)	3 (2·2)	0·667	1 (4)	2 (5)	0·930	0 (0)	1 (1)	0·462
Recurrent disease*	15 (20)	25 (18·2)	0·797	1 (4)	0 (0)	0·186	14 (27)	25 (27)	0·933
Biliary complications	4 (5)	5 (3·6)	0·578	0 (0)	0 (0)	–	4 (8)	5 (5)	0·573
Other	8 (11)	34 (24·8)	0·040	3 (13)	10 (23)	0·374	5 (10)	24 (26)	0·059
Unknown	5 (7)	11 (8·0)	0·739	0 (0)	2 (5)	0·295	5 (10)	9 (10)	0·968
Graft still functioning at death	26 (35)	33 (24·1)	0·222	7 (29)	10 (23)	0·682	19 (37)	23 (24)	0·235

Values in parentheses are percentages. *Includes recurrence of hepatitis C virus, and cholestatic liver diseases (primary sclerosing cholangitis and primary biliary cholangitis). TACE, transarterial chemoembolization. †χ^2 test.

Five-year patient survival rates were similar for patients who received TACE and those who did not: 75·2 (95 per cent c.i. 68·8 to 80·5) and 75·0 (70·5 to 78·8) per cent respectively (HR 0·93, 95 per cent c.i. 0·69 to 1·27; $P = 0·661$) (*Fig. 1* and *Table 3*). Five-year graft survival rates were also comparable: 71·3 (64·9 to 76·8) and 71·1 (66·6 to 75·1) per cent (HR 0·95, 0·72 to 1·25; $P = 0·602$). Adjustment for both patient and recipient characteristics had little impact on these comparisons ($P = 0·821$ and $P = 0·964$ respectively). Neither patient mortality (2 or more *versus* 1 TACE treatment: HR 0·97, 0·61 to 1·55; $P = 0·903$) nor graft failure (HR 1·02, 0·66 to 1·56; $P = 0·672$) increased with the number of TACE treatments received (*Table S2*, supporting information).

The impact of TACE on mortality after transplantation did not differ within 90 days (HR 0·69, 0·34 to 1·41) or after 90 days (HR 1·04, 0·71 to 1·54) (P for interaction = 0·291) (*Table S3*, supporting information). Similarly, TACE had no impact on graft survival within (HR 0·92, 0·55 to 1·55) and after (HR 1·05, 0·75 to 1·52) 90 days (P for interaction = 0·676). There was also no evidence to suggest that the impact of TACE on outcomes after transplantation was affected by whether DCD or DBD livers were used (*Table S4*, supporting information).

The biggest difference in causes of death between TACE and no-TACE groups was in the recurrence of malignant disease in patients who died between 90 days and 5 years after transplantation (*Table 4*). Among patients who died in that interval, 16 of 52 patients (31 per cent) who had TACE

developed recurrence of malignant disease compared with 15 of 90 patients (17 per cent) who did not have TACE ($P = 0{\cdot}121$). Among patients who lost the graft owing to occlusive events (including vascular occlusion, acute vascular occlusion and non-thrombotic infarction), the proportions of patients who did and did not receive TACE were similar: five of 75 (7 per cent) and 11 of 137 (8·0 per cent) respectively ($P = 0{\cdot}739$) (*Table 5*).

Discussion

Recipients who were treated with TACE were more likely to have negative tumour characteristics, but less likely to have signs of end-stage liver disease. TACE recipients were more likely to have waited longer for liver transplantation but there was no evidence that TACE increased the risk of surgical complications, including HAT. Treatment with TACE before transplantation did not affect the risk of death or graft failure after transplantation, and these results did not depend on the number of TACE treatments or the type of donor organ (DCD or DBD).

A key limitation is that information on tumour characteristics at the time of transplantation was not available. Therefore, the extent to which response of tumour characteristics to TACE acts as a prognostic marker for survival following transplantation could not be assessed. Another limitation is that only patients who went on to receive a liver transplant were included. The included cohort may therefore represent a selected sample of patients with HCC who had more favourable tumour biology than those who died before transplantation and those removed from the waiting list owing to tumour progression beyond transplantable criteria. The frequency of HAT and biliary complications after transplantation may represent an underestimation of their true frequency[4]. These post-transplant complications, although known to be rare, can be quiescent in their clinical presentation, especially HAT, where the rapid development of collateral circulation can quickly compensate for occlusion of the hepatic artery[21]. Therefore, the small number of these complications identified in the Standard National Liver Transplant Registry may have precluded the detection of significant differences between those who received TACE and those who did not. However, the frequency of complications is consistent with that in other studies[4,5].

The results are in line with those of the two recent multicentre studies[6,7] carried out in the USA and Europe, although it is not known whether any UK liver transplant centres contributed data for analysis in the European study. An important difference is that, with about 40 per cent of patients with HCC receiving TACE before transplantation, the use of TACE in England was considerably lower than that in the US (79 per cent) and European (72 per cent) studies[6,7], which is likely to be explained by the waiting list time for liver transplantation being relatively short in England. On the other hand, there was no evidence of more HAT, biliary tract strictures or leaks, which is in contrast to a recent meta-analysis[5] of the impact of TACE on post-transplant complications that found a 1·6-fold increase in the frequency of hepatic artery complications.

The characteristics of patients with HCC who received TACE before transplantation reflect the current aims of this therapy. TACE was given to those who had more severe tumour biology, those who were considered at least risk of hepatic and renal decompensation, and those who had to wait longer to receive a transplant[1]. It must therefore be acknowledged that patients selected to receive TACE before transplantation were different from those who were not. Possible residual confounding may explain why a post-transplant survival advantage linked to TACE was not observed, even after adjustment for recipient and donor characteristics[1]. Similarly, differences in tumour characteristics may also explain why patients who received TACE more often died from tumour recurrence. Finally, TACE itself might also have caused an increase in circulating tumour cells, but it is unlikely that this contributed to a higher mortality rate from HCC[22].

No differences in the incidence of HAT and other potentially TACE-related complications, such as biliary strictures and leaks, were identified, as reported in previous studies[21,23]. Therefore, TACE either does not confer an increased risk of early post-transplant complications, which are sometimes attributed to surgical technical failure[24], or improvements in administration of TACE and surgical technique mean that TACE-related intimal injuries, including oedema, aneurysm, fibrosis and thrombosis, do not translate into increases in postoperative complications or early graft failure[23]. In this context, it is also important to note that no difference was observed in the impact of TACE on outcomes after transplantation according to whether DBD or DCD organs were used[25]. It has been shown by statistical modelling that, under the new national recipient selection and organ allocation scheme introduced in 2018, patients with HCC who have preserved liver function may have to wait significantly longer to receive a liver transplant[26]. Furthermore, the use of TACE in patients on the waiting list for transplantation should not be considered as a contraindication to the use of DCD livers.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

SUPPLEMENTAL INFORMATION

Figure 1: Flow chart detailing selection of study population (2006-2016).

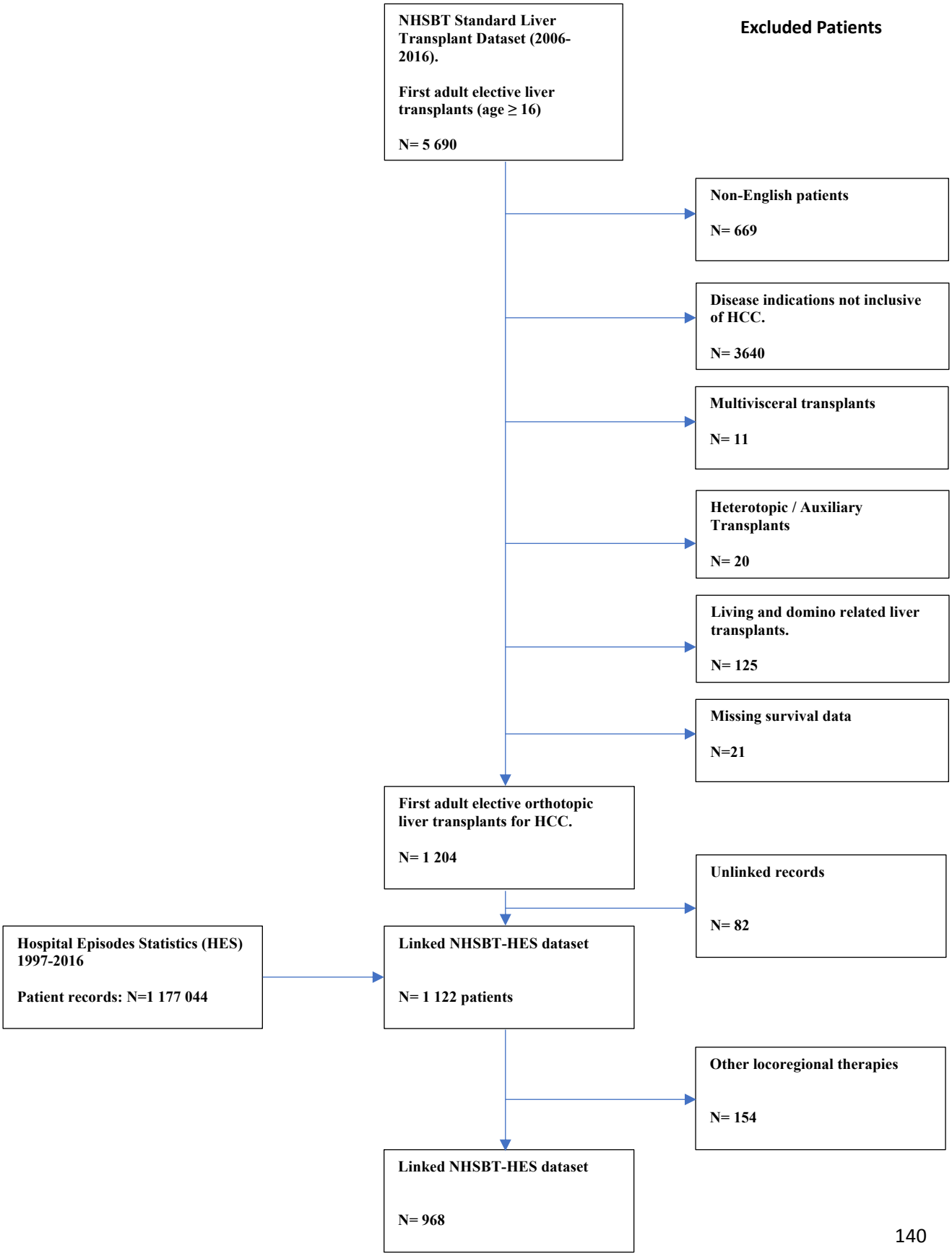

Table S1: Comparison of recipients' characteristics in linked and unlinked NHSBT records (n=1204).

Indication group		Unlinked N=82	Linked N=1122
DONOR		**% / N**	**% / N**
Sex	Female	46.3% (38)	41.8% (469)
Cause of death	Trauma	9.8% (8)	9.8% (110)
Donor Type	DCD	31.7% (26)	31.6% (354)
ABO Match	Identical	93.9% (77)	98.4% (1 104)
Graft Type	Segmental	3.7% (3)	6.2% (69)
Organ appearance	Abnormal	23.2% (19)	26.2% (294)
Steatosis	Presence	56.1% (46)	46.2% (518)
Capsular damage	Presence	8.5% (7)	14.5% (163)
Age (years)	Mean (SD)	54.1 (15.8)	49.0 (15.9)
Donor BMI, kg/m^2	Mean (SD)	27.0 (4.9)	26.5 (5.0)
Cold Ischaemic Time (mins)	Mean (SD)	514.1 (164.3)	499.7 (163.5)
RECEIPIENT			
Sex	Female	23.2% (19)	18.5% (208)
Age (years)	Mean (SD)	57.5 (8.5)	57.5 (6.9)
Ethnicity	Non-White	17.1% (14)	17.7% (198)
Tumor Characteristics	Max tumour >3cm	7.3% (6)	7.0% (78)
	Total tumour diameter >5cm	3.7% (3)	1.7% (19)
	>1 nodule	25.6% (21)	26.3% (295)
	Radiological evidence of vascular invasion	3.7% (3)	2.1% (24)
	AFP (Mean/SD)	214.8 (773.2) – Median 12	95.3 (348.7) – Median 10
UK Selection Criteria (Milan / Extended)	Extended	4.9% (4)	3.9% (44)
AJCC Criteria	T2	24.4% (20)	26.3% (295)
Era of Transplantation	Era 1: 2006-2010	65.9% (54)	45.8% (514)
	Era 2: 2011-2016	34.1% (28)	54.2% (608)
HCV status	Positive	37.8% (31)	40.1% (450)
Diabetes	Positive	20.7% (17)	27.9% (313)
Cirrhosis	Positive	91.5% (75)	92.1% (1 033)
Pre-transplant in patient status	Inpatient	7.3% (6)	4.7% (53)
Pre-transplant renal support	Presence	3.7% (3)	3.6% (40)
Previous abdominal surgery	Presence	12.4% (10)	7.9% (88)
Ascites	Presence	24.4% (20)	30.3% (340)
Encephalopathy	Presence	13.4% (11)	14.4% (161)
Varices	Presence	22.0% (18)	18.3% (205)
Functional Status	Restricted	52.4% (43)	42.8% (481)
BMI, Kg/m2	Mean (SD)	27.6 (4.5)	27.9 (4.8)
Creatinine	Mean (SD)	82.1 (23.2)	83.5 (28.5)
UKELD	Mean (SD)	51.4 (4.7)	51.0 (5.0)
MELD	Mean (SD)	14.0 (5.4)	12.8 (5.8)
Days on waiting list	Mean (SD)	149.2 (140.1)	128.1 (139.8)

Table S2: Impact of multiple TACE treatment on post-transplant patient and graft survival in two separate epochs of follow-up time (n=968).

	TACE compared to no TACE Hazard ratio (95% CI)	
Post-transplant survival	**Patient Survival**	**Graft Survival**
Unadjusted analysis		
- One TACE treatment (n=219)	0·85 (0·58-1·24)	0.91 (0.65-1.28)
- ≥ 2 TACE treatments (n=166)	1.06 (0.70-1.58)	0.99 (0.69-1.45)
Adjusted for recipient characteristics only*[1]		
- One TACE treatment (n=219)	0·90 (0·60-1·36)	0·96 (0·67-1·38)
- ≥ 2 TACE treatments (n=166)	0.98 (0.62-1.53)	0.97 (0.64-1.46)
Adjusted recipient and donor characteristics*[2]		
- One TACE treatment (n=219)	0.95 (0.62-1.45)	1.04 (0.72-1.51)
- ≥ 2 TACE treatments (n=166)	0.97 (0.61-1.55)	1.02 (0.66-1.56)

*[1]Adjusted for a) Recipient characteristics; sex, age, ethnicity, socioeconomic status, size of maximum tumour, total tumour diameter, no of tumours, AFP, vascular invasion, diabetes, HCV status, pre-transplant inpatient status, presence of cirrhosis, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, presence of varices, functional status, bmi, ukeld, waiting list time era of transplantation and b) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (Kg/m^2), cold ischaemic time.

Table S3: Impact of TACE on post-transplant patient and graft survival before and after 90 days post-transplantation (n=968).

	TACE compared to no TACE Hazard ratio (95% CI)		p-value for interaction*[2]
POST-TRANSPLANT PATIENT SURVIVAL	**0 to 3 months**	**3 to 60 months**	
Unadjusted analysis	0·75 (0·39-1·47)	0·99 (0·70-1.40)	0·47
Adjusted for recipient characteristics only*[1]	0·73 (0·37-1·45)	1·00 (0·68-1·45)	0·42
Adjusted recipient and donor characteristics*[2]	0.69 (0.34-1.41)	1.04 (0.71-1.54)	0.29
POST-TRANSPLANT GRAFT SURVIVAL			
Unadjusted analysis	0.89 (0.55-1.45)	0.98 (0.70-1.37)	0.76
Adjusted for recipient characteristics only*[1]	0.91 (0.55-1.51)	0.98 (0.68-1.40)	0.81
Adjusted recipient and donor characteristics*[2]	0.92 (0.55-1.55)	1.05 (0.75-1.52)	0.67

**[1]Adjusted for a) Recipient characteristics; sex, age, ethnicity, socioeconomic status, sixe of maximum tumour, total tumour diameter, no of tumours, AFP, vascular invasion, diabetes, HCV status, pre-transplant inpatient status, presence of cirrhosis, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, presence of varices, functional status, bmi, ukeld, waiting list time era of transplantation and b) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (Kg/m^2), cold ischaemic time.*

**[2] P-values represent whether HRs in each epoch of follow-up time differ significantly from each other.*

Table S4: Impact of TACE on post-transplant patient and graft survival in two separate epochs of follow-up time and according to donor type (n=968).

	TACE compared to no TACE Hazard ratio (95% CI)		P-value time dependency*[2]
POST-TRANSPLANT PATIENT SURVIVAL	**DCD**	**DBD**	
Unadjusted analysis	0·82 (0·47-1·43)	0·99 (0·69-1.49)	0·57
Adjusted for recipient characteristics only*[1]	0·84 (0·47-1·53)	0·98 (0·65-1·53)	0·67
Adjusted recipient and donor characteristics*[2]	0.82 (0.44-1.51)	1.03 (0.68-1.55)	0.53
POST-TRANSPLANT GRAFT SURVIVAL			
Unadjusted analysis	0.79 (0.48-1.32)	1.05 (0.73-1.52)	0.37
Adjusted for recipient characteristics only*[1]	0.79 (0.49-1.29)	1.04 (0.74-1.46)	0.36
Adjusted recipient and donor characteristics*[2]	0.83 (0.49-1.40)	1.11 (0.76-1.63)	0.35

**[1]Adjusted for a) Recipient characteristics; sex, age, ethnicity, socioeconomic status, size of maximum tumour, total tumour diameter, no of tumours, AFP, vascular invasion, diabetes, HCV status, pre-transplant inpatient status, presence of cirrhosis, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, presence of varices, functional status, bmi, ukeld, waiting list time era of transplantation and b) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (Kg/m^2), cold ischaemic time.*

**[2] P-values represent whether HR's in each epoch of follow-up time differs significantly from each other.*

9.0 DISCUSSION

9.1 Summary of results

In the last two decades, mortality after liver transplantation in the UK has more than halved for HCC patients despite the increased use of DCD livers in these patients.[72] However, one in four HCC recipients still die within five years compared to only one in six non-HCC patients.[33] Improvements in survival for HCC and non-HCC recipients can be explained by significant era-specific advancements in short-term mortality and in particular the short-term mortality of those receiving a DCD liver.[33,72] In fact, such has been the improvement over time in the use of DCD livers, mortality in those receiving these organs is now comparable to those who receive the historically more optimal DBD livers.

Impaired PS at the time of transplantation was found to be independently associated with post-transplant mortality in non-HCC recipients only, whilst in both HCC and non-HCC recipient's poorer PS was also associated with an increase in the incidence of major post-transplant complications and length of hospital stay.[73-74] The impact of PS on each of these post-transplant outcomes was limited only to the early post-transplantation time-period [73-74]

A total of 40% of HCC recipients in the UK received at least one treatment of TACE prior to their liver transplant.[75] There was however no evidence that TACE increased the risk of post-operative complications nor did it affect the risk of post-transplant mortality or graft failure.[75] These results did not depend on the number of TACE treatments, the type of donor organ (DBD or DCD), or the time-period after transplantation.[75]

With the exception of TACE, the impact on post-transplantation outcomes of all the risk factors that were tested in this thesis were proven to change with different epochs of follow-up time.[33,73-75] The impact of HCC – compared to non-HCC patients – was proven to be similar in the first 90 days following liver transplant and worse thereafter.[33] Era-specific improvements in the mortality of those who received a DCD liver were found in the first year after transplantation but not thereafter and impaired PS was associated with a poorer mortality but this lasted only in the first 3 months following transplantation.[73]

9.2 Main methodological themes:

a. Time-dependency of risk factors for post-transplantation outcomes.

There are number of assumptions when performing Cox regression analysis. The most important one is the so-called proportional hazards (PH) assumption which accepts that the effect of a given risk factor on post-transplant mortality is constant over the predefined period follow-up time.[68] The main methodological theme in this PhD was to test this PH assumption by consistently partitioning the post-transplantation time-period into two or more distinct relatively short epochs of follow-up time, generate hazard ratios for each of these epochs and then compare these hazard ratios to see if they differed from significantly each other. If they did, the effect of the risk factor is not constant and should be considered to be time-dependent effect.

Employing this method of statistical analysis was not new to the assessment of post-transplantation outcomes but in recent decades seemed to have been overlooked within the literature.[31-32] However, by consistently testing the PH assumption in this thesis I was able to identify several risk factors – including HCC, DCD donor type and PS – whose prognostic effect on mortality changes over different epochs of follow-up time.[33,72-73]

Methodologically, these are important findings as the results from the thesis have consistently shown that by identifying violations of the PH assumption and then searching for clinically plausible explanations it can be established whether there is a comparatively increased risk of mortality in the early post-operative time-period and thus more associated with surgical complications or peri-operative care or there is an increased mortality in the later post-operative period and more associated with chronic rejection or recurrence of an underlying liver disease. [33,72-73]

There are however two main limitations to this approach of testing the PH assumption.[76] First, there is still an acceptance that throughout the duration of each epoch the PH assumption still applies and the effect of a given risk factor on mortality within the epoch remains constant.[71-76] However, this is plausible given that the duration of our epochs were relatively short. Second, the epochs that were used to investigate and accommodate the time-dependency of the different risk factors were pre-defined.[76] The advantage of this approach is that the hazard ratios can be estimated using standard Cox regression methods and the results are easy to interpret.[76] The disadvantage is that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration are arbitrary.[33,76]

However, partitioning follow-up time in these pre-defined epochs is a recognised method to handle time risk factors with time-dependent effects and it can be justified on both clinical and statistical grounds.[76] Clinically, pre-defining the epochs in this way allowed us to test the impact of risk factors on time-periods in the post-operative follow-up where we would expect clinical complications to occur.[15,66] Statistically, each pre-defined epoch was of sufficient duration to contain enough events (i.e. patient death or graft failure) and thus statistical power to identify meaningful differences in mortality or graft failure if they did indeed exist.[68] This method of testing the PH assumption was also relatively easy to interpret and more applicable to a clinically orientated audience compared to other methods (i.e. Schoenfeld residuals, plotting Kaplan-Meier curves of the survival function of risk factor versus survival time, and the generation of time-dependent covariates using interaction terms).[33]

Other options to test the time-varying impact of risk factors could have been considered in this thesis.[76] For example, testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals on functions of time could have been used.[76] In this instance, a non-zero slope on visual inspection of each risk factor indicates violation of the proportional hazards (PH) assumption. Statistical tests of the PH assumption for each risk factor in the Cox model or a global test of proportionality (for all risk factors) can also be performed.[76] In fact , it is recommended that when using Schoenfeld residuals both methods of testing for the non-zero slope are employed.[76] This is because there are certain types of

non-proportionality that will not be detected by statistical tests of non-zero slopes alone but might become more obvious when looking at graphs of the residuals such as non-linear relationship between the residuals and the function of time or the influence on the proportionality of outliers.[76] The other issue with using scaled Schoenfeld residuals – from a clinical perspective at least - is that the interpretation of the results can be confusing and their relevance difficult to translate into clinical practice.[76]

Another alternative method of testing the PH assumption is through visual inspection of Kaplan-Meier curves.[76] If the selected risk factor satisfies the PH assumption then the graph of the survival function versus the survival time should result in graphs with parallel curves.[76] Similarly, the graph of the log(-log(survival)) versus the log of survival time should also result in parallel lines if the variable is proportional.[76] However, with respect to this thesis this method of testing the PH is limited as it does not work well for continuous risk factors or risk factors, like PS that have many levels as the graph becomes too cluttered.[73] In contrast, the Kaplan-Meier curves can also look sparse when there are fewer time points and under these circumstances it can be difficult to determine how close to parallel is close enough.

The use of time-dependent covariates - generated by creating interactions of the potential risk factors and different survival time periods – can also be used within Cox models to test the PH assumption.[33] In this instance, if any of the time-dependent risk factors are significant then they are considered not to be proportional. It is important to note that if the duration of the different survival time periods that I used for the analyses described in my thesis are relatively short, and the impact of risk factors being time dependent will therefore be small.

In addition to alternative approaches to test the PH assumption there are also other statistical methods that would allow the effect of risk factors to vary over time that are worth considering for the future. We also must acknowledge the emerging role of machine-based learning and methods that have been developed to test the PH assumption within this approach. However, it is important to note that machine learning was not the methodological focus of this research.

b. Issues with data quality

At the start of this project I had three datasets linked including the SNLTR, HES and a cohort HCC patients from the National Cancer Registration and Analysis Service (NCRAS).[78] One of the intentions of this linked dataset was to use to the use staging information in NCRAS to supplement the information held on recipient characteristics in the SNLTR. Unfortunately, when exploring the staging information in the NCRAS dataset I identified that it was not adequately complete enough to allow a better assessment of the suitability of HCC patients for liver transplantation.[78] In fact in most years, 98% of the information on tumour characteristics were missing.[79] This NCRAS dataset was therefore not used for the research described in this thesis.[77,79] However, thanks to this project and that of collaborative partnership

between NCRAS and the British Association of the Study of the Liver (BASL) national efforts have been instituted to improve data collection from HCC multidisciplinary teams (MDTs) across the UK.

Another intention for this thesis was to use the linked NCRAS and HES datasets to identify the changing prevalence of the PLD's that lead to HCC. However, when this analysis was conducted we found the proportion of HCC patients with a recorded PLD in HES to be markedly lower than expected. For example, in comparison to a previously published single centre analysis from the UK, the proportion of PLD's identified in my HCC cohort of patients was only a third of that identified in this study.[12] Also, when comparing our national results with those of NCRAS – who linked their own national NCRAS-HES dataset – we were again identifying significantly less PLD's.

In response, considerable efforts throughout the PhD were committed to identifying why the results of my analysis were so different from others. This included checking the coding and the quality of the data linkage. My coding was validated by an external analyst at NCRAS and found to be satisfactory whilst the linkage rate in my dataset was 95%. On repeated correspondence with analysts at NCRAS I did discover that in comparison to the linked dataset held at NCRAS my dataset had from 2007 onwards significantly less linked HES records per HCC patient. Searching for explanations two important issues were identified. First, NCRAS analysts admitted to a 'looser' linkage practice explaining why after 2007 they had more HES records per patient and potentially identified more PLD's per patient. Second, prior to this year they also admitted they may have records without updated or even incorrect NHS numbers making linkage unreliable.

To explore these issues further additional CAG approval was obtained to re-link our NCRAS and HES datasets and review whether we were still observing an under ascertainment of PLD's in comparison with NCRAS own linked dataset. However, there were considerable logistical and data governance issues to address this next step and there was little enthusiasm from either data controllers, NCRAS or NHS Digital. Therefore, the issues of data quality and linkage will need to be explored in ongoing projects and its importance must not be underestimated as the results could have potentially drastic implications for all linked datasets utilised by either of the data controllers.

c. Missing data

To prevent the loss of patients due to missing data values we decided to use multiple imputation techniques.[70-71] Missing data are unavoidable in epidemiological research, especially research that involves the use of linked large national healthcare datasets.[74,77] To avoid bias or loss of information that can result from missing data there are number of different methods that can be utilised.[70-71,77]

In single imputation missing values can be replaced with values imputed from the mean of observed values using a missing category indicator.[77] In this method of imputation, missing values can also be replaced with the last measured value (i.e. the last value is carried forward) within that data item –

albeit only if you have multiple points of measurement in your dataset.[77] However, neither of these approaches is considered statistically valid and both can lead to bias.[71,77] Single imputation of missing values can often result in an underestimation of the variability (standard error) because each unobserved value carries the same weight in the analysis as the known observed value.[77] Also, the validity of single imputation does not depend on the data missing at random but instead the specific assumptions that are being made to replace the missing value i.e. the missing value is identical to the last observed value.[77] These assumptions are often biased and therefore this method of imputation should be use with great caution.[77]

Another method of imputation include full information maximum likelihood.[77] The principal of this method is to estimate parameters of the joint distribution of outcome and covariates that if true would maximise the probability of observing values that we in fact observed.[77] For example, if values are missing in a given patient, we obtain the likelihood by summing the usual likelihood over all possible values of the missing data provided.[77] The strengths of this approach is that it is easier to implement than multiple imputation, there is no issue with the incompatibility between the imputation model and the analysis model, and different from multiple imputation analysis using full information maximum likelihood on the same data will produce the same results each time the analysis is performed.[77] The weakness of this approach is in its applicability.[77] Specially designed software – which we did not have – is required to use the full maximum likelihood estimation method.[77] Another limitation, is that there might be an assumption of multivariate normality.[77]

It is also sometimes valid to ignore missing data.[77] There are circumstances where complete case analysis (as opposed to imputation) and the exclusion individuals with missing data will not lead to bias.[77] For example, when missing data occurs only in an outcome variable that is measured once per individual (i.e. patient death or graft failure) then such analyses will not be biased as long as all the variables associated with that outcome being missing can be included as covariates and that the missing data is assumed to be missing at random.[77] Similarly, missing data in predictor (risk factor) variables do not cause bias in analysis of complete cases as long as the reasons for missing data are also unrelated to the outcome variable.[77] In these circumstances specialist imputation methods to address missing data may lessen the loss of power and precision that would result from having to exclude individuals with incomplete risk factor variables however these methods would – as explained – not be needed to avoid bias.[77]

In this thesis however I opted not to lose power by excluding individuals with missing values and instead explored methods to produce statistically more powerful analyses by including individuals with incomplete data.[77] For example, if I made the assumption that missing data in the linked datasets was missing at random, I could have used random-effect models to incorporate information on partially observed variables from intermediate time points or used Bayesian methods to incorporate partially observed variables into a statistical model from which the analysis of interest can be derived.[70-71,77] Alternatively, I could have weighted the analyses to allow for missing data.[77] However, in order to be

able to ultimately use standard statistical methods – like Cox regression – to investigate associations with the outcomes (usually patient death and or graft failure) I ultimately opted to use multiple imputation techniques. It was important to use Cox regression not only to incorporate our time-dependent analysis technique but also for ease of interpretability for the clinical orientated audience.

To maximise the benefit of multiple imputation certain recommend criteria had to be met with my analysis.[33,72-75,77] First, the proportion of the missing data in the linked dataset was not too large to reliably impute and did not exceed 40% nor was the proportion of missing data was not less than 5% in which case multiple imputation is unlikely to confer any benefit over complete-case analysis.[33,77] Second, the missing data was not solely confined to the dependent variable and fourth, the data was not assumed to be either missing completely at random (again if this was the case and it could be proven complete case analysis could be utilised.[77]

Even having met this criteria there are also limitations to the use of multiple imputation that must be recognised. For example, there is the potential to include bias if the included variables are not – as multiple imputation assumes – normally distributed.[70-71,77] Similarly, if data are not missing at random (as can sometimes happen inherently) then the bias that can be introduced is almost as big or bigger than the bias of analyses that use only complete cases.[70-71,77] In fact, to gain plausibility with the 'missing at random' assumption then it is important to include – as I did - a wide range of variables in the imputation models, including all variables that will be included in the Cox regression model.[70-71,77]

9.3 Main clinical themes

a. Liver transplantation for HCC.

In the first of my analyses in chapter three, I identified that the number of patients being transplanted for HCC significantly increased across the four pre-determined eras of transplantation.[72] Between 1997 and 2001, just over 1 in 10 first elective liver transplants were performed for HCC compared to almost 1 in 4 between 2012 and 2016.[72] In fact, such was the demand placed on liver transplantation services that from 1997 to 2016 increases in the total number of first-time elective liver transplants were almost purely driven by increases in the transplantation of patients with HCC.[72]

In the same analysis, overall 5-year post-transplant mortality in HCC and non-HCC recipients was found to decrease by half and graft failure by forty percent.[72] Defining era-specific improvements in outcome is difficult and rarely attributable to a singular factor.[15,72,80] In this instance improvements in the survival of both cohorts are likely due to a combination of better matching of donor and recipients, developments in immunosuppression and anti-viral medications, and decreases in cold ischaemic time.[15,72,81]

Impressively, these huge improvements in post-transplant outcome were achieved during a time in which donor quality was found to have significantly decreased.[72,81-84] By employing time-dependent methods I was able to demonstrate that for both HCC and non-HCC patients the factors associated with the early post-transplant epoch of follow-up time (up to 90 days post-operatively), such as surgical technique and peri-operative care, had the more substantial impact on improved overall post-transplant mortality.[23,33,72-75] The scale of era-specific improvement in outcomes in the post-transplant epochs beyond 90 days were not so marked.[72]

In chapter four, the post-transplant outcomes of HCC and non-HCC patients were compared. Interestingly, previously published international consensus guidelines from 2012 state that the expected survival of those receiving a liver transplant for HCC should be the same as the expected survival of those who receive a transplant for other PLD's.[26] However, despite the introduction of the Milan HCC selection criteria in 1996, post-transplantation outcomes between the two cohorts are unlikely to have ever been comparable.[33] This was evidenced in my results where the 5-year post-transplant survival in HCC recipients was found to 75% compared to the 85% survival observed in non-HCC recepients.[33] Analysing these same outcomes in pre-defined epochs of follow-up time, no difference in mortality between HCC and non-HCC patients was identified in the first 90 days following transplantation but thereafter patients with HCC had a significantly poorer survival.[33]

Following this time-dependent analysis - which included the stepwise adjustment for recipient and then donor factors - I was able to demonstrate that it in HCC recipients it was post-transplant tumour recurrence rather than an unequal distribution of DCD and sub-optimal livers that is still the mitigating factor that prevents comparable post-transplant outcomes with non-HCC patients.[33] Therefore, until we can add to the selection criteria new parameters that better predict the behaviour of HCC post-transplant outcomes between these cohorts are unlikely to be comparable.[3,33] Acceptance of this reality is may be best demonstrated by the behaviour of the UK liver transplant community whose reluctance to transplant patients beyond the Milan HCC selection criteria (less than 7% of patients) reflects an apprehension about the risks of post-transplant tumour recurrence.[33]

Irrespective of international consensus guidelines, new donor liver allocation schemes in the UK now seem to reflect my findings by accepting that outcomes of HCC and non-HCC patients are not comparable.[42,47] For example, national selection criteria is now based on transplant 'benefit' – in which they aim to maximise the net life years gained from the point of registration on the waiting rather than providing the greatest chance of surviving after transplantation.[86] However, the decision to offer HCC patients a liver transplant is further complicated as other treatments, including liver resection and RFA, have to be considered, which is all the more important considering the impact that an increased use of liver transplantation in HCC patients will have on outcomes for non-HCC patients given the ongoing donor organ shortage.[3,37]

In the future, identifying the exact cause of death in HCC recipients is also imperative. Specifically, it needs to be identified whether post-transplant mortality is linked to tumour related or non-tumour related

characteristics (i.e. co-morbidity). This will help inform patient selection and organ allocation policies and allow us to better understand which patients with HCC do well with a liver transplant.

b. Liver transplantation for HCC patients using livers donated after circulatory death.

Increases in the number of patients who require a liver transplantation in the UK and elsewhere have contributed to a chronic shortage of donors.[3,23,33,85-87] In response, DCD livers have increasingly been used in the UK to address the discrepancy and in particular in patients with HCC.[33,84] Between 2002 and 2006 only 5.0% of all HCC recipients had received a DCD liver compared to 35.2% between 2012 and 2016.[72]

The use of DCD livers varies internationally.[85-86] Early reports of poorer graft and patient survival[88-91] led to a reluctance of some countries, such as the US, to maximise DCD utilisation, whilst in other countries, such as the UK, there was a reliance on DCD donors to provide liver transplantation to patients before their disease progressed beyond transplantable criteria.[33,86-87]

International variation in the use of DCD livers must also be correlated with pressures on waiting lists. In the US in 2018, there were 13,000 patients on the waiting list for a liver transplant with a median waiting time of 11 months with only 7% using DCD livers.[85] In comparison, median waiting time was less than 5 months in the UK with 30% of transplants using DCD livers.[86] A reluctance to increase DCD utilisation in some countries is surprising for several reasons. Firstly, waitlist dropout of HCC (and non-HCC) patients in many countries is known to be increasing.[36] Secondly, my analyses show that donor characteristics, including donor type (DCD/DBD) have little to no impact on the risk of post-transplant mortality.[33] Finally, international research including the analysis presented in chapter five shows significant era-specific improvements in outcomes following DCD liver transplantation.[45] Interestingly, in this same analysis, no statistically significant difference in mortality between those receiving a DCD compared to a DBD donor liver was identified between 2012 and 2016.

The substantial era-related improvements in overall 3-year mortality that were observed following DCD liver transplantation (and not DBD transplantation) were again driven almost solely by improvements in early post-transplant mortality and in particular in the first year following transplantation. Reductions in the proportion of patients who died as a result of sepsis and cardiac failure, and the proportion of patients whose post-operative rehabilitation was complicated by renal failure help explain improvements in early post-operative outcomes. This also most likely indicates the UK have become better at selecting the operative candidates who are able to tolerate the systemic ischaemic reperfusion effects of DCD transplantation and also better at providing peri and post-operative care for these patients.[45]

In this same analysis, era-related improvements in graft failure were also identified but again only in DCD patients and only in the first year following transplantation. More optimal allocation of DCD donor livers can explain some of this improvement as can improvements in surgical and endoscopic techniques (the latter for the post-operative treatment of biliary complications), and reductions in overall ischaemic times.

Nevertheless, I found that graft failure was still markedly more common in those who received a DCD liver than in those receiving a DBD liver. Consequently, further analysis in chapter five did indicate that era-specific improvements in mortality in patients receiving a DCD liver have most like been aided by an increase rate of retransplantation and in this cohort of patients retransplantation is almost universally with DBD livers. It can therefore be argued that although increases in DCD utilisation have increased the number of patients who can be transplanted they have also increased the average number of organs that each patient requires.

An increasingly limited potential donor pool, less than optimal DBD donation rates, and increases in the number of patients with HCC who require liver transplantation indicate that the need to use of DCD donor livers is set to remain.[33,87] My finding that mortality following liver transplantation now appears to be comparable for patients receiving DCD and DBD donor livers therefore has major implications and in particular for countries with high waiting list mortalities and low rates of DCD utilisation.[39]

Ongoing work in the use of DCD livers should concentrate on reducing graft failure. In my study, changes over time in the rates of graft failure did not reflect those of mortality and more work needs to be done on optimising DCD graft function.[92-93] Improvements in graft failure have long been linked to improvements in patient mortality.[92-93] As such, the transplant community eagerly await the longer terms outcomes of multinational organ perfusion studies to see whether either in-vivo or ex-vivo restoration of donor liver grafts prior to implantation translate into better longer term outcomes.[92-93]

c. Performance status in HCC and non-HCC patients who received a liver transplant.

In chapters six and seven, it became evident from both of my analyses that frailty at the time of transplantation was strongly associated with the indication for transplantation itself.[73-74] For example, only one in fifteen HCC recipients had the poorest PS score compared to one in three non-HCC recepients.[73] These differences in the distribution of PS scores very much reflect the differences in the disease processes that require transplantation. HCC patients are known to present more often with relatively preserved liver function, fewer complications of end-stage liver disease and better functional ability whereas non-HCC patients suffer more often with the clinical sequelae of liver cirrhosis and are more likely to be confined to the bed or chair.[73]

These analyses also found that the impact of pre-transplant PS on post-transplant mortality differed according to the indication for transplantation.[73] In non-HCC patients, those with the worst pre-transplant PS scores were found to have a worse mortality in the 90 days after surgery but not thereafter.[73] Admittedly, no similar association with PS and post-transplant mortality was identified in HCC patients although it must be acknowledged that a larger sample of HCC patients with worst pre-transplant PS scores (PS4 or PS5) would be needed to definitively confirm there really was no association with post-transplant mortality.[73]

Having adjusted extensively for liver disease severity, I postulated that the time-dependent association of PS and post-transplant mortality observed in non-HCC patients is most likely explained by the fact that PS scores are a more inclusive assessment of patients health status than specific measurements of end-organ dysfunction.[53,73] It may also be that PS scores may also better reflect the waiting list behaviours such as prolonged immobilization and reduced physical activity that in other surgical specialities have been found to be associated with poorer mortality.[51-52,73,93] A clinically plausible explanation as to the limited association of PS on mortality beyond 90 days could be that the rapid reversal of severe liver dysfunction that follows restoration of liver function after transplantation reduces the risk of post-operative complications and death.[73]

In other metrics of surgical outcome, I also found impaired PS at the time of transplantation to be associated with an increased length of hospital stay immediately after transplantation and this was the same in both HCC and non-HCC patients.[74] Again, it is the more global assessment of health and health behaviours provided by PS scores that most likely explains why when compared to individual measures of organ dysfunction they are better prognostic indicators of post-transplant complications and hospital stay.[73-74,94]

There are limitations to the use of PS scores to help predict outcomes. There are a variety of metrics available to quantify PS and it must be acknowledged that ECOG scores are one of the more subjective scoring systems.[95-96] Although this makes them more reproducible it also leaves them more susceptible to inter-observer error.[95-96] In some studies, the coefficient recording the agreement between clinicians of ECOG status was as low as 50% whilst in others it was as high as 91%.[95] However, in multiple epidemiological analyses, ratings of overall health status have consistently been found to be powerful predictors of subsequent mortality.[73,95]

In summary, asking patients questions about their general health including their ability to perform ADLs remains an important part of the transplant work-up. Looking to the future, the primary importance of the association of PS and mortality or length of hospital stay may be through its potential to identify patients who would benefit from pre- or even post-transplant interventions that are designed to improve frailty.[53-54] Therefore, these more subjective tools to measure PS such as ECOG status might be best viewed as screening tools that can be used alongside other more objective and specific measurements of PS.

d. The impact on post-transplant outcomes of TACE administered to HCC patients on the liver transplant waiting list.

In chapter eight of this thesis, I found that between 2006 and 2016 about 40% of HCC patients who received a liver transplant in England had received at least one treatment of TACE. I also found that those who did receive TACE were more likely to have the tumour characteristics that were predictive of poorer post-transplantation outcomes but were less likely to have signs of end-stage liver disease. There was no evidence that the

administration of TACE prior to transplant affected the risk of mortality of graft failure after it. Hence, it was evident that TACE was given to those who had more severe tumour biology, to those who were considered at least risk of hepatic and renal decompensation, and to those who had to wait longer to receive a transplant. Therefore, in the UK the characteristics of the HCC recipients who received TACE seem to reflect the current aims of the therapy.

In further analysis, I also found TACE not to confer an increased risk of the early post-transplantation complications – HAT and biliary strictures – that are sometimes attributed to surgical technical failure. This was also found to be the case, irrespective of whether a DBD or DCD liver had been used. I concluded that improvements in the administration of TACE and or compensation by improved surgical technique has meant that the almost inevitable TACE-related intimal injuries, including oedema, aneurysm, fibrosis and thrombosis, do not seem to be translating into increases in post-operative complications or early graft failure.[18-22]

In summary, my final analysis identified that TACE is neither a risk factor for early complications nor a protective factor for longer-term patient outcomes. These are important findings as it is unlikely that in the future the use of TACE before transplantation will decline and my study provides evidence that the use of TACE in patients on the waiting list for transplantation should not be considered as a contra-indication for the use of DCD livers. However, future research should focus on quantifying the potential benefit of TACE to those HCC patients waiting to receive a liver transplant.

9.4 Future recommendations

a. Recommendations for policy makers and clinicians in the liver transplantation community.

1. The increasing use of DCD livers with substantial improvement of post-transplant outcomes in the UK is a guiding example for countries with a high waiting list mortality and a low DCD utilisation as well as for countries where a high proportion of potential liver transplant recipients have HCC.

2. Donor liver allocation schemes should employ criteria based on transplant 'benefit' – in which they aim to maximise the net life years gained from the point of registration on the waiting list rather than providing the greatest chance of surviving after transplantation.

3. PS scores should remain an important part of the transplantation workup as they can help determine the suitability for transplantation, the risk of mortality and complications after it, and the length of hospital stay.

4. The use of TACE to modulate tumour growth on the waiting list should therefore be encouraged in HCC patients.

5. The use of TACE in patients on the waiting list for transplantation should not be considered as a contra-indication for the use of DCD livers.

b. Recommendation for future research

1. Further research needs to continue to add to the Milan selection criteria new parameters – beyond tumour size and number – that better predict tumour recurrence in HCC patients.

2. Collaborative research projects between the UK and other countries should focus on investigating how best to increase the use of DCD in these countries with the primary goal to reduce waitlist dropout.

3. The benefit of targeted prehabilitative interventions to patients with poor PS on the waiting list should be explored. Firstly, it should be determined whether prehabilitative interventions improve the PS status of patients on the waiting list. Secondly, it should be determined whether these improvements in PS on the waiting list translate into improvements in post-transplant survival, quality of life, and length of hospital stay.

4. The true benefit of TACE on preventing waiting list dropout in HCC patients will therefore have to be determined.

5. The application of more sophisticated statistical methods to test the PH assumption of potential risk factors should encouraged as searching for clinically plausible explanations for the time-dependent effects of these risk factors can help guide service development and lead to positive changes in clinical practice.

6. The linked datasets should be made publicly available for further research and audit purposes both for this research group and others. To facilitate these amendments applications to the HRA ethical and CAG should be made, identifiable data items anonymised, and data controllers contacted to change data sharing contracts.

10. CONCLUSION:

In the last two decades, the number of patients receiving a liver transplant has increased significantly in the UK as well as in many other countries. However, despite the rise in use of DCD and other sub-optimal donor organs, post-transplantation mortality for both HCC and non-HCC patients has more than halved. Improvements in overall survival have been driven predominantly by decreases in short-term mortality but post-transplant outcomes for HCC recipients are still worse compared to non-HCC patients.

The mortality of patients receiving a DCD liver has more than halved and as a result survival following liver transplantation is now comparable to recipients of a DBD liver. Therefore, the increasing use of DCD livers in the UK coupled with the substantial improvement of post-transplant outcomes is a guiding example for countries with a high waiting list mortality and a low DCD utilisation as well as for countries where a high proportion of liver transplant recipients have HCC.

In HCC and non-HCC recipient's, PS scores prior to transplantation improves the ability to predict post-transplant mortality, post-operative complications and hospital length of stay. The use of pre-operative PS scores could therefore be useful to counsel patients prior to surgery and inform policy makers such that appropriate resources can be allocated. The use of PS scores at the time of transplantation may also be used to guide waiting list interventions that could improve pre-transplant PS and in doing so improve post-transplant survival and reduce post-operative LOS and complications.

In HCC recipients alone, TACE has been identified as neither a risk factor for early complications nor a protective factor for longer-term patient outcomes. It is unlikely that in the future the use of TACE before transplantation will decline but we must acknowledge that in the context of liver transplantation, the potential benefit of the use of TACE in early-stage HCC patients is restricted to its impact on tumour growth on the waiting list and prevention of disease progressing beyond transplantable criteria.

Finally, re-establishing the relevance of using more flexible statistical methods to study outcomes after liver transplantation should be encouraged. By testing the prognostic impact of a range of risk factors in different epochs of follow-up time, their relative impact on post-transplant mortality has been more specifically demonstrated in both HCC and non-HCC recipients. This method of time-dependent analysis moves beyond the conventional assumptions of the commonly used Cox regression (i.e. the effect of risk factors on post-transplant mortality is constant over time) and re-introduces after decades an exemplar of statistical modelling that is likely to be informative for a wider range of questions about determinants of outcomes after liver transplantation.

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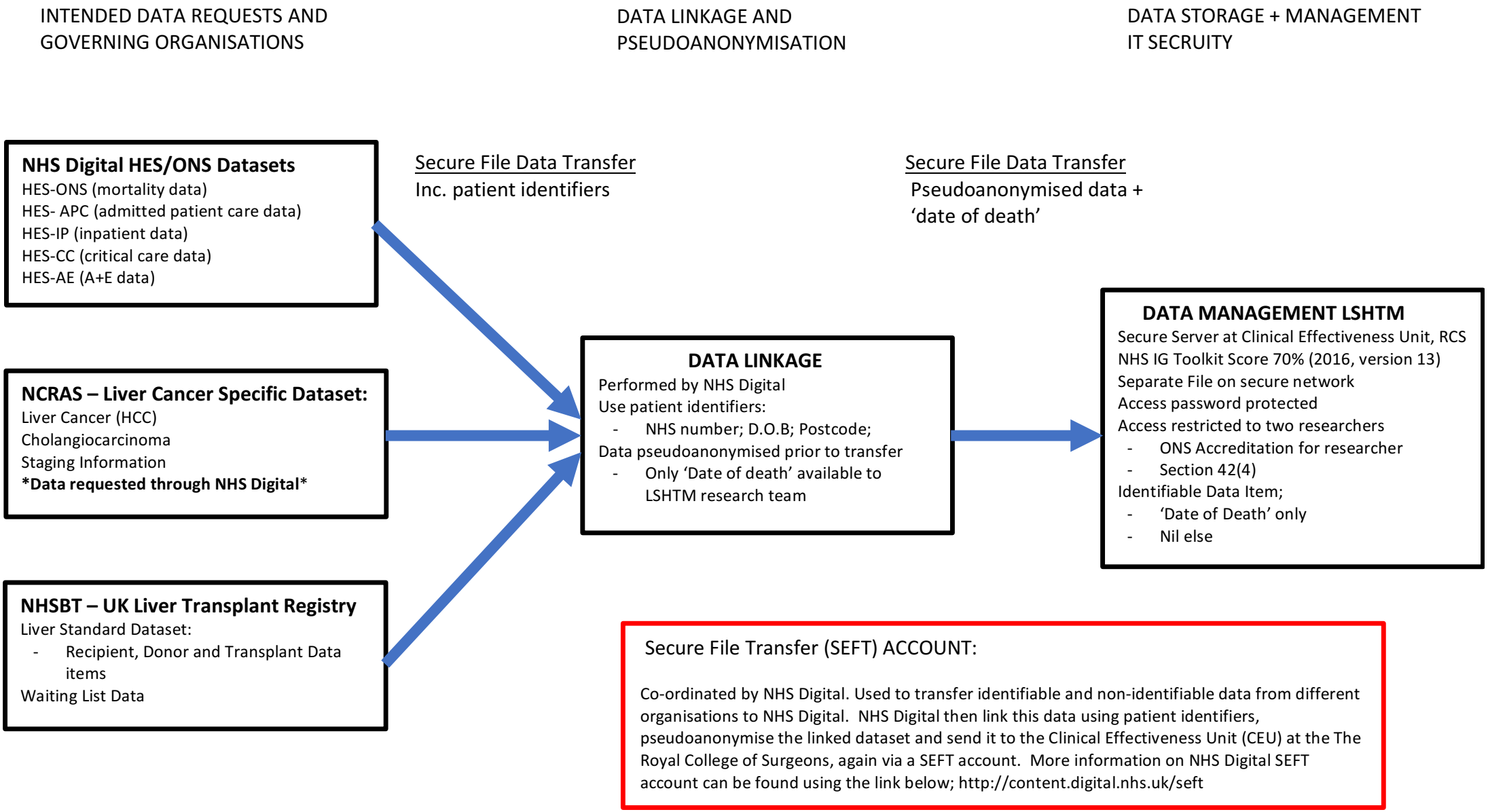
APPENDICES

12.1 APPENDIX A – DATA FLOW DIAGRAM



12.2 APPENDIX B – NHS DIGITAL DATA SHARING AGREEMENT

1 Parties

This Data Sharing Agreement is made between:

1.1 The **Health and Social Care Information Centre ("NHS Digital")**, a non-departmental public body established pursuant to section 252 of the Health and Social Care Act 2012 whose address is 1 Trevelyan Square, Boar Lane, Leeds LS1 6AE; and

1.2 The party whose details are set out in Annex A: section 1b (the **"Data Recipient"**).

2 Status of this Agreement

2.1 This Data Sharing Agreement ("**DSA**") is subject to the terms of the Data Sharing Framework Contract made between NHS Digital and the Data Recipient, as detailed in Annex A: section 1b. This DSA comprises:

2.1.1 the details set out in this document;

2.1.2 the Annexes to this document.

2.2 In the event of any conflict between any provision of this DSA and the Data Sharing Framework Contract:

2.2.1 the Special Conditions in Annex A section 6 of this DSA shall prevail, followed by,

2.2.2 Part 1 of the Data Sharing Framework Contract, followed by,

2.2.3 Part 2 of the Data Sharing Framework Contract, followed by,

2.2.4 the Data Sharing Framework Contract Schedules, followed by,

2.2.5 the remainder of the terms of this DSA (other than the Annexes), and then followed by,

2.2.6 the other Annexes to this DSA.

3 Term and Termination of this DSA

3.1 This DSA shall commence on the start date specified in Annex A: section 1a and, unless otherwise terminated in accordance with the terms of this DSA and/or the Data Sharing Framework Contract, shall continue until the end date specified in Annex A: section 1a (the **"Term"**).

3.2 This DSA will terminate automatically on the termination or expiry of the Data Sharing Framework Contract, save where a New Contract has been agreed by the parties.

3.3 This DSA may be terminated prior to the end of the Term:

3.3.1 by the Data Recipient at any time by notifying NHS Digital in writing;

3.3.2 by NHS Digital at any time by giving to the Data Recipient not less than one months' prior notice in writing; or

3.3.3 in accordance with the provisions of the Data Sharing Framework Contract (or any New Contract) from time to time in force.

3.4 This DSA may be updated or varied from time to time by:

3.4.1 NHS Digital notifying the Data Recipient of the update in accordance with Clause 18.2 of the Data Sharing Framework Contract; or

3.4.2 NHS Digital and the Data Recipient agreeing the variation in accordance with Clause 18.3 of the Data Sharing Framework Contract.

3.5 Where this DSA is updated or varied in accordance with Clause 3.4, NHS Digital shall issue an updated version of the DSA to the Data Recipient to reflect the update or variation to the terms ("Updated DSA"). NHS Digital shall allocate a new sequential version number to the Updated DSA to identify that the DSA is updated or varied. For example, a DSA with reference DARS-NIC-NNNNN-NNNNN-v1.1, would be updated to DSA DARS-NIC-NNNNN-NNNNN-v2.0.

3.6 The parties acknowledge that this DSA, as updated or varied in accordance with Clause 3.4, shall be read and construed as the same appears in an Updated DSA. Except as updated or varied in accordance with Clause 3.4, this DSA shall continue in full force and effect.

4 Data

4.1 Annex B: section 2, sets out the details of the Data that will be provided by NHS Digital to the Data Recipient under this DSA.

4.2 NHS Digital shall supply the Data to the Data Recipient or its nominated Data Processor in accordance with the data transfer method set out in Annex B: section 2.

4.3 The Data Recipient shall:

4.3.1 comply with the provisions set out in Annex A and Annex B; and

4.3.2 only process and store the Data at the location(s) specified in Annex A: Section 2.

4.4 Where Annex A states that the Data Recipient is entitled to sub-licence the Data, the Data Recipient shall enter into a Sub-Licence which is compliant with the requirements set out in Annex A: section 10 together with Clause 3.3 of Part 2 and Schedule 4 of the Data Sharing Framework Contract, and shall procure that the sub-licensee complies with its obligations as set out in Annex A: Section 10 and Schedule 4 (Sub-licensing conditions) of the Data Sharing Framework Contract.

4.5 The Data Recipient shall comply with the requirements of Clause 3 of the Data Sharing Framework Contract in respect of any sub-licensing of the Data.

5 Data Processor

5.1 The Data Recipient wishes to engage the party whose details are set out in Annex A: section 1c to act as its Data Processor to carry out the processing activities set out in Annex A: section 5.

5.2 NHS Digital consents to the appointment by the Data Recipient of the party whose details are set out in Annex A: section 1c to act as its Data Processor solely for the processing activities set out Annex A: section 5. No other processing or use is permitted by the Data Processor.

5.3 The Data Recipient shall be responsible for all acts and omissions of the Data Processor as if they were acts and omissions of the Data Recipient under this DSA.

6 Charges

6.1 The Data Recipient shall pay the Charges set out in Annex A: section 11 in accordance with the payment terms contained there and in the Data Sharing Framework Contract.

7 Data Access

7.1 Under the terms of this DSA, the Data Recipient must ensure that access to the Data is managed, auditable and restricted to those individuals who need to process the Data for the Purpose outlined in this DSA.

SCHEDULE 1

1 Interpretation

1.1 In this DSA the following expressions have the following meanings. Defined terms not detailed below shall be interpreted in accordance with the defined terms set out in the DSFC:

Data Recipient	means the party named in Annex A: section 1b who will be a Data Controller of any Personal Data to be shared under and in accordance with this DSA;
Data Sharing Framework Contract or DSFC	means the Data Sharing Framework Contract as detailed in Annex A: section 1b;
Identifiable Data	means Personal Data, but extended to apply to dead as well as living individuals;
Non-identifiable Data	means Data that is not Identifiable Data;
Term	has the meaning given in Clause 3.1 of this DSA.

1.2 The rules of interpretation in the DSFC shall apply to this DSA.

Annex A: Application Summary

1a: General

Request Number:	DARS-NIC-72064-V5V2X-v3.4
Request Title:	Liver transplantation as treatment for patients with hepatocellular carcinoma; a study using existing electronic data.
DSA Start Date:	19/06/2019
DSA End Date:	30/09/2020

1b: Data Controller(s)

- **London School of Hygiene and Tropical Medicine**

Data Controller: London School of Hygiene and Tropical Medicine

Keppel Street
London
WC1E 7HT
England

Organisation Type: Research

Data Controller Type: Joint Data Controller

NHS Digital Framework Contract Reference: CON-324540-Z1Y8C

Contract Expiry Date: 09/04/2021

Security Assurances for Data Controller

Type: IG Toolkit

Version: 14.1

Date Completed: 01/02/2018

ODS Code: 8J134

Comments:

DSPT Published

IGT Score: 88% Satisfactory (Reviewed Grade)

IGT Reviewed Date: 12/06/2018

Date Checked by NHS Digital: 13/06/2019

DPA Registration

DPA Registration Number: Z7513362

DPA Organisation Name: London School of Hygiene and Tropical Medicine

Expiry Date: 22/12/2019

DPA Checked On : 13/06/2019

- **The Royal College of Surgeons of England**

Data Controller: The Royal College of Surgeons of England

35-43 Lincoln's Inn Fields
London
WC2A 3PE
ENGLAND

Hospital Episode Statistics Outpatients	Extract	Pseudo/Anonymised	Non Sensitive	2003/04 2004/05 2005/06 2006/07 2007/08 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 2016/17	Processing : General Data Protection Regulation Article 6 (1) (e), General Data Protection Regulation Article 6 (1) (f), General Data Protection Regulation Article 9 (2) (j) Dissemination : Health and Social Care Act 2012 - s261(1) and s261(2)(b)(ii)	One-off
Data Minimisation						
Data will be limited to patients in either the liver cancer or liver transplant cohorts. Cohort of 84,000						
Hospital Episode Statistics Accident and Emergency	Extract	Pseudo/Anonymised	Non Sensitive	2007/08 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 2016/17	Processing : General Data Protection Regulation Article 6 (1) (e), General Data Protection Regulation Article 6 (1) (f), General Data Protection Regulation Article 9 (2) (j) Dissemination : Health and Social Care Act 2012 - s261(1) and s261(2)(b)(ii)	One-off
Data Minimisation						
Data will be limited to patients in either the liver cancer or liver transplant cohorts. Cohort of 84,000						
HES:Civil Registration (Deaths) bridge	Extract	Pseudo/Anonymised	Non Sensitive	N/A	Processing : General Data Protection Regulation Article 6 (1) (e), General Data Protection Regulation Article 6 (1) (f), General Data Protection Regulation Article 9 (2) (j) Dissemination : Health and Social Care Act 2012 - s261(1) and s261(2)(b)(ii)	One-off
Data Minimisation						
Data will be limited to IDs to connect patients in either the liver cancer or liver transplant cohorts with mortality records if deceased. Cohort of 84,000						
Civil Registration (Deaths) - Secondary Care Cut	Extract	Pseudo/Anonymised	Sensitive Date of Registration, Match rank, Death Record Used, Sex, Primary Care Trust of usual residence of deceased, Match rank, Strategic Health Authority of usual residence of deceased, Date of Death, Original Underlying Cause of Death	1997-1998 1998-1999 1999-2000 2000-2001 2001-2002 2002-2003 2003-2004 2004-2005 2005-2006 2006-2007 2007-2008 2008-2009 2009-2010 2010-2011 2011-2012 2012-2013 2013-2014 2014-2015 2015-2016 2016-2017	Processing : GDPR does not apply to data solely relating to deceased individuals Dissemination : Health and Social Care Act 2012 - s261(1) and s261(2)(b)(ii)	One-off
Data Minimisation						

5. Purpose/Methods/Outputs

Sa. Objective for processing:

The Clinical Effectiveness Unit (CEU) based at The Royal College of Surgeons (RCS) requires linked data from four large national databases containing information on all patients in the last two decades who have had liver cancer (Hepatocellular Carcinoma (HCC) being the most common liver cancer) and of those patients who have subsequently received a liver transplantation. The CEU is a collaborative research unit formed from both the RCS and London School of Hygiene & Tropical Medicine (LSHTM) and therefore both RCS and LSHTM are joint data controllers.

The London School of Hygiene and Tropical Medicine lawful basis for processing data under GDPR is Article 6(1)(e) (processing is necessary for the performance of a task in the public interest or in the exercise of official authority vested in the controller):
The London School of Hygiene and Tropical Medicine falls into this category as they have a Royal Charter which states for example, "There shall be one Body Corporate and Politic under the name of the London School of Hygiene and Tropical Medicine {"London School") for the purpose of and with the objects of promoting original research...".
Necessary for the performance of the task (for the individual): Consideration has been given to whether the volume of data being requested is proportionate to the expected benefit and, through examination of the expected benefits consideration has been given to whether the task is itself necessary.

The Royal College of Surgeons of England's lawful basis for processing data under GDPR is Article 6 (1)(f) - (processing is necessary for the purposes of the legitimate interests pursued by the controller or by a third party except where such interests are overridden by the interests of fundamental rights and freedoms of the data subject which require protection of personal data, in particular where the data subject is a child).
The Royal College of Surgeons (RCS) is a registered charity (No.212808) with the Charities Commission and is subject to the Charities Act 2011. Chapter 1, Section 4 of the Charities Act establishes that the nature of a charity is to operate for the public benefit if it is for charitable purposes. The purpose of medical research is compatible with the purposes defined within Chapter 3, Section 1(d) of the Charities Act for the advancement of health or for the saving of lives, paragraph 3(b) states that this includes the prevention or relief sickness disease or human suffering.
RCS has conducted a legitimate interests assessment to confirm processing is necessary for the purposes of the legitimate interests. RCS have assessed this against the ICO's checklist (https://ico.org.uk/for-organisations/guide-to-the-general-data-protection-regulation-gdpr/lawful-basis-for-processing/legitimate-interests/) and are content that the requirements are met and has been reviewed by NHS Digital.
Processing personal data is necessary for RCS's legitimate interests which are described in this application. The data to which access is requested are proportionate and necessary to achieve those interests.

Both data controllers are using Article 9(2)(j): The data are required for research purposes in the public interest - meeting the conditions in the DPA 2018 Schedule 1 Part 1 (4) - which GDPR Recital 52(2) determines is an appropriate derogation from the prohibition on processing special categories of personal data.

Background:
Hepatocellular carcinoma (HCC) is the most common liver cancer. Each year, more than 4,000 patients are being diagnosed with HCC in the UK. The incidence of HCC has increased four-fold in the last 30 years. Liver diseases such as obesity and hepatitis C lead to liver cirrhosis and eventually cancer. There is often a lag time of two decades between the acquisition of liver disease and the development of HCC.

Overall survival of patients diagnosed with HCC is poor. Despite small improvements in outcome, less than 30% of the patients are alive at one year after diagnosis. The available treatment options depend on the size and spread of the cancer at the time of diagnosis. Patients who are eligible to receive a liver transplantation have the best prognosis with about 75% being alive at five years.

Liver transplantation is increasingly being used as a treatment for patients with HCC. As a result, HCC is now the most common indication for liver transplantation. This development has increased the gap between the number of patients waiting for liver transplantation and the availability of suitable livers.

In response, the transplant centres have started to use more and more livers from donors who have sustained a cardiac death. They accept that transplant outcomes with livers from these donors might be worse than with livers from the normal donors who have sustained brainstem death. However, transplant surgeons have little choice as they need to find a donor for patients with HCC before their disease spreads to the bloodstream and they become unfit for potentially

curative transplantation.

The linked data requested is minimised to two cohorts of liver cancer patients and liver transplantation patients.

The project is funded by the NIHR as part of a Doctoral Research Fellowship (DRF) grant.

The databases include the National Cancer Registration and Analysis Service (NCRAS) to identify all patients with liver cancer in England, the Hospital Episode Statistics (HES) database and Civil Registration Mortality database to determine comorbidities, treatments and outcomes, and the UK Liver Transplant Audit (UKLTA) database to evaluate the outcome of transplantation.

The National Cancer Registration and Analysis Service (NCRAS) is run by Public Health England and is responsible for cancer registration. UK Liver Transplant Audit (UKLTA) is run by NHS Blood and Transplant (NHSBT) who manage blood and platelet donation, and organ, stem cell and tissue donation and transplantation.

The datasets to be linked from each national database are as follows: -

Liver cancer specific dataset: - records of patients diagnosed with liver cancer between 1996 and 2016, including date of diagnosis, TNM stage, cancer morphology, and treatment indicators will be used, including already linked: Chemotherapy (SACT), Radiotherapy (RTDS) and Radiology Datasets (DID) supplied from NCRAS;

UK Liver Transplant Audit (UKLTA): - records of all patients who received a liver transplant since 1994 and all patients on the liver transplant waiting list, including 'standard liver dataset' and 'waiting list data', supplied from NHSBT

Hospital Episode Statistics (HES) datasets (Admitted Patient Care (APC), Outpatients (OP), Critical Care (CC), Accident and Emergency (A&E)) and Civil Registration mortality data supplied from NHS Digital.

Project aim:
To maximise the benefit of liver transplantation as a treatment option for patients with liver cancer.

Work packages:
Detailed below are five separate work packages, each with specific objectives, that have been constructed in order address the project aim.

Work package 1: Identifying the rising incidence and mortality of Hepatocellular carcinoma (HCC) in England and worldwide
Identifying the main risk factors causing the rise in HCC will encourage NHS services to better identify HCC earlier in patients and thus increase their treatment options. It will also help to educate the public in avoiding the high-risk behaviours that can lead to the development of liver disease and subsequent risk of HCC.

Work package 2: Assessing the validity of the linked national databases as a data source for HCC research
Large linked health databases will provide the data to answer the research questions. Prior to conducting any analysis, the validity of the national databases will be evaluated by checking the consistency of the recorded liver disease and treatment information.

Work package 3: Assessing the impact of sociodemographic and clinical factors on treatment selection and survival of patients with HCC
Evaluating treatment options for patients with HCC will help the study identify the best treatment available for patients based on their individual disease and medical conditions. This will promote the use of effective alternative treatments for HCC whilst potentially easing the pressure on liver transplant services.

Work package 4: Analysing outcomes of liver transplantation in patients with HCC
Identifying individual patient characteristics that are associated with the best and worst outcomes following liver transplantation will help the study better identify HCC patients suitable for transplantation. This could lead to an improvement in post-operative survival and increase the number of patients with HCC considered suitable for liver transplantation.

Work package 5: Analysing outcomes of liver transplantation in patients with HCC who receive a cardiac death donor liver?

Exploring the transplantation of livers from cardiac death donors as compared with brainstem death donor livers could potentially increase the number of livers suitable for donation. This could lead to the earlier transplantation of patients with HCC and reduce the number of patients falling of the waiting list due to spread of their cancer.

5b. Processing activities:

PHE (NCRAS) will submit the following identifiers for a cohort of liver cancer patients to NHS Digital: NHS number, gender, date of birth, and postcode plus unique Liver Cancer ID. This is for the Cancer Cohort. PHE (NCRAS) will not have access to the NHS Digital data and are providing a cohort only.

NHSBT will submit the following identifiers for a cohort of liver transplant patients to NHS Digital: NHS number, gender, date of birth, and postcode plus unique Liver Transplant ID. This will be for the Transplant Cohort.
NHSBT will have not have access to the NHS Digital data and are providing a cohort only.

PHE (NCRAS) and NHSBT will send additional data about these individuals from their respective databases to CEU. These datasets will contain no identifiers other than unique Liver Cancer ID and Liver Transplant ID respectively.

NHS Digital will then add both cohorts together to make one cohort and will link the combined cohort to HES and mortality data. The data will be pseudonymised containing no identifiers other than encrypted HESID, Liver Cancer or Liver Transplant person ID and, where applicable, Date of Death. The encrypted HESID will be the common identifier across all datasets.

NHS Digital will supply the linked HES and mortality data for each matched patient within the cohort of liver cancer and liver transplant patients to a secure data handling facility at the Clinical Effectiveness Unit (CEU) based at The Royal College of Surgeons of England (RCS). The CEU is a collaborative research unit formed from both the RCS and London School of Hygiene & Tropical Medicine (LSHTM).

NHS Digital will also supply to the CEU the unique Liver Cancer ID or Liver Transplant ID for any patients from the respective cohorts whose data could not be matched to HES and/or mortality data. In any deterministic linkage of data, there will be a small percentage of patients whose records did not match (i.e. none of the identifiers such as NHS number, D.O.B, postcode correlated). The Liver Cancer and Liver Transplant IDs of unmatched patients will be used by CEU to link back to additional data supplied by NHSBT and NCRAS. These will be used to compare the characteristics of patients who were not matched to HES with those that were in order to assess potential bias arising from the exclusion of their HES and/or mortality data from the analyses. Bias is dangerous to any epidemiological study as it affects the strength of causality that any analysis may display it then also affects the interpretation of the results and credibility of the research.

In order to test (and hopefully disprove bias) in this study CEU need to make sure the patient characteristics are not different between matched and unmatched patients.

CEU will compare patients with HCC who underwent liver transplant against patients with HCC who received other forms of treatment (i.e. liver resection, radiotherapy, chemotherapy etc). In addition, CEU also need to compare patients who had a liver transplant for HCC against patients who had a liver transplant for other indications (i.e. alcohol, hepatitis etc).

The CEU requires the HES and mortality data for all matched patients whether they were included in the PHE (NCRAS) cohort, the NHSBT cohort or both. There will be quite a few patients who are in one cohort but not the other as only a small proportion of patients unfortunately receive a liver transplant. CEU require all the records to compare the outcomes for patients who do receive a liver transplant against those who do not receive a liver transplant. CEU need the records to identify the characteristics (age, sex, sociodemographic status, co-morbidities) that influence patients with HCC who receive a liver transplant against those who do not.

Additionally, the CEU requires all HES records of patients with an ICD10 code of 'C22' (liver cancer) and / or an OPCS4 code of 'J01' (liver transplantation) who are not linked to either the NHSBT or NCRAS data set. This will provide an even better opportunity to explore if there is a case ascertainment issue (i.e. that NHSBT or NCRAS have not identified 100% of instances of liver transplantation or liver cancer). The characteristics of omitted individuals' hospital episodes will be considered to explore the possible bias that this will produce.

Data supplied by NHS Digital will only be accessed by the clinical researcher and statistical supervisor who are substantive employees of LSHTM and the data manager who is a substantive employee of RCS. No data will be shared with a third

party in any form. All outputs will be aggregated with small numbers supressed in line with the HES analysis guide. All data will be processed and accessed at the CEU.

Justification of years requested in each dataset:
Much of CEU's intended analysis is determining trends over time in the incidence and outcomes of patients with HCC hence the request of historical data across all 5 datasets.

An Important consideration in identifying any potential improvements (or even decline) in outcomes is assessing the changing patient characteristics of patients with HCC in addition to identifying any significant changes in the services (and or treatment options) that these patients receive i.e. better post-op critical care, reduced post-op emergency department attendances, increase outpatient surveillance etc.

Fundamentally important to the initial analysis (work package 1) is also mapping the pathway to the development of HCC. CEU know the development of HCC is often part of a 20-year process from the development of a primary liver disease to cirrhosis and then to cancer. Hence, in order to identify what clinical and sociodemographic factors (in addition to cirrhosis) are important in the development of HCC, CEU need the historical data. This is especially relevant of the inpatient (APC) dataset which contain the diagnosis and procedural codes necessary to perform this analysis.

The linked dataset will be validated by checking the consistency of cancer diagnoses and treatment across all three databases. The level of agreement will be detailed using statistics.

CEU will perform statistical analysis on the linked dataset to address five work packages (research questions).

There will be no data linkage undertaken with NHS Digital data provided under this agreement that is not already noted in the agreement.

Data will only be accessed and processed by substantive employees of The Royal College of Surgeons of England and London School of Hygiene and Tropical Medicine
and will not be accessed or processed by any other third parties not mentioned in this agreement.

5c. Specific Outputs Expected, Including Target Date:

Publications:
During the project, CEU would look to publish a minimum of four to five high quality research papers in high impact transplant and cancer specific journals (Target:- January 2018-2020). Selected journals include; Transplantation; Liver Transplantation; American Journal of Transplantation and The British Journal of Cancer. Significant research findings will also be put forward to the external relations departments at the London School of Hygiene and Tropical Medicine and The Royal College of Surgeons, London for further distribution. It will be mandatory to recognise all contributory organisations in all publications.

Presentations:
Research outputs will be presented at national and international meetings. CEU aim for yearly presentations at the British Transplant Society (BTS) Conference with international presentations focused on conferences hosted by the European Society of Transplantation (ESOT). CEU will also aim for an oral presentation at the two-yearly World Transplant Conference (WTC). Cancer specific workshops hosted by the National Cancer Intelligence Network (NCIN) will provide the platform for oral presentations on the main determinants of HCC.

These meetings will provide the opportunity for CEU's results to positively affect the wider public through influencing policy on prevention strategies of the risk factors identified as causing the greatest burden to the hepatocellular carcinoma (HCC) epidemic.

Intended Presentation Dates and Venue
British Transplant Society Annual Conference: March 2019
World Transplant Conference: 2018 - venue to be determined

Patient Groups:
An update of progress will be made to local patient groups. This will be part of the process of informing NHS patients of CEU's findings and allowing them to help further influence their research by working with the HCC advisory group to formulate the best platforms to disseminate the research findings to the public.

Local NHS Trust Feedback:
CEU will use select local meetings within the Institute of Liver Sciences at Kings College Hospital to feedback the results of this thesis. In attendance, will be consultant hepatobiliary and transplant surgeons, hepatologists, junior doctors, clinical nurse specialists, transplant coordinators and NHS service managers.

This forum presents an efficient way of translating the output of this research into active clinical practice. It is therefore imperative that these meetings, are conducted on a regular basis throughout the duration of the thesis. The major theme of the project is identifying the extent to which this study can increase the capacity of liver transplantation to meet the increasing demand driven by HCC. It is hoped that highlighting this information will help regulate and in turn drive improvements in treatment selection and outcomes for individual HCC patients.

NHSBT:
The research outputs indicating the influence of the HCC epidemic and its impact on liver transplantation will be discussed with NHSBT's Liver Selection and Allocation Working Party and Liver Advisory Group. Results from this thesis can be potentially used by these national committees to determine allocation policy by contributing to the construction of further complex statistical models that NHSBT can use to determine the allocation policy of donor organs. This will result in rapid improvements in patient outcome through maximising the survival benefit of deceased donor livers in HCC patients.

All outputs will be aggregated with small numbers supressed in line with the HES analysis guide.

5d. Benefits

i. Benefits Type:

ii. Expected Measurable Benefits to Health and/or Social Care Including Target Date:

The incidence of HCC in the UK is increasing. Given the observed time trends in etiological and contributing factors and the considerable lag time between first onset of liver disease and the development of HCC, this increase is likely to continue over the next decade. It is imperative that this study is equipped with the necessary information to combat this devastating disease and to determine the role of liver transplantation. This project aims to make a significant contribution in this area.

CEU expect this research can make three fundamental contributions. First, it is now recognised that using linked national health based datasets will expand the scope of clinical questions that can be addressed (10). CEU will demonstrate how linked data can be used to study an entire disease pathway from recognising the first presence of aetiological agents and contributing factors to the development of cirrhosis and HCC. A better understanding of the entire disease pathway will guide NHS services in developing a comprehensive response to the increasing burden of HCC that may include developing measures to prevent viral hepatitis and cirrhosis, screening patients at risk of developing HCC, and improving the capacity of liver transplantation as a potentially curative treatment option for HCC.

Second, evaluating liver transplantation as a curative treatment and exposing the liver diseases and treatments options associated with the best and worst outcome has an immediate benefit as it will help to improve the information that is available for the selection of potential recipients of a liver transplant and the allocation of donor organs. The potential of liver transplantation as a treatment option for HCC is determined by the limited availability of suitable donor organs. Using the linked dataset, it is hoped to determine whether transplanting organs from DCD donor's produces improved survival outcomes. Furthermore, identifying risk factors of post-transplant survival in HCC patients, including the use of organs from DCD and other marginal donors, can improve patient selection and organ allocation policy which will further improve the potential of liver transplantation as a treatment option for HCC patients.

Third, the work using the linked national databases will also demonstrate how this resource can contribute to the investigation of potential inequity of access and variation in treatment and outcomes across NHS providers. A better understanding of the determinants of treatment and outcomes has the potential to inform how HCC services, including liver transplantation, can be further improved, ultimately leading to an overall improvement of the quality of care for patients with HCC.

Research Questions and benefit to patients and public

Research Question 1: What are the risk factors causing the rising incidence of Hepatocellular carcinoma (HCC)? Identifying the main risk factors causing the rise in HCC will encourage NHS services to better identify HCC earlier in

patients and thus increase their treatment options. It will also help to educate the general public in avoiding the high risk behaviors that can lead to the development of liver disease and subsequent risk of HCC.

Research Question 2: What factors are associated with the selection and outcome of the different treatment options in patient's with HCC?
Evaluating treatment options for patients with HCC will help identify the best treatment available for patients based on their individual disease and medical conditions. This will promote the use of effective alternative treatments for HCC whilst potentially easing the pressure on liver transplant services.

Research Question 3: What are the factors associated with the best and worst outcomes in patients with HCC, who recieve a liver transplant? Identifying individual patient characteristics that are associated with the best and worst outcomes following liver transplantation will help better identify HCC patients suitable for transplantation. This will lead to an improvement in post-operative survival and increase the number of patients with HCC who can undergo liver transplantation.

Research Question 4: What are the factors associated with the best and worst outcomes in patients with HCC who receive a cardiac death donor liver?
Exploring the transplantation of livers from cardiac death donors as compared with brain stem death donor livers could potentially increase the number of livers suitable for donation. This could lead to the earlier transplantation of patients with HCC and reduce the number of patients falling of the waiting list due to spread of their cancer.

iii. Yielded Benefits:

The overarching theme of the results is that livers donated following circulatory death (DCD) - previously thought to be sub-optimal - produce equivocal results as livers donated after brain stem death (DBD) traditionally thought to be of higher quality. The results will therefore encourage clinicians and patients alike to increase the utilisation of DCD livers and thus increase the number of patients who are receiving a potentially life-saving liver transplantation and decrease the number patients waiting to receive a liver transplantation.

To date outputs for the project include:

Poster Presentations
1. British Transplant Society (BTS) Annual Congress, Harrogate, March 2017
2. British Association for study of the liver (BASL) Annual Congress, Warwick, September 2017.

Oral Presentations
1. BASL Annual HCC-UK Research Meeting, Newcastle, April 2017
2. British Transplant Society (BTS) Annual Congress, Brighton, March 2018 (x2 presentations)
3. BASL Annual HCC-UK Research Meeting, London, April 2018
4. European Society of Transplantation Annual Conference: July 2018

5e. Is the Purpose of this Application in Anyway Commercial?

No

6. Special Conditions

London School of Hygiene and Tropical Medicine must inform NHS Digital DARS team if when the DSPT is reviewed by NHS Digital it is deemed to have not passed or if any issues are raised with the submission

The Royal College of Surgeons must inform NHS Digital DARS team if when the DSPT is reviewed by NHS Digital it is deemed to have not passed or if any issues are raised with the submission

Awarding Institution:	National Institute of Health Research (NIHR)
EU/International programme:	
Reference and title of project/activity:	SD4 - Liver transplantation as treatment for patients with hepatocellular carcinoma; DRF-2016-09-132
Year of submission/award:	16/01/2017
Applicant or Partner:	Applicant
Funding evidence URL:	

9. Approved Users

10. Sub-licensing

Does sub-licensing apply? No

The Data Recipient is responsible for entering into a Sub-Licence that meets the requirements set out in Clause 3.3 and Schedule 4 of the Data Sharing Framework Contract.

11. Charges

Set up and first year service charge

Annual Service Charge £5,830.00

Principles of charging: NHS Digital operates on a cost recovery basis and does not seek to make an operating profit from providing its services. The following costs to NHS Digital are included in the Service Charges and Annual Charges below:

- all design and/or implementation specific services required to generate bespoke datasets or extracts;
- all administration services associated with providing access to the same;
- delivery and maintenance services to support the ongoing provision of bespoke datasets or extracts;
- administration costs associated with carrying out annual reviews of Data Recipients.

These charges do not include the costs associated with the investigation of a breach, planning and performance of audit(s), and any prosecution activity.

Service Charge: setup, licence, service and annual review charges

The Service Charge is a one-off fee per DSA, and is payable in advance. The Annual Review charges included in the Service Charge are based on the number of annual reviews to be carried out during the Term of the DSA.

Audit fees are payable where NHS Digital undertakes an audit or investigation which in NHS Digital's reasonable opinion, reveals that the Data Recipient either has not complied, or is not complying, with any of its obligations under the Data Sharing Framework Contract and / or this DSA. The audit fees stated in the table below are an estimate only and the Data Recipient is responsible for promptly reimbursing NHS Digital for all reasonable costs of the audit and the full cost of any investigation which NHS Digital may commence prior to an audit taking place in accordance with Clause 7 (Audit and specific rights) of the Data Sharing Framework Contract. Audit fees are payable at cost, and shall include the costs for all activity for investigation, as well as activities associated with the performance of the audit:

Estimated audit fees per audit: **£1S,000 (variable depending on circumstances).**

Annex B: Additional technical information

1. Data to be received by NHS Digital under this agreement

The customer will provide a cohort to NHS Digital

Cohort data already held by NHS Digital under this agreement will be used

There will be ongoing recruitment to this cohort

The approximate maximum size the cohort could reach over the lifetime of the DSA is 50,000

The data items being supplied to NHS Digital by the Customer are :

- Study ID
- NHS Number
- Date OfBirth
- Gender
- Postcode

The legal basis for the data being sent to (or reused by) NHS Digital is

2. NHS Digital data covered by this agreement

A summary of the datasets covered by this agreement is shown in section 3 above.

2a. Data already held

- **Hospital Episode Statistics Admitted Patient Care**

Periods

1997/98
1998/99
1999/00
2000/01
2001/02
2002/03
2003/04
2004/05
2005/06
2006/07
2007/08
2008/09
2009/10
2010/11
2011/12
2012/13
2013/14
2014/15
2015/16
2016/17

Sensitive fields

Identifiable fields

Other fields

[ACPDISP_N] Augmented care period disposal,

[ACPDQIND_N] Augmented care period data quality indicator,
[ACPEND_N] Augmented care period end date,
[ACPLOC_N] Augmented care location,
[ACPN_N] Augmented care period number,
[ACPOUT_N] Augmented care period outcome indicator,
[ACPPLAN_N] Augmented care period planned indicator,
[ACPSOUR_N] Augmented care period source,
[ACPSPEF_N] Augmented care period speciality function code,
[ACPSTAR_N] Augmented care period start date,
[ACSCFLAG] Ambulatory Care Sensitive Condition Flag,
[ACTIVAGE] Age at activity date,
[ADMIAGE] Age on admission,
[ADMIDATE] Date of admission,
[ADMIMETH] Method of admission,
[ADMINCAT] Administrative category,
[ADMINCATST] Admin category at start of episode,
[ADMISORC] Source of admission,
[AEKEY] Record identifier,
[ALCDIAG] Principal alcohol related diagnosis,
[ALCDIAG_4] 4 character concatenated alcohol related diagnosis,
[ALCFRAC] Principal alcohol related fraction,
[AT_GP_PRACTICE] Area Team of GP Practice,
[AT_RESIDENCE] Area Team of Residence,
[AT_TREATMENT] Area Team of Treatment,
[BEDYEAR] Bed days within the year,
[CANNET] Cancer network,
[CANREG] Cancer registry,
[CAUSE] Cause code,
[CAUSE_3] Cause code - 3 characters,
[CCG_GP_PRACTICE] CCG of GP Practice,
[CCG_RESIDENCE] CCG of Residence,
[CCG_RESPONSIBILITY] CCG of Responsibility,
[CCG_RESPONSIBILITY_ORIGIN] Origin of CCG of Responsibility,
[CCG_TREATMENT] CCG of Treatment,
[CCG_TREATMENT_ORIGIN] Origin of CCG of Treatment,
[CDSEXTDATE] CDS extract date,
[CDSVERPROTID] CDS protocol identifier,
[CDSVERSION] CDS version number,
[CLASSPAT] Patient classification,
[CR_GP_PRACTICE] Commissioning Region of GP Practice,
[CR_RESIDENCE] Commissioning Region of Residence,
[CR_TREATMENT] Commissioning Region of Treatment,
[CURRWARD] Current electoral ward,
[CURRWARD_ONS] Current electoral ward (ONS),
[DEPDAYS_N] High-dependency care level,
[DIAG_COUNT] Count of diagnoses,
[DIAG_NN] All Diagnosis codes,
[DISDATE] Date of discharge,
[DISDEST] Destination on discharge,
[DISMETH] Method of discharge,
[DISREADYDATE] Discharge ready date,
[EARLDATOFF] Earliest reasonable date offered,
[ELECDATE] Date of decision to admit,
[ELECDUR] Waiting time,
[ELECDUR_CALC] Calculation of Elecdur,
[ENDAGE] Age at end of episode,
[EPIDUR] Episode duration,
[EPIEND] Date episode ended,
[EPIKEY] Record identifier,

[EPIORDER] Episode order,
[EPISTART] Date episode started,
[EPISTAT] Episode status,
[EPITYPE] Episode type,
[ETHNOS] Ethnic category,
[ETHRAW] Ethnic character (audit version),
[FAE] Finished Admission Episode,
[FAE_EMERGENCY] Finished Admission Episode, emergency classification,
[FDE] Finished In-Year Discharge Episode,
[FIRSTREG] First regular day or night admission,
[GORTREAT] Government office region of treatment,
[GPPRACHA] Health Authority area where patient's GP is registered,
[GPPRPCT] Primary Care Trust area where patient's GP was registered,
[GPPRSTHA] Strategic Health Authority area where patient's GP was registered,
[HATREAT] Health Authority of treatment,
[IMD04] IMD Index of Multiple Deprivation,
[IMD04_DECILE] IMD Decile Group,
[IMD04C] IMD Crime Domain,
[IMD04ED] IMD Education Training and Skills Domain,
[IMD04EM] IMD Employment Deprivation Domain,
[IMD04HD] IMD Health and Disability Domain,
[IMD04HS] IMD Barriers to Housing and Service Domain,
[IMD04I] IMD Income Domain,
[IMD04IA] IMD Income affecting Adults Domain,
[IMD04IC] IMD Income affecting Children Domain,
[IMD04LE] IMD Living Environment Domain,
[IMD04RK] IMD Overall Rank,
[INTDAYS_N] Intensive care level days,
[INTMANIG] Intended management,
[LAD98] Local authority district in 1998,
[LSOA01] Lower Super Output Area (LSOA01),
[LSOA11] Lower Super Output Area (LSOA11),
[MAINSPEF] Main specialty,
[MATCH_RANK] MATCH_RANK,
[MSOA01] Middle Super Output Area, 2001,
[MSOA11] Middle Super Output Area, 2011,
[MYDOB] Date of Birth - month and year,
[NEWNHSNO_CHECK] NHS Number valid flag,
[NHSNOIND] NHS number status indicator,
[NUMACP] Number of augmented care periods within episode,
[OACODE6] Census Output Area, 2001 (6 character),
[OPCS43] OPCS4.3 vesion flag,
[OPDATE_NN] Date of operation,
[OPERSTAT] Operation status code,
[OPERTN_COUNT] Total number of procedures per episode,
[OPERTN_NN] Primary Operative Procedure Codes ,
[ORGPPPID] Organisation code (patient pathway ID issuer),
[ORGSUP_N] Number of organ systems supported,
[PCFOUND] Postcode Found,
[PCGORIG] Origin of primary care group,
[PCTCODE02] Primary care trust of responsibility - historic,
[PCTCODE06] Primary care trust of responsibility - current,
[PCTORIG02] Origin of primary care trust of responsibility - historic,
[PCTORIG06] Origin of primary care trust of responsibility - current,
[PCTTREAT] Primary Care Trust area of main provider,
[POSOPDUR] Post-operative duration,
[POSTDIST] Postcode district of patient's residence,
[PREOPDUR] Pre-operative duration,
[PROVSPNOPS] Pseudonymised hospital provider spell number,

[RESCTY] County of residence,
[RESCTY_ONS] County of residence (ONS),
[RESHA] Health Authority of residence,
[RESLADST] Local authority district,
[RESLADST_ONS] Local authority district (ONS),
[RESPCT_HIS] The primary care trust of residence - mapped according to source year,
[RESPCT02] Patient's Primary Care Trust of residence - historic,
[RESPCT06] Patient's Primary Care Trust of residence - current,
[RESSTHA02] Patient's Strategic Health Authority of residence - historic,
[RESSTHA06] Patient's Strategic Health Authority of residence - current,
[ROTREAT] Region of treatment,
[RTTPEREND] RTT period end date,
[RTTPERSTART] RTT period start date,
[RTTPERSTAT] RTT period status,
[RURURB_IND] Rural/Urban Indicator,
[SEX] Sex of patient,
[SITETRET] Site code of treatment,
[SPELBGIN] Beginning of spell,
[SPELDUR] Duration of spell,
[SPELEND] End of spell,
[STARTAGE] Age at start of episode,
[STARTAGE_CALC] Age of patients at start of episode, babies restated,
[STHATRET] Strategic Health Authority area of treatment,
[STUDY_ID] STUDY_ID,
[SUBDATE] Submission date,
[SUSLDDATE] SUS loaded staging date,
[SUSRECID] SUS record id,
[SUSSPELLID] SUS generated spell id,
[TRETSPEF] Treatment specialty,
[WAITDAYS] Duration of elective wait,
[WAITLIST] Method of Admission - Waiting List

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts
Cohort of 84,000

Data Transfer Method

- **Hospital Episode Statistics Critical Care**

Periods

2008-2009
2009-2010
2010-2011
2011-2012
2012-2013
2013-2014
2014-2015
2015-2016
2016-2017

Sensitive fields

Identifiable fields

Other fields

[acardsupdays] Advanced cardiovascular support days,
[aressupdays] Advanced respiratory support days,
[bcardsupdays] Basic cardiovascular support days,
[bestmatch] Best match flag,
[bressupdays] Basic respiratory support days,
[ccadmisorc] Critical care admission source,
[ccadmitype] Critical care admission type,
[ccapcrel] Critical care APC relationship,
[ccdisdate] Critical care discharge date,
[ccdisdest] Critical care discharge destination,
[ccdisloc] Critical care discharge location,
[ccdisrdydate] Critical care discharge ready date,
[ccdisrdytime] Critical care discharge ready time,
[ccdisstat] Critical care discharge status,
[ccdistime] Critical care discharge time,
[cclev2days] Critical care level 2 days,
[cclev3days] Critical care level 3 days,
[ccsorcloc] Critical care source location,
[ccstartdate] Critical care start date,
[ccstarttime] Critical care start time,
[ccunitfun] Critical care unit function,
[dermsupdays] Dermatological support days,
[gisupdays] Gastro-intestinal support days,
[liversupdays] Liver support days,
[neurosupdays] Neurological support days,
[orgsupmax] Organ support maximum,
[rensupdays] Renal support days,
[susrecid] SUS record ID,
[unitbedconfig] Critical care unit bed configuration

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts
Cohort of 84,000

Data Transfer Method

- **Hospital Episode Statistics Outpatients**

Periods

2003/04
2004/05
2005/06
2006/07
2007/08
2008/09
2009/10
2010/11
2011/12
2012/13
2013/14
2014/15
2015/16
2016/17

Sensitive fields

Identifiable fields

Other fields

[ACTIVAGE] Age at activity date,
[ADMINCAT] Administrative category,
[APPTAGE] Age on day of appointment,
[APPTAGE_CALC] Appointment Age - babies decimalised,
[APPTDATE] Appointment date,
[AT_GP_PRACTICE] Area Team of GP Practice,
[AT_RESIDENCE] Area Team of Residence,
[AT_TREATMENT] Area Team of Treatment,
[ATENTYPE] Attendance type,
[ATTENDED] Attended or did not attend,
[ATTENDKEY] Record identifier,
[ATTENDKEY_FLAG] Attendence Key Flag,
[BABYAGE] Age of Baby,
[CANNET] Cancer network,
[CANREG] Cancer registry,
[CARERSI] Carer support indicator,
[CSNUM] Commissioning serial number,
[DIAG_COUNT] Count of diagnoses,
[DIAG_NN] Diagnosis,
[DNADATE] Last DNA or patient cancelled date,
[EARLDATOFF] Earliest reasonable date offered,
[ENCRYPTED_HESID] Encrypted HESID,
[ETHNOS] Ethnic category,
[ETHRAWL] Ethnic category (audit version),
[FIRSTATT] First attendance,
[FYEAR] Financial Year,
[GPPRAC] Code of GP practice,
[GPPRACHA] Health Authority area where patient's GP is registered,
[GPPRACRO] Regional office area where patient's GP practice was registered,
[GPPRPCT] Primary Care Trust area where patient's GP was registered,
[GPPRSTHA] Strategic health authority area where patient's GP practice was registered,
[IMD04] IMD Index of Multiple Deprivation,
[IMD04_DECILE] IMD Decile Group,
[IMD04C] IMD Crime Domain,
[IMD04ED] IMD Education, Skills and Training Domain,
[IMD04EM] IMD Employment Deprivation Domain,
[IMD04HD] IMD Health and Disability Domain,
[IMD04HS] IMD Barriers to Housing and Services Domain,
[IMD04I] IMD Income Domain,
[IMD04IA] IMD Income Affecting Older People Index,
[IMD04IC] IMD Income Affecting Children Index,
[IMD04LE] IMD Living Environment Domain,
[IMD04RK] IMD Overall Ranking,
[LOCCLASS] Location class,
[LOCTYPE] Location type,
[MAINSPEF] Main specialty,
[MARSTAT] Marital Status,
[MATCH_RANK] MATCH_RANK,
[MYDOB] Date of Birth - month and year,
[NEWNHSNO_CHECK] NHS Number valid flag,
[NHSNOIND] NHS number status indicator,
[NODIAGS] Number of Diagnosis,
[NOPROCS] Number of Procedures,
[OPCS43] OPCS43,
[OPERSTAT] Operation status code,
[OPERTN_NN] Operative procedure,
[ORGPPPID] Organisation code of patient pathway ID issuer,
[OUTCOME] Outcome of attendance,

[PARTYEAR] Year and month of data,
[PCFOUND] Postcode Found,
[PCTCODE_HIS] PCTCODE_HIS,
[PCTCODE02] Primary care trust of responsibility - historic,
[PCTCODE06] Primary care trust of responsibility - current,
[PCTORIG_HIS] PCTORIG_HIS,
[PCTORIG02] Origin of primary care trust of responsibility - historic,
[PCTORIG06] Origin of primary care trust of responsibility - current,
[POSTDIST] Postcode district of patient's residence,
[PREFERER] Pseudonymised referrer code,
[PRIORITY] Priority type,
[PROCODE] Organisation code {code of provider),
[PROCODE3] Provider code (3 character),
[PROCODE5] Provider code (5 character),
[PROCODET] Provider code,
[PROTYPE] Provider type,
[PURCODE] Commissioner code,
[PURSTHA] Commissioner's strategic health authority,
[PURVAL] Commissioner code status,
[REFSOURC] Source of referral,
[REQDATE] Referral request received date,
[RESPCT_HIS] RESPCT_HIS,
[RESSTHA_HIS] RESSTHA_HIS,
[RTTPEREND] RTT period end date,
[RTTPERSTART] RTT period start date,
[RTTPERSTAT] RTT period status,
[SENDER] SENDER,
[SERVTYPE] Service type requested,
[SEX] Sex of patient,
[STAFFTYP] Medical staff type seeing patient,
[STUDY_ID] STUDY_ID,
[SUBDATE] Submission date,
[SUSLDDATE] SUS loaded staging date,
[SUSLDDATE] SUS loaded staging date,
[SUSLDDATE] SUS loaded staging date,
[SUSLDDATE] SUS loaded staging date,
[SUSRECID] SUS record id,
[SUSSPELLID] SUS generated spell id,
[TRETSPEF] Treatment specialty,
[WAIT_IND] Waiting calculation indicator,
[WAITDAYS] Duration of elective wait,
[WAITING] Days waiting

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts.
Cohort of 84,000

Data Transfer Method

- **Hospital Episode Statistics Accident and Emergency**

Periods

2007/08
2008/09
2009/10
2010/11
2011/12
2012/13
2013/14
2014/15
2015/16
2016/17

Sensitive fields

Identifiable fields

Other fields

[ACTIVAGE] Age at activity date,
[AEATTEND_EXC_PLANNED] Attendances excluding planned,
[AEATTENDCAT] Attendance category,
[AEATTENDDISP] Attendance disposal,
[AEDEPTTYPE] Department type,
[AEKEY] Record identifier,
[AEKEY_FLAG] AEKEY Flag,
[AEPATGROUP] Patient group,
[AEREFSOURCE] Source of referral for A&E,
[APPDATE] Net applicable date,
[ARRIVALAGE] Age on arrival,
[ARRIVALAGE_CALC] Age on arrival calculated,
[ARRIVALDATE] Arrival date,
[AT_GP_PRACTICE] Area Team of GP Practice,
[AT_RESIDENCE] Area Team of Residence,
[AT_TREATMENT] Area Team of Treatment,
[CANNET] Cancer network,
[CANREG] Cancer registry,
[CARERSI] Carer support indicator,
[CCG_GP_PRACTICE] CCG of GP Practice,
[CCG_RESIDENCE] CCG of Residence,
[CCG_RESPONSIBILITY] CCG of Responsibility,
[CCG_RESPONSIBILITY_ORIGIN] Origin of CCG of Responsibility,
[CCG_TREATMENT] CCG of Treatment,
[CCG_TREATMENT_ORIGIN] Origin of CCG of Treatment,
[CDSEXTDATE] CDS extract date,
[CDSUNIQUEID] CDS unique ID,
[CDSVERPROTID] CDS protocol ID,
[CR_GP_PRACTICE] Commissioning Region of GP Practice,
[CR_RESIDENCE] Commissioning Region of Residence,
[CR_TREATMENT] Commissioning Region of Treatment,
[DIAG_NN] A&E diagnosis,
[DIAGA_NN] A&E diagnosis - anatomical area,
[DIAGS_NN] A&E diagnosis - anatomical side,
[DIAGSCHEME] Diagnosis Scheme in Use,
[DOMPROC] Dominant procedure,
[EPIKEY] Record identifier,
[ETHNOS] Ethnic category,
[GORTREAT] Government office region of treatment,
[GPPRAC] Code of GP practice,
[HATREAT] Health authority of treatment,

[IMD04] IMD Index of Multiple Deprivation,
[IMD04_DECILE] IMD Decile group,
[IMD04C] IMD Crime domain,
[IMD04ED] IMD Education, skills and training,
[IMD04EM] IMD Employment domain,
[IMD04HD] IMD Health and disability domain,
[IMD04HS] IMD barriers to housing and services,
[IMD04I] IMD Income domain,
[IMD04IA] IMD Income affecting adults domain,
[IMD04IC] IMD Income affecting children domain,
[IMD04LE] IMD Living Environment domain,
[IMD04RK] IMD Overall rank,
[INVEST_NN] A&E investigation,
[LSOA01] Lower Super Output Area,
[LSOA11] Lower Super Output Area,
[MATCH_RANK] MATCH_RANK,
[MSOA01] Middle Super Output Area, 2001,
[MSOA11] Middle Super Output Area, 2011,
[MYDOB] Date of Birth - month and year,
[NEWNHSNO_CHECK] NHS Number valid flag,
[NHSNOIND] NHS number status indicator,
[NODIAGS] Number of Diagnosis values,
[NOINVESTS] Number of Invesitgations,
[NOTREATS] Number of Treatments,
[OACODE6] 2001 Census Output Area (6 chars),
[ORGPPPID] Organisation code of patient pathway ID issuer,
[PCFOUND] Postcode Found,
[PCTCODE_HIS] Primary Care Trust,
[PCTORIG02] Origin of primary care trust of responsibility - historic,
[PCTTREAT] Primary Care Trust area of main provider,
[PEREND] Reporting period end date,
[PGPPRAC] Pseudonymised practice code,
[POSTDIST] Postcode district,
[PREGGMP] Pseudonymised registered GP code,
[PROCODE] Organisation code {code of provider),
[RESCTY] County of residence,
[RESCTY_ONS] County of residence (ONS),
[RESHA] Health authority of residence,
[RESLADST] LA district of residence,
[RESLADST_ONS] Local authority district (ONS),
[RESPCT06] Current PCT of residence,
[RESRO] Region of residence,
[RESSTHA02] Historic Strategic HA of residence,
[RESSTHA06] Current strategic HA of residence,
[ROTREAT] Region of treatment,
[RTTPEREND] RTTP period end,
[RTTPERSTART] RTT period start,
[RTTPERSTAT] RTT period status,
[RURURB_IND] Rural/Urban Indicator,
[SEX] Sex of patient,
[STHATRET] Strategic HA of treatment,
[STUDY_ID] STUDY_ID,
[SUBDATE] Submission date,
[SUSLDDATE] SUS loaded staging date,
[SUSRECID] SUS record ID,
[SUSSPELLID] SUS generated spell id,
[TREAT_NN] A&E treatment,
[TRETDUR] Duration to treatment,
[WAITDAYS] Waitdays

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts.
Cohort of 84,000

Data Transfer Method

- **HES:Civil Registration (Deaths) bridge**

Periods

N/A

Sensitive fields

Identifiable fields

Other fields

[All Available Fields] All Available Fields

Filters/minimisation efforts

Data will be limited to IDs to connect patients in either the liver cancer or liver transplant cohorts with mortality records if deceased.
Cohort of 84,000

Data Transfer Method

- **Civil Registration (Deaths) - Secondary Care Cut**

Periods

1997-1998
1998-1999
1999-2000
2000-2001
2001-2002
2002-2003
2003-2004
2004-2005
2005-2006
2006-2007
2007-2008
2008-2009
2009-2010
2010-2011
2011-2012
2012-2013
2013-2014
2014-2015
2015-2016
2016-2017

Sensitive fields

[AT_RESIDENCE Area Team of Residence,
[AT_TREATMENT Area Team of Treatment,
[BEDYEAR Bed days within the year,
[CANNET Cancer network,
[CANREG Cancer registry,
[CAUSE Cause code,
[CAUSE_3 Cause code - 3 characters,
[CCG_GP_PRACTICE CCG of GP Practice,
[CCG_RESIDENCE CCG of Residence,
[CCG_RESPONSIBILITY CCG of Responsibility,
[CCG_RESPONSIBILITY_ORIGIN Origin of CCG of Responsibility,
[CCG_TREATMENT CCG of Treatment,
[CCG_TREATMENT_ORIGIN Origin of CCG of Treatment,
[CDSEXTDATE CDS extract date,
[CDSVERPROTID CDS protocol identifier,
[CDSVERSION CDS version number,
[CLASSPAT Patient classification,
[CR_GP_PRACTICE Commissioning Region of GP Practice,
[CR_RESIDENCE Commissioning Region of Residence,
[CR_TREATMENT Commissioning Region of Treatment,
[CURRWARD Current electoral ward,
[CURRWARD_ONS Current electoral ward (ONS),
[DEPDAYS_N High-dependency care level,
[DIAG_COUNT Count of diagnoses,
[DIAG_NN All Diagnosis codes,
[DISDATE Date of discharge,
[DISDEST Destination on discharge,
[DISMETH Method of discharge,
[DISREADYDATE Discharge ready date,
[EARLDATOFF Earliest reasonable date offered,
[ELECDATE Date of decision to admit,
[ELECDUR Waiting time,
[ELECDUR_CALC Calculation of Elecdur,
[ENDAGE Age at end of episode,
[EPIDUR Episode duration,
[EPIEND Date episode ended,
[EPIKEY Record identifier,
[EPIORDER Episode order,
[EPISTART Date episode started,
[EPISTAT Episode status,
[EPITYPE Episode type,
[ETHNOS Ethnic category,
[ETHRAW Ethnic character (audit version),
[FAE Finished Admission Episode,
[FAE_EMERGENCY Finished Admission Episode, emergency classification,
[FDE Finished In-Year Discharge Episode,
[FIRSTREG First regular day or night admission,
[GORTREAT Government office region of treatment,
[GPPRACHA Health Authority area where patient's GP is registered,
[GPPRPCT Primary Care Trust area where patient's GP was registered,
[GPPRSTHA Strategic Health Authority area where patient's GP was registered,
[HATREAT Health Authority of treatment,
[IMD04 IMD Index of Multiple Deprivation,
[IMD04_DECILE IMD Decile Group,
[IMD04C IMD Crime Domain,
[IMD04ED IMD Education Training and Skills Domain,
[IMD04EM IMD Employment Deprivation Domain,
[IMD04HD IMD Health and Disability Domain,
[IMD04HS IMD Barriers to Housing and Service Domain,

[IMD04I IMD Income Domain,
[IMD04IA IMD Income affecting Adults Domain,
[IMD04IC IMD Income affecting Children Domain,
[IMD04LE IMD Living Environment Domain,
[IMD04RK IMD Overall Rank,
[INTDAYS_N Intensive care level days,
[INTMANIG Intended management,
[LAD98 Local authority district in 1998,
[LSOA01 Lower Super Output Area (LSOA01),
[LSOA11 Lower Super Output Area (LSOA11),
[MAINSPEF Main specialty,
[MATCH_RANK MATCH_RANK,
[MSOA01 Middle Super Output Area, 2001,
[MSOA11 Middle Super Output Area, 2011,
[MYDOB Date of Birth - month and year,
[NEWNHSNO_CHECK NHS Number valid flag,
[NHSNOIND NHS number status indicator,
[NUMACP Number of augmented care periods within episode,
[OACODE6 Census Output Area, 2001 (6 character),
[OPCS43 OPCS4.3 vesion flag,
[OPDATE_NN Date of operation,
[OPERSTAT Operation status code,
[OPERTN_COUNT Total number of procedures per episode,
[OPERTN_NN Primary Operative Procedure Codes ,
[ORGPPPID Organisation code (patient pathway ID issuer),
[ORGSUP_N Number of organ systems supported,
[PCFOUND Postcode Found,
[PCGORIG Origin of primary care group,
[PCTCODE02 Primary care trust of responsibility - historic,
[PCTCODE06 Primary care trust of responsibility - current,
[PCTORIG02 Origin of primary care trust of responsibility - historic,
[PCTORIG06 Origin of primary care trust of responsibility - current,
[PCTTREAT Primary Care Trust area of main provider,
[POSOPDUR Post-operative duration,
[POSTDIST Postcode district of patient's residence,
[PREOPDUR Pre-operative duration,
[PROVSPNOPS Pseudonymised hospital provider spell number,
[RESCTY County of residence,
[RESCTY_ONS County of residence (ONS),
[RESHA Health Authority of residence,
[RESLADST Local authority district,
[RESLADST_ONS Local authority district (ONS),
[RESPCT_HIS The primary care trust of residence - mapped according to source year,
[RESPCT02 Patient's Primary Care Trust of residence - historic,
[RESPCT06 Patient's Primary Care Trust of residence - current,
[RESSTHA02 Patient's Strategic Health Authority of residence - historic,
[RESSTHA06 Patient's Strategic Health Authority of residence - current,
[ROTREAT Region of treatment,
[RTTPEREND RTT period end date,
[RTTPERSTART RTT period start date,
[RTTPERSTAT RTT period status,
[RURURB_IND Rural/Urban Indicator,
[SEX Sex of patient,
[SITETRET Site code of treatment,
[SPELBGIN Beginning of spell,
[SPELDUR Duration of spell,
[SPELEND End of spell,
[STARTAGE Age at start of episode,
[STARTAGE_CALC Age of patients at start of episode, babies restated,

[STHATRET Strategic Health Authority area of treatment,
[STUDY_ID STUDY_ID,
[SUBDATE Submission date,
[SUSLDDATE SUS loaded staging date,
[SUSRECID SUS record id,
[SUSSPELLID SUS generated spell id,
[TRETSPEF Treatment specialty,
[WAITDAYS Duration of elective wait,
[WAITLIST Method of Admission - Waiting List

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts
Cohort of 84,000

Data Transfer Method

- **Hospital Episode Statistics Outpatients**

Periods

2017/18

Sensitive fields

Identifiable fields

Other fields

[ACTIVAGE Age at activity date,
[ADMINCAT Administrative category,
[APPTAGE Age on day of appointment,
[APPTAGE_CALC Appointment Age - babies decimalised,
[APPTDATE Appointment date,
[AT_GP_PRACTICE Area Team of GP Practice,
[AT_RESIDENCE Area Team of Residence,
[AT_TREATMENT Area Team of Treatment,
[ATENTYPE Attendance type,
[ATTENDED Attended or did not attend,
[ATTENDKEY Record identifier,
[ATTENDKEY_FLAG Attendence Key Flag,
[BABYAGE Age of Baby,
[CANNET Cancer network,
[CANREG Cancer registry,
[CARERSI Carer support indicator,
[CSNUM Commissioning serial number,
[DIAG_COUNT Count of diagnoses,
[DIAG_NN Diagnosis,
[DNADATE Last DNA or patient cancelled date,
[EARLDATOFF Earliest reasonable date offered,
[ENCRYPTED_HESID Encrypted HESID,
[ETHNOS Ethnic category,
[ETHRAWL Ethnic category (audit version),
[FIRSTATT First attendance,
[FYEAR Financial Year,
[GPPRAC Code of GP practice,
[GPPRACHA Health Authority area where patient's GP is registered,
[GPPRACRO Regional office area where patient's GP practice was registered,
[GPPRPCT Primary Care Trust area where patient's GP was registered,
[GPPRSTHA Strategic health authority area where patient's GP practice was registered,
[IMD04 IMD Index of Multiple Deprivation,
[IMD04_DECILE IMD Decile Group,

[IMD04C IMD Crime Domain,
[IMD04ED IMD Education, Skills and Training Domain,
[IMD04EM IMD Employment Deprivation Domain,
[IMD04HD IMD Health and Disability Domain,
[IMD04HS IMD Barriers to Housing and Services Domain,
[IMD04I IMD Income Domain,
[IMD04IA IMD Income Affecting Older People Index,
[IMD04IC IMD Income Affecting Children Index,
[IMD04LE IMD Living Environment Domain,
[IMD04RK IMD Overall Ranking,
[LOCCLASS Location class,
[LOCTYPE Location type,
[MAINSPEF Main specialty,
[MARSTAT Marital Status,
[MATCH_RANK MATCH_RANK,
[MYDOB Date of Birth - month and year,
[NEWNHSNO_CHECK NHS Number valid flag,
[NHSNOIND NHS number status indicator,
[NODIAGS Number of Diagnosis,
[NOPROCS Number of Procedures,
[OPCS43 OPCS43,
[OPERSTAT Operation status code,
[OPERTN_NN Operative procedure,
[ORGPPPID Organisation code of patient pathway ID issuer,
[OUTCOME Outcome of attendance,
[PARTYEAR Year and month of data,
[PCFOUND Postcode Found,
[PCTCODE_HIS PCTCODE_HIS,
[PCTCODE02 Primary care trust of responsibility - historic,
[PCTCODE06 Primary care trust of responsibility - current,
[PCTORIG_HIS PCTORIG_HIS,
[PCTORIG02 Origin of primary care trust of responsibility - historic,
[PCTORIG06 Origin of primary care trust of responsibility - current,
[POSTDIST Postcode district of patient's residence,
[PREFERER Pseudonymised referrer code,
[PRIORITY Priority type,
[PROCODE Organisation code {code of provider),
[PROCODE3 Provider code (3 character),
[PROCODE5 Provider code (5 character),
[PROCODET Provider code,
[PROTYPE Provider type,
[PURCODE Commissioner code,
[PURSTHA Commissioner's strategic health authority,
[PURVAL Commissioner code status,
[REFSOURC Source of referral,
[REQDATE Referral request received date,
[RESPCT_HIS RESPCT_HIS,
[RESSTHA_HIS RESSTHA_HIS,
[RTTPEREND RTT period end date,
[RTTPERSTART RTT period start date,
[RTTPERSTAT RTT period status,
[SENDER SENDER,
[SERVTYPE Service type requested,
[SEX Sex of patient,
[STAFFTYP Medical staff type seeing patient,
[STUDY_ID STUDY_ID,
[SUBDATE Submission date,
[SUSLDDATE SUS loaded staging date,
[SUSLDDATE SUS loaded staging date,

[SUSLDDATE SUS loaded staging date,
[SUSLDDATE SUS loaded staging date,
[SUSRECID SUS record id,
[SUSSPELLID SUS generated spell id,
[TRETSPEF Treatment specialty,
[WAIT_IND Waiting calculation indicator,
[WAITDAYS Duration of elective wait,
[WAITING Days waiting

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts.
Cohort of 84,000

Data Transfer Method

- **Hospital Episode Statistics Accident and Emergency**

Periods

2017/18

Sensitive fields

Identifiable fields

Other fields

[ACTIVAGE Age at activity date,
[AEATTEND_EXC_PLANNED Attendances excluding planned,
[AEATTENDCAT Attendance category,
[AEATTENDDISP Attendance disposal,
[AEDEPTTYPE Department type,
[AEKEY Record identifier,
[AEKEY_FLAG AEKEY Flag,
[AEPATGROUP Patient group,
[AEREFSOURCE Source of referral for A&E,
[APPDATE Net applicable date,
[ARRIVALAGE Age on arrival,
[ARRIVALAGE_CALC Age on arrival calculated,
[ARRIVALDATE Arrival date,
[AT_GP_PRACTICE Area Team of GP Practice,
[AT_RESIDENCE Area Team of Residence,
[AT_TREATMENT Area Team of Treatment,
[CANNET Cancer network,
[CANREG Cancer registry,
[CARERSI Carer support indicator,
[CCG_GP_PRACTICE CCG of GP Practice,
[CCG_RESIDENCE CCG of Residence,
[CCG_RESPONSIBILITY CCG of Responsibility,
[CCG_RESPONSIBILITY_ORIGIN Origin of CCG of Responsibility,
[CCG_TREATMENT CCG of Treatment,
[CCG_TREATMENT_ORIGIN Origin of CCG of Treatment,
[CDSEXTDATE CDS extract date,
[CDSUNIQUEID CDS unique ID,
[CDSVERPROTID CDS protocol ID,
[CR_GP_PRACTICE Commissioning Region of GP Practice,
[CR_RESIDENCE Commissioning Region of Residence,
[CR_TREATMENT Commissioning Region of Treatment,
[DIAG_NN A&E diagnosis,
[DIAGA_NN A&E diagnosis - anatomical area,
[DIAGS_NN A&E diagnosis - anatomical side,

[DIAGSCHEME Diagnosis Scheme in Use,
[DOMPROC Dominant procedure,
[EPIKEY Record identifier,
[ETHNOS Ethnic category,
[GORTREAT Government office region of treatment,
[GPPRAC Code of GP practice,
[HATREAT Health authority of treatment,
[IMD04 IMD Index of Multiple Deprivation,
[IMD04_DECILE IMD Decile group,
[IMD04C IMD Crime domain,
[IMD04ED IMD Education, skills and training,
[IMD04EM IMD Employment domain,
[IMD04HD IMD Health and disability domain,
[IMD04HS IMD barriers to housing and services,
[IMD04I IMD Income domain,
[IMD04IA IMD Income affecting adults domain,
[IMD04IC IMD Income affecting children domain,
[IMD04LE IMD Living Environment domain,
[IMD04RK IMD Overall rank,
[INVEST_NN A&E investigation,
[LSOA01 Lower Super Output Area,
[LSOA11 Lower Super Output Area,
[MATCH_RANK MATCH_RANK,
[MSOA01 Middle Super Output Area, 2001,
[MSOA11 Middle Super Output Area, 2011,
[MYDOB Date of Birth - month and year,
[NEWNHSNO_CHECK NHS Number valid flag,
[NHSNOIND NHS number status indicator,
[NODIAGS Number of Diagnosis values,
[NOINVESTS Number of Invesitgations,
[NOTREATS Number of Treatments,
[OACODE6 2001 Census Output Area (6 chars),
[ORGPPPID Organisation code of patient pathway ID issuer,
[PCFOUND Postcode Found,
[PCTCODE_HIS Primary Care Trust,
[PCTORIG02 Origin of primary care trust of responsibility - historic,
[PCTTREAT Primary Care Trust area of main provider,
[PEREND Reporting period end date,
[PGPPRAC Pseudonymised practice code,
[POSTDIST Postcode district,
[PREGGMP Pseudonymised registered GP code,
[PROCODE Organisation code {code of provider),
[RESCTY County of residence,
[RESCTY_ONS County of residence (ONS),
[RESHA Health authority of residence,
[RESLADST LA district of residence,
[RESLADST_ONS Local authority district (ONS),
[RESPCT06 Current PCT of residence,
[RESRO Region of residence,
[RESSTHA02 Historic Strategic HA of residence,
[RESSTHA06 Current strategic HA of residence,
[ROTREAT Region of treatment,
[RTTPEREND RTTP period end,
[RTTPERSTART RTT period start,
[RTTPERSTAT RTT period status,
[RURURB_IND Rural/Urban Indicator,
[SEX Sex of patient,
[STHATRET Strategic HA of treatment,
[STUDY_ID STUDY_ID,

[SUBDATE Submission date,
[SUSLDDATE SUS loaded staging date,
[SUSRECID SUS record ID,
[SUSSPELLID SUS generated spell id,
[TREAT_NN A&E treatment,
[TRETDUR Duration to treatment,
[WAITDAYS Waitdays

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts.
Cohort of 84,000

Data Transfer Method

- **HES:Civil Registration (Deaths) bridge**

Periods

Latest available

Sensitive fields

Identifiable fields

Other fields

[All Available Fields All Available Fields

Filters/minimisation efforts

Data will be limited to IDs to connect patients in either the liver cancer or liver transplant cohorts with mortality records if deceased.
Cohort of 84,000

Data Transfer Method

- **Civil Registration (Deaths) - Secondary Care Cut**

Periods

Latest available

Sensitive fields

[cause_of_death] Original Underlying Cause of Death,
[death_record_used] Death Record Used,
[dod] Date of Death,
[dor] Date of Registration,
[Match rank] Match rank,
[Match rank] Match rank,
[respct] Primary Care Trust of usual residence of deceased,
[resstha] Strategic Health Authority of usual residence of deceased,
[sex] Sex

Identifiable fields

Other fields

[STUDY_ID STUDY_ID

Filters/minimisation efforts

Data will be limited to patients in either the liver cancer or liver transplant cohorts.
Cohort of 84,000

Data Transfer Method

3. Additional Information

Recommended product(s)

List Clean	No
Patient Status	No
Patient Tracking	No

Additional Technical Detail

Provider of Liver Cancer (LC) cohort: Dominic Dwyer (Dominic.Dwyer@phe.gov.uk) at National Cancer Registration and Analysis Service (NCRAS).

Provider of Liver Transplant (LT)cohort: Elisa Allen (elisa.allen@nhsbt.nhs.uk) at NHS Blood and Transplant (NHSBT).

Providers to supply one cohort files in the format of a CSV containing header row with the following columns:
-STUDY_ID - unique person id for study (100% populated)
-NHS - 10 digit NHS number or null if unknown or not approved
-DOB - yyyy-mm-dd or null if unknown or not approved
-SEX - 1 for male, 2 for female or null if unknown or not approved
-POSTCODE maximum of 8 digits or null if unknown or not approved

Process Steps

-Providers to send in cohorts.
NHS Digital to :
-Append the cohort adding LT/LC to the STUDY_ID to enable identification of which study the data belongs to.
-Apply Type-2 Objections to the cohorts.
-Link the cohort to the HESID index using the standard 8 step algorithm.
-Create a HES cohort based on HES APC and HES OP where Diag_concat like '%C22%' or OPERTN_concat like '%J01%'.
-Add the HESIDS from the HES cohort into the linked cohort.
-Extract all records for the final cohort and apply Type-2 Objections to the extracts.

The NHSBT and NCRAS linkage table should include the full cohorts, patients that matched to each other and null where they don't.

In data extracts check for "suspect" fields like CDSUNIQUEID in A&E which should be "nulled" if they are not already blank in the underlying data

Annex C: Approval Information

Signed for and on behalf of the Information Asset Owner:	
Name:	Kimberley Watson
Electronic approval reference:	8E953223-3DF7-7129-3994-0FF4F8F95202
Organisation Name:	NHS Digital
Role:	Senior Business and Operational Delivery Manager
Date/time:	19/06/2019

Signed for and on behalf of NHS Digital:	
Name:	Garry Coleman
Electronic approval reference:	309D6821-824C-6BB0-D076-F116EAACEE7B
Role:	Head of Business and Operational Delivery
Date/time:	19/06/2019

Signed for and on behalf of the Data Controller:	
Organisation Name:	
Electronic approval reference:	
Name:	
Position in organisation:	
Date:	
Organisation Name:	
Electronic approval reference:	
Name:	
Position in organisation:	
Date:	

12.3 APPENDIX C – ETHICAL APPROVALS

NHS
Health Research Authority

South East Coast - Brighton & Sussex Research Ethics Committee

Health Research Authority
Ground Floor, Skipton House
80 London Road
London
SE1 6LH

Telephone: 02071048308
Fax:

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

10 February 2017

Mr David Wallace
15-17 Tavistock Place
London
WC1H 9SH

Dear Mr Wallace

Study title:	**Liver transplantation as treatment for patients with hepatocellular carcinoma; a study using existing electronic data.**
REC reference:	**17/LO/0231**
Protocol number:	**N/A**
IRAS project ID:	**218152**

The Research Ethics Committee reviewed the above application at the meeting held on 02 February 2017. Thank you for attending to discuss the application.

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

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

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

1. The study should be registered on a public database, and the IRAS form should be amended accordingly.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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

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

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

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

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

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

Registration of Clinical Trials

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

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

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

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

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

Ethical review of research sites

NHS Sites

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

Summary of discussion at the meeting

The Committee commended the applicant on their application.

- **Social or scientific value; scientific design and conduct of the study**

The Committee asked what information would be obtained from the databases and what other data was available.

It was stated that this data would help to define the cohort, and that the transplantation database was a source of data as well. It was stated that researchers would look at participants' pre-existing disease, and whether obesity or alcohol had been a factor. Such information could then be conveyed to Public Health Organisations for public education. It was stated that there was not much information available about the causes of liver cancer, for instance people were not aware that obesity could cause it. The best treatment was not known. The cancer registry would provide the stage of the cancer, and the last part of the project was transplantation. It was stated that 25% of liver transplants were for liver cancer, and that there was an organ shortage.

The Committee asked whether the liver could be divided up between patients.

It was stated that an adult liver could be split for paediatric patients.

The Committee asked where data was kept.

It was stated that this was at the clinical effective unit at the royal college of surgeons.

The Committee asked if the study had CAG approval.

It was stated that a response was being awaited.

The Committee asked whether the study was registered on a public database.

It was stated that this would be followed up, and the IRAS form amended appropriately.

The Committee was satisfied with the responses provided.

- **Recruitment arrangements and access to health information, and fair participant selection**

The Committee stated that it was impressed with the numbers of recruitment, and asked why it was so high.

It was stated that alcohol was a driving factor, as well as hepatitis C. 40% of patients were said to have hepatitis C. It was hoped that with antivirals this would decrease.

The Committee was satisfied with the responses provided.

- **Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity**

The Committee asked whether the date of transplant was potentially identifiable data.

It was stated that there was more than one transplant a day in the UK, and so it was not considered identifiable.

The Committee was satisfied with the responses provided.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_19012017]		19 January 2017
Letter from funder [NIHR Funding Document]	1	03 October 2016
Letter from sponsor [LSHTM Insurance Indemnity Document]	1	15 December 2016
Other [Summary CV for Academic Supervisor Susan Charman]	1	18 January 2017
Research protocol or project proposal [Study Protocol]	1	13 January 2017
Summary CV for Chief Investigator (CI) [CV (full) Chief Investigator]	1	19 December 2016
Summary CV for student [Summary CV of student]	1	09 December 2016
Summary CV for supervisor (student research) [Summary CV Investigator]	1	09 December 2016

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

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

After ethical review

Reporting requirements

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

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

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

User Feedback

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

HRA Training

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

17/LO/0231	**Please quote this number on all correspondence**

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

Yours sincerely

PP

Dr Simon Walton
Chair

E-mail: NRESCommittee.SECoast-BrightonandSussex@nhs.net

Enclosures:	*List of names and professions of members who were present at the meeting and those who submitted written comments*
	"After ethical review – guidance for researchers" [*SL-AR2 for other studies]*
Copy to:	*Dr David Wallace*
	Confidentiality Advise Team

South East Coast - Brighton & Sussex Research Ethics Committee

Attendance at Committee meeting on 02 February 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Duncan Angus	Consultant Psychiatrist	Yes	
Dr John Bull	Consultant Physician (retired)	Yes	
Miss Philippa Case	Mental Health Nurse	No	
Mr Gerard Cronin	Business Development Manager	No	
Mrs Janine Hobbs	Retired Civil Servant	Yes	
Mr Bill Kent	Retired Civil Servant	Yes	
Dr Tom Levett	Clinical Research Fellow	Yes	
Mr Maurice Marchant	Public Health Information Specialist (retired)	No	
Mrs Carrie Ridley	Clinical Research Nurse (Emergency Medicine)	Yes	
Mrs Kathy Stott	Pharmacist	Yes	
Dr Simon Walton	Consultant in Anaesthesia and Intensive Care	Yes	
Dr Stuart White	Consultant Anaesthetist	No	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Ryan Erfani-Ghettani	

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr David Wallace,
LSHTM

8 February 2017

Dear David,

Study Title: Liver Transplantation as treatment for hepatocellular carcinoma; a study using existing electronic data

LSHTM Ethics Ref: 12043

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Study Protocol	14/12/2016	1
Investigator CV	CV Chief+Investigator	14/12/2016	1
Investigator CV	CV Academic+Supervisor	14/12/2016	1
Covering Letter	Clarification Letter	03/02/2017	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Health Research Authority
Skipton House
80 London Road
London
SE1 6LH

Telephone: 020 7972 2557
Email: hra.cag@nhs.net

20 March 2017

Mr David Wallace
Clinical Research Fellow / PhD student
15-17 Tavistock Place
London
WC1H 9SH

Dear Mr Wallace

Application title:	**Liver transplantation as treatment for patients with hepatocellular carcinoma; a study using existing electronic data.**
CAG reference:	**17/CAG/0025**
IRAS project ID:	**218152**
REC reference:	**17/LO/0231**

Thank you for your research application, submitted for approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was previously considered at the precedent set CAG meeting held on 27 January 2017, at which it was escalated for review at the full CAG meeting held on 09 March 2017.

Health Research Authority Decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

1. The application is conditionally approved, subject to compliance with the standard and specific conditions of approval outlined below.

   Please note that the legal basis to allow access to the specified confidential patient information without consent is now in effect.

   This letter should be read in conjunction with previously outcome letter dated 09

February 2017.

Context

Purpose of Application

This application from the LSHTM set out the purpose of improving the role that liver transplantation could play as a treatment for patients with Hepatocellular carcinoma (HCC), a cancer of the liver. Survival rates were poor and liver transplantation was increasingly used as a treatment, leading to a shortage of livers. This in turn had led to an increase in the use of liver donors after cardiac death as well as brainstem death donors. The researcher aimed to explore the incidence and mortality of HCC, assess the validity of linked national databases as a data source for HCC research, identify the impact of sociodemographic and clinical factors on treatment selection and survival of patients, and identify the outcomes of liver transplantation for patients who received a cardiac death liver donor.

The applicant requested linkage with three national databases: the National Cancer Registration and Analysis (NCRAS) database, the Hospital Episode Statistics (HES) linked to ONS database and the UK Liver Transplant (UKLT) database in order to evaluate the outcome of transplantation in HCC patients.

A recommendation for class 4, 5 and 6 support was requested to cover access to the linkage of patient identifiable information obtained from more than one source, for auditing, monitoring and analysing patient care and treatment and to allow access to an authorised user for one or more of the above purposes.

Confidential Patient Information Requested

Access was requested to data items listed on the application, including full date of death.

The patient's NHS number, gender, date of birth and postcode would be provided by the applicant to NHS Digital who would perform linkage with HES/ONS datasets and manage linkage with NHSBT and NCRAS datasets (data sent from NHSD and returned to NHSD).

Confidentiality Advisory Group Advice

Promotion from Precedent Set Review

Members considered the information provided in the outcome letter from the previous precedent set sub-committee review of the application and it was acknowledged that the application had been escalated for consideration at a full CAG meeting as the proposal did not meet the precedent set criteria, as date of death was included within the dataset required for final analysis.

The CAG considered the additional issues which had been identified by the precedent set sub-committee to which the applicant had provided further written response.

Practicable alternatives

Members considered whether a practicable alternative to the disclosure of patient identifiable data without consent existed, taking into account the cost and technology available in line with Section 251 (4) of the NHS Act 2006.

- Feasibility of consent

The CAG acknowledged the previous acceptance from the sub-committee review that consent was not feasible given the cohort size of over 50,000, many who were likely to be deceased.

- Use of anonymised/pseudonymised data

Members acknowledged that the applicants were able to pseudonymise the data items requested with the exception of date of death, which was required in full for final analysis. The applicants had explained that the date of death was essential to enable analysis of outcomes following treatment (or not) for patients with HCC. The CAG considered the rationale and agreed that this supported the request to retain date of death for analysis.

Justification of Identifiers

The precedent set sub-committee identified that the applicant aimed to assess validity across datasets but repeatedly mentioned linking all three datasets. Members had requested further clarification if an individual appeared in two but not the third dataset, as it was not clear whether the research team would receive the individual's details in this circumstance.

The applicants provided confirmation in writing that they would receive information on patients in this instance. It was explained that due to the nature of the study it was feasible that the applicants would receive details of the same patient in either all three databases, two databases or even just one database if linkage was incomplete. The applicants provided the example that they would receive patients in the NHSBT transplant database that had been transplanted for reasons other than HCC and as such, their records would not be available from the NCRAS database but should be linked to HES.

The applicants advised that access to these records, without the NCRAS record, was vital as it allowed comparison of those transplanted with HCC (NCRAS, HES and NHSBT databases) against those transplanted for other indications, such as alcoholic liver disease (HES and NHSBT). Members were satisfied with the response provided and no further issues were raised.

Clarification had also been sought from the previous review around whether the Kings College HCC dataset referenced within the protocol involved the use of identifiers, or was used for comparison of aggregate statistics only and therefore did not require consideration as part of this application of support.

The applicant confirmed in writing that the Kings College HCC database required comparison of aggregate statistics only and was outside of the scope of the request for support. Members received the clarification and no further issues were raised in this area.

Patient and Public Involvement and Engagement

Members commended the level of public and patient engagement which had been undertaken throughout the application process.

Patient Notification and Objection

The CAG considered the previous recommendation provided by the Sub-Committee which requested that information about the study was placed on the NCRAS and UKLT

(NHS Blood and Transplant) websites, with a lead-in time to allow for any objections to be registered. Whilst it was acknowledged by Members that this previous request had only been a recommendation with report due at first annual review, the applicant had provided an interim response on this point. The applicant confirmed that contact would be made with both NCRAS and NHSBT to request that the study information was placed on their respective websites; however, the applicant was unable to provide confirmation that this would occur. The applicants advised that the study would be advertised on both the Royal College of England and the LSTHM websites and as a NIHR funded project, information would also be available on the NIHR website.

Members received the response and agreed that report should be made back at annual review around the progress of the study advertisement on the NCRAS and NHSBT websites.

The CAG queried how the study results would be disseminated as it was acknowledged that the outcomes would be of national significance. It was agreed that the applicant would be asked to report back at first annual review around the intended publication for the project.

Confidentiality Advisory Group Advice Conclusion

The CAG agreed that the minimum criteria under the Regulations appeared to have been met and that there was a public interest in projects of this nature being conducted, and therefore advised recommending support to the Health Research Authority, subject to compliance with the specific and standard conditions of support as set out below.

Specific Conditions of Support

1. Patient Notifications – provide an update at first annual review around the progress with displaying study information on the NCRAS and NHSBT websites.
2. Study Findings Dissemination and Publication – provide an overview at first annual review around the proposed dissemination of study findings and publication.
3. Favourable opinion from a Research Ethics Committee. **(Confirmed – Brighton and Sussex REC issued on 10 February 2017).**
4. Confirmation from the IGT Team at the NHS Digital of suitable security arrangements via Information Governance Toolkit (IGT) submission. **(Confirmed – Version 13 2015-16 shows a reviewed satisfactory grade at 70%).**

Reviewed Documents

The documents reviewed at the meeting were:

Document	*Version*	*Date*
CAG application from (signed/authorised) [CAG Form Snapshot]		
Research protocol or project proposal [Study Protocol]	1	

Annual Review

Please note that your approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. An annual review should be provided no later than **20 March 2018** and preferably 4 weeks before this date. If at any stage you no

longer require support under the Regulations as you will cease processing confidential patient information without consent you should inform the Confidentiality Advice Team of this in writing as soon as possible.

Membership of the Committee

The members of the Confidentiality Advisory Group who were present at the consideration of this item or submitted written comments are listed below.

Yours sincerely

Ms Kathryn Murray
Senior Confidentiality Advisor
On behalf of the Health Research Authority

Email: HRA.CAG@nhs.net

Enclosures:	*List of members who considered application* *Standard conditions of approval*
Copy to:	NRESCommittee.SECoast-BrightonandSussex@nhs.net HRA Approval

Confidentiality Advisory Group Meeting 09 March 2017

Group Members:

This meeting was Chaired by Dr Tony Calland and Ms Clare Sanderson.

Name	*Present*	*Notes*
Dr Tony Calland	Yes	Vice Chair
Professor Barry Evans	Yes	
Mr Anthony Kane	Yes	
Dr Harvey Marcovitch	Yes	
Ms Clare Sanderson	Yes	Alternate Vice Chair
Dr Murat Soncul	Yes	Alternate Vice Chair
Ms Gillian Wells	Yes	

In attendance:

Name	*Present*	*Capacity*
Ms Kathryn Murray	In Attendance	Senior Confidentiality Advisor

NHS
Health Research Authority

Standard Conditions of Approval

The approval provided by the Health Research Authority is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.

2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.

3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.

4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.

5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.

6. Activities are consistent with the Data Protection Act 1998.

7. Audit of data processing by a designated agent is facilitated and supported.

8. The wishes of patients who have withheld or withdrawn their consent are respected.

9. The Confidentiality Advice Team is notified of any significant changes (purpose, data flows, data items, security arrangements) prior to the change occurring.

10. An annual report is provided no later than 12 months from the date of your final confirmation letter.

11. Any breaches of confidentiality / security around this particular flow of data should be reported to CAG within 10 working days, along with remedial actions taken / to be taken.

12.4 APPENDIX D – CONFERENCE PRESENTATIONS

As part of my PhD I have attended and presented (oral and poster presentations) at several conferences. The complete abstract submitted to each conference can be found in the following pages.

Conference	Year	Conference Session	Presentation type
British Transplant Society Annual Congress	2017	Exhibit Hall	Poster (P0097)
	2018	Calne-Williams Medal Award Presentation	Oral (CW2)
	2018	'Six of the Best'	Oral (007)
	2019	Calne-Williams Medal Award Presentation	Oral (CW1)
	2019	Calne-Williams Medal Award Presentation	Oral (CW3)
	2019	Calne-Williams Medal Award Presentation	Oral (CW5)
	2020	Calne-Williams Medal Award Presentation	Oral (CW3)
	2021	Medawar Medal Presentation	Oral (M2)
	2021	Calne-Williams Medal Award Presentation	Oral (CW3)
	2021	Exhibit Hall	Poster (P007)
BASL Annual Congress*[1]	2018	Exhibit Hall	Poster (P97)
	2018	Exhibit Hall	Poster (P99)
	2018	Exhibit Hall	Poster (104)
AASLD Annual Congress*[2]	2018	Exhibit Hall	Poster (1164)
	2018	Exhibit Hall	Poster (1188)*[4]
	2018	Exhibit Hall	Poster (1190)
	2018	Exhibit Hall	Poster (1208)
ILTS Annual Congress*[3]	2019	Short and Long-term Patient and Allograft Outcomes	Oral (O-107)*[5]
	2019	Short and Long-term Patient and Allograft Outcomes	Oral (O-108)
	2020*[6]	Plenary Session 1	Oral (O-066)
	2020*[6]	Poster Round II	Poster (P-502)

*[1] British Association for the Study of the Liver
*[2] American Association for the Study of Liver Disease
*[3] International Liver Transplant Society
*[4] Award Winner: AASLD Liver Transplant Surgical Fellow Travel Award 2018
*[5] Award Winner: ILTS Young Investigator Award 2019
*[6] Conference cancelled due to Coronavirus pandemic. Abstracts carried forward to virtual conference in 2021.

Annual British Transplant Society Congress 2017

Harrogate 1st – 3rd March

Poster Presentation

P0097

The escalating impact of hepatocellular carcinoma on UK liver transplantation; an analysis of the United Kingdom Liver Transplant database

David Wallace[1,2], Susan Charman[1,2], Abid Suddle[3], Nigel Heaton[3], Jan van der Meulen[1,2]

1. *Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK*
2. *Clinical Effectiveness Unit (CEU), Royal College of Surgeons of England, London, UK*
3. *Institute of Liver Studies, King's Healthcare Partners at Denmark Hill campus, Kings College Hospital, London, UK*

Introduction: The exponential rise in the incidence and mortality of hepatocellular carcinoma in the UK is placing a huge demand on liver transplantation services.

Methods: The United Kingdom Liver Transplant Audit database was explored (1994-2012) to assess the frequency of adults receiving a first elective liver transplant for hepatocellular carcinoma, hepatitis C, hepatitis B, primary sclerosing cholangitis, primary biliary cirrhosis, alcoholic liver disease, autoimmune liver disease, metabolic liver disease and 'other' indications. Graft and patient survival were estimated for all indications and across four successive eras from 1994-2012. Cox regression analysis was calculated to compare survival across all indications for liver transplantation with HCC used as the reference (HR = 1).

Results: Hepatocellular carcinoma was the fastest growing indication for transplantation and now accounts for 22.5% of all UK liver transplants. Post-transplantation survival for all primary liver diseases improved across the study period. HCC had the poorest overall five and ten-year graft and patient survival (5-year; 60.5% and 63.5% respectively, 10-year; 44.3% and 47.3% respectively) and the worst comparative risk-adjusted mortality (all other indications HR < 0.8).

Discussion: Strategies to increase the donor pool and decrease the demand are vital to improve the capacity of UK liver cope with the escalating burden of HCC.

Annual British Transplant Society Congress 2018

Brighton March 14th – 16th

Calne-Williams Medal Award Presentation:

Oral Presentation

CW02

Assessing the time-varying impact of hepatocellular carcinoma on survival following liver transplantation

David Wallace [1,2,3], Kate Walker [1,2], Susan Charman[1], Abid Suddle[3], Nigel Heaton[3], Jan van der Meulen[1,2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Clinical Effectiveness Unit (CEU), Royal College of Surgeons of England, London, United Kingdom.*
3. *Institute of Liver Studies, Kings College Hospital, London, United Kingdom.*

Introduction: Historic studies have shown that patients with hepatocellular carcinoma (HCC) have favourable outcomes in the first 3 months following liver transplantation, but higher mortality thereafter. It had previously been argued that the introduction of the Milan criteria would reduce rates of tumour recurrence and negate this negative effect of HCC. We aimed to address this important research question by performing an updated analysis that identified the prognostic impact of HCC on mortality at different periods of follow-up time after liver transplantation.

Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 2007 and 2016. We compared the donor and recipient characteristics of HCC and non-HCC patients and used Kaplan-Meier methods to compare patient survival. We used Cox regression to examine the prognostic impact of HCC status on mortality at three separate periods of follow-up time: 0-90 days, 90 days-2 years and 2 years-5 years.

Results: 5780 first-time adult elective liver transplants were included. Patients transplanted for HCC had lower UKELD scores but were more likely to receive segmental grafts and grafts from circulatory death donors (P<0.05). No difference in 90-day mortality between HCC (n=1397) and non-HCC (n=4383) groups was identified (HR 0.82, 95% CI 0.58-1.15, p=0.25). HCC was associated with a statistically significant increased risk of mortality from 90 days-2 years (1.77, 1.32-2.38 and 1.55, P<0.001) and from 2 years - 5 years (1.58, 1.18- 2.05, P<0.01). The effect of HCC was found to vary significantly across the three periods of follow-up time (p for interaction=0.0006).

Discussion: HCC remains a significant risk factor for mortality after 3 months of follow-up time. Despite the implementation of the Milan criteria we are still transplanting patients who are at risk of early tumour recurrence and death.

Annual British Transplant Society Congress 2018

Brighton March 14th – 16th

'Six of the best' Medal Award Presentation:

Oral Presentation

O07

Have changes in the utilisation of livers donated following circulatory death affected survival in patients undergoing liver transplantation for hepatocellular carcinoma?

David Wallace[1,2,3], Kate Walker[1,2], Susan Charman[1,2], Abid Suddle[3], Nigel Heaton[3], Jan van der Meulen[1,2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Clinical Effectiveness Unit (CEU), Royal College of Surgeons of England, London, United Kingdom.*
3. *Institute of Liver Studies, Kings College Hospital, London, United Kingdom.*

Introduction: The rising incidence of hepatocellular carcinoma (HCC) has placed a considerable strain on liver transplantation services. In response, donated livers following circulatory death (DCD) are increasingly being utilised as clinicians strive to transplant patients with HCC in an acceptable oncological time-frame. We aimed to identify how post-transplantation survival in patients with HCC has changed over successive eras of liver transplantation and to what extent changes in survival can be explained by changes in both donor and recipient characteristics.

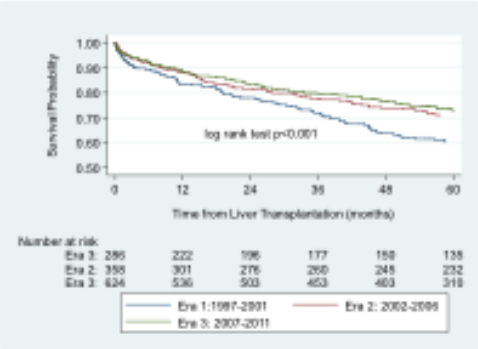
Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 1997 and 2016. We stratified the cohort into 4 eras of transplantation a)1997-2001 b) 2002-2006 c) 2007- 2011 and d) 2012-2016, and compared the change in the donor and recipient characteristics of HCC and non-HCC patients over eras. We used Kaplan-meier estimates to compare changes in 5-year patient survival and Cox regression to examine how, after adjustment for donor and recipient characteristics, the risk of undergoing liver transplantation for HCC successively changed from eras 1-3.

Results: 10,166 fist-time elective liver transplants were included. Across the entire study period, the utilisation of DCD livers disproportionately increased in HCC compared to non-HCC patients (32.7% vs 22.9%, $p<0.05$). 5-year patient survival improved from eras 1 to 3 in both HCC (59.9% to 73.2%) and non-HCC patients (74.8% to 83.4%, figure 1). Patient survival was consistently worse for HCC patients across all 3 eras of transplantation (log rank test $p<0.05$). This effect remained following adjustment for donor and recipient characteristics (table 1).

Discussion: Despite the increasing utilisation of DCD livers, survival for patients transplanted for HCC has improved considerably over last decade. However, in comparison to patients transplanted for non-HCC indications patients with HCC still have significantly worse long-term post-transplant outcomes.

Figure 1: 5-year patient survival for patients with HCC and non-HCC undergoing liver transplantation, stratified by era (n=7009).

a) HCC (n=1237)



b) Non-HCC (n=5772)

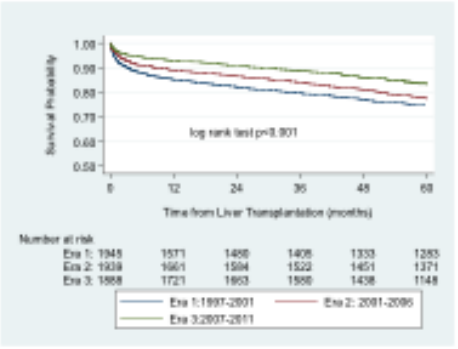


Table 1: Unadjusted and adjusted hazard ratios comparing liver transplantation for HCC vs non-HCC indications over eras 1-3 (n=7009)

	Era 1 (1997-2001)	Era 2 (2002-2006)	Era 3 (2007-2011)
HCC with era	1.59 (1.35-1.88)	1.26 (1.06-1.51)	1.66 (1.40-1.98)
HCC with era +adjustment for patient characteristics	1.42 (1.19-1.70)	1.17 (0.97-1.41)	1.52 (1.23-1.81)

**P=>0.05 for unadjusted and adjusted interaction of HCC status with era*

Annual British Transplant Society Congress 2019

Harrogate 6th – 8th March

Calne-Williams Medal Award Presentation:

Oral Presentation

CW1
The impact of transarterial chemoembolisation on complications and survival after liver transplantation

David Wallace[1, 2,] Kate Walker[1], Susan Charman[1], Abid Suddle[2], Alex Gimson[3], Ian Rowe[4], Chris Callaghan[5], Thomas Cowling[1], Jan van der Meulen[1], Nigel Heaton[2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*
3. *The Liver Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.*
4. *Liver Unit, St James' Hospital and University of Leeds, Leeds, UK / Leeds Institute for Data Analytics, University of Leeds, Leeds, United Kingdom.*
5. *Department of Transplantation, Renal Unit, Guy's Hospital, London, United Kingdom*

Introduction: The impact of transarterial chemoembolisation (TACE) on early and late post-transplantation outcomes has never been identified in a representative cohort of recipients with hepatocellular carcinoma (HCC). We linked the UK Standard National Liver Transplant registry to a hospital administrative dataset and assessed the impact of TACE on post-operative complications and mortality following liver transplantation.

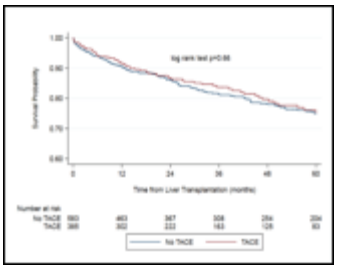
Methods: We identified a population-based cohort of HCC recipients of a liver transplant (aged ≥ 16 years) between 2006 and 2016. We stratified our cohort according to HCC recipients who had received TACE on the transplant waitlist and used Cox regression to compare mortality and estimate hazard ratios (HR), adjusted for relevant donor and recipient characteristics.

Results: 385 TACE and 583 non-TACE recipients were included. 5-year post-transplant survival was 75.2% (95%CI: 68.8% to 80.5%) in patients who received TACE and 75.0% (95%CI: 70.5% to 78.8%) in those who did not. With adjustment for donor and recipient characteristics, no significant differences in mortality (HR 0.96, 95%CI: 0.67-1.38, p=0.82) or graft survival were identified (HR: 1.01, 95%CI: 0.73-1.40, p=0.96). Also, the impact of TACE on mortality did not differ according to the number of TACE treatments (≥2 TACE treatments HR: 0.97, 95%CI: 0.61-1.55, p=0.90), the time-period after transplantation (p for interaction = 0.29) or the use of circulatory death donors (p for interaction = 0.97). The incidence of hepatic artery thrombosis was lower in those who received TACE (1.3% vs 2.5%, respectively, p=0.09).

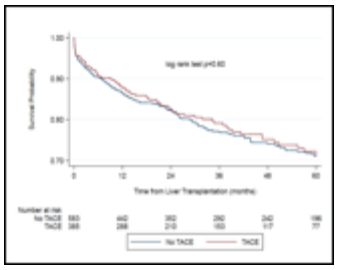
Discussion: The use of TACE on HCC patients on the liver transplant waitlist does not increase the risk of early post-operative complications or graft failure nor does it improve long-term patient survival or rates of tumour recurrence.

Figure 1: Five-year patient and graft survival stratified by TACE status 2006-2016 (n=968).

a) Patient survival



b) Graft survival



Annual British Transplant Society Congress 2019

Harrogate 6th – 8th March

Calne-Williams Medal Award Presentation:

Oral Presentation

CW3

The impact of pre-transplantation performance status on hospital resource use following liver transplantation

David Wallace[1], Thomas Cowling[1], Jan van der Meulen[1], Nigel Heaton[2], William Bernal[2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*

Introduction: The impact of frailty and compromised performance status (PS) on hospital resource use following liver transplantation (LT) has had limited characterisation. In this study, we linked the United Kingdom LT registry to a national administrative dataset and examined the impact of Pre-LT PS on hospital resource use.

Methods: 7940 patients with cirrhotic CLD who received a first LT between 1995-2016 were studied. Pre-LT PS was assessed using a 5-point scale (modified Eastern Cooperative Oncology Group (ECOG) score). We compared the prevalence of post-operative complications according to ECOG status and used linear regression techniques to examine the association between PS and length of hospital stay (LOS) in the initial transplantation admission and at 1, 2 and 3 years' post-transplantation (excluding initial admission).

Results: Recipients with increasingly impaired PS had an increased risk of renal failure, post-operative haemorrhage, biliary tract leak, CMV infection and sepsis ($P<0.05$). Compared to those able to carry out normal activity (ECOG PS1), recipients with ECOG PS5 had increased LOS during the initial post-LT admission (adj mean: 25.6 days 95%CI: 18.5, 32.6, $p<0.01$) but no statistically significant increased LOS at 1,2 or 3-years following LT ($p>0.05$). ECOG PS5 recipients also required longer post-operative ventilation (adj mean: 2.1 days 95%CI: 0.6,3.7) and had significantly longer ITU LOS (adj mean: 3.2 95%CI:1.3, 5.1).In contrast, patients with ECOG PS3 and 4 had no increased LOS after initial LT but longer LOS in the 3-years following LT (PS3; adj mean 9.8 days 95%CI:1.3,18.4 and PS4; adj mean 12.3 days 95%CI:2.8,21.8).

Discussion: LT recipient PS assessed using a simple measure was independently predictive of post-LT hospital resource use. Overall, poorer PS at the time of LT was associated with increased post-LT complications and prolonged ITU and Hospital LOS admission, with increased hospitalisation seen up to 3-years following surgery.

Annual British Transplant Society Congress 2019

Harrogate 6th – 8th March

Calne-Williams Medal Award Presentation:

Oral Presentation

CW5

The impact of performance status at the time of transplantation on outcomes following liver transplantation: a national cohort study in the United Kingdom and Ireland

David Wallace[1, 2], Mark McPhail[2], Sarah Brown[2], Varuna Aluvihare[2], Abid Suddle[2], Georg Auzinger[2], Michael Heneghan[2], Julia Wendon[2], Nigel Heaton[2], Jan van der Meulen[2], William Bernal[2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*

Introduction In the setting of liver transplantation (LT) the impact of frailty and compromised performance status (PS) on post-transplant outcomes are not well characterised in patients with chronic liver disease (CLD). In a national cohort of patients with CLD we examined the association of pre-LT PS on post-LT patient survival.

Methods: 7285 patients with cirrhotic CLD who received a first LT between 1997 and 2016 were studied. Pre-LT PS was assessed using a 5-point scale (modified Eastern Cooperative Oncology Group (ECOG) score). We used stratified cox-regression methods to estimate hazard ratios (HR) that compared post-transplantation mortality for ECOG status in three post-transplantation time-periods (epochs): 0 to 90 days, 90 days to 1-year and 1 year to 5-years, and across different eras of transplantation (1995 to 2005 and 2006 to 2016).

Results: 5-year post-LT patient survival was 84.6% in patients able to carry out normal activity without restriction (ECOG PS1) decreasing to 71.0% in those completely reliant on nursing and medical care (ECOG PS5; p <0.001). With adjustment for donor and recipient characteristics, the impact of ECOG PS5 on mortality was significantly poorer in the first 90-days (HR: 2.14 95%CI: 1.43-3.20), but not significantly worse thereafter (90 days to 1-year: HR 1.59, 0.84-3.01; 1-year to 5-years: HR 0.82, 0.46-1.47). Over era, survival improved for patients in all ECOG status (PS1: 0.65, 0.31-1.37; PS2: 0.54, 0.41-0.70, PS3: 0.57, 0.48-0.68, PS4: 0.67, 0.50-0.90 and PS5 0.51, 0.30-0.89), however the effect of era did not different between ECOG status (p for interaction 0.81).

Conclusions: LT recipient PS assessed using a simple measure is independently predictive of post-transplant mortality with strongest association in those with greatest compromise. In these patients, its impact is most marked in the first 3-months after surgery. Over time, mortality has decreased by at least one third for patients in each ECOG category.

Annual British Transplant Congress 2020

Belfast 4th – 6th March

Calne-Williams Medal Award Presentation:

Oral Presentation

CW3

Time-trends in patient mortality and graft survival of patients receiving a DCD or DBD liver transplantation in the UK and Ireland between 2008 and 2016.

David Wallace[1, 2,] Thomas Cowling[1], Abid Suddle[2], Alex Gimson[3], Ian Rowe[4], Chris Callaghan[5], Gonzalo Sapisochin[6,7], Neil Mehta[8], Jan van der Meulen[1], Kate Walker[1], Nigel Heaton[2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*
3. *The Liver Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.*
4. *Liver Unit, St James' Hospital and University of Leeds, Leeds, UK / Leeds Institute for Data Analytics, University of Leeds, Leeds, United Kingdom.*
5. *Department of Transplantation, Renal Unit, Guy's Hospital, London, United Kingdom*
6. *Multi-Organ Transplant, Toronto General Surgery, Canada, Toronto, Canada*
7. *Department of General Surgery, University of Toronto, Toronto, Canada*
8. *Division of Gastroenterology, Department of Medicine, University of California, San Francisco, USA*

Introduction: Internationally, the UK is the primary exponent in the transplantation of livers from controlled donation after circulatory death (DCD). However, concerns exist in the efficacy of these grafts. We evaluated the mortality, graft failure and post-operative complications of DCD and DBD donor liver transplantation in successive eras between 2008 and 2016.

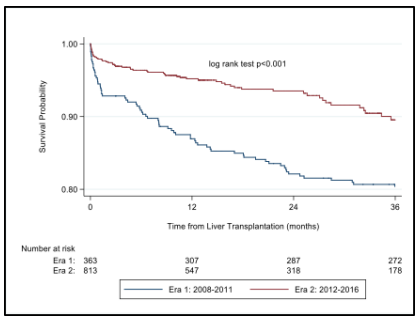
Methods: All first-time elective adult liver transplant recipients in the UK were identified and hazard ratios comparing the impact of era (2008-2011 and 2012-2016) on post-transplant mortality, graft failure and complications were estimated.

Results: 1 176 DCD recipients and 3 749 DBD recipients were included. The use of livers from DCD donors increased from 19.3% in era 1 to 26.7% in era 2. 3-year patient mortality decreased markedly from 19.6% in era 1 to 10.4% in era 2 (aHR:0.43, 95%CI: 0.30-0.62) for DCD recipients but only decreased from 12.8% to 11.3% (aHR:0.96, 0.78-1.19) in DBD recipients. Between eras no improvements in overall 3-year graft failure were observed for DCD (aHR:0.80, 0.61-1.05, p=0.11) or DBD recipients (aHR:0.95, 0.79-0.60, p=0.60) but the rate of re-transplantation increased from 7.2% to 10.1% in DCD recipients (p=0.14) and decreased from 4.8% to 3.7% in DBD recipients (p=0.01). In era 2, there was no difference in mortality between those receiving a DCD or DBD liver (aHR: 0.78, 0.56-1.09, p=0.14) however the incidence of biliary tract strictures increased for both cohorts (5.0% to 6.9% and 3.8% to 4.8%, respectively).

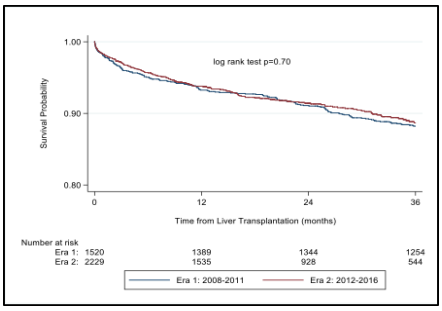
Conclusion: Between 2008 and 2016, mortality more than halved in those who received a DCD donor liver. In the UK, mortality following liver transplantation now appears to be comparable for patients receiving DCD and DBD donor livers.

Figure 1: 3-year patient survival across different eras of transplantation (2008-2011 and 2012-2016) in recipients receiving DCD or DBD livers (n=4 925).

a; DCD (n=1 176)



b; DBD (n=3 749)



Annual British Transplant Congress 2021

BTS NHSBT Live 24th – 25th February

Medawar Medal Award Presentation:

Oral Presentation

M2

Survival after liver transplantation: an international comparison between the United States and the United Kingdom and Ireland.

David Wallace[1, 2], Tommy Ivanics[3,4] Thomas Cowling[1], Kate Walker[1] Neil Mehta[5], Gonzalo Sapisochin[3,4], Jan van der Meulen[1], Nigel Heaton[2]

1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*
3. *Multi-Organ Transplant, Toronto General Surgery, Canada, Toronto, Canada*
4. *Department of General Surgery, University of Toronto, Toronto, Canada*
5. *Division of Gastroenterology, Department of Medicine, University of California, San Francisco, USA*

Introduction: Compared to the US, risk-adjusted mortality in the UK has historically been worse in the first 90-days following liver transplant (LT) but better thereafter. Despite changes in LT practice, no recent international comparison of post-transplant outcome has been conducted. We compared the disease-specific short and long-term mortality of LT recipients in the UK & Ireland with that in the US.

Methods: The UK Transplant Registry and the United Network Organ Sharing Dataset were harmonized and all first-time elective recipients (aged ≥18 years) of a LT between 2008 and 2016 identified. Time-dependent Cox-regression methods were used to estimate hazard ratios (HR) that compared disease-specific risk adjusted mortality between the UK and US in the first 90 days after transplantation, between 90 days and 1-year, and between 1 and 5-years.

Results: 4950 LT recipients from the UK and 42874 from the US were included (Table 1). The main indications for LT in the UK & Ireland and in the US were hepatocellular carcinoma (HCC, 24.9% and 25.4%, respectively) and alcoholic liver disease (ALD, 27.1% and 20.3%). From 0 to 90 days no difference in mortality between the UK & Ireland and the US was observed (comparing the UK with the US, HR; 0.96, 95%CI: 0.82-1.12, p=0.63, Figure 1); however, between 90 days and 1-year (HR; 0.71, 95%CI: 0.59-0.85, p<0.001) and 1 and 5-years (HR; 0.71, 95%CI: 0.63-0.81, p<0.001) the UK was found to have lower mortality. International differences in longer-term survival were most marked in patients with HCC (HR; 0.71, 95%CI: 0.58-0.88, p=0.002) and ALD (HR; 0.64, 95%CI: 0.45-0.89, p<0.001).

Conclusion: Long-term survival outcomes are superior in the UK& Ireland. International comparisons for LT may highlight differences in health care delivery and help identify modifiable factors that can improve post-LT outcomes.

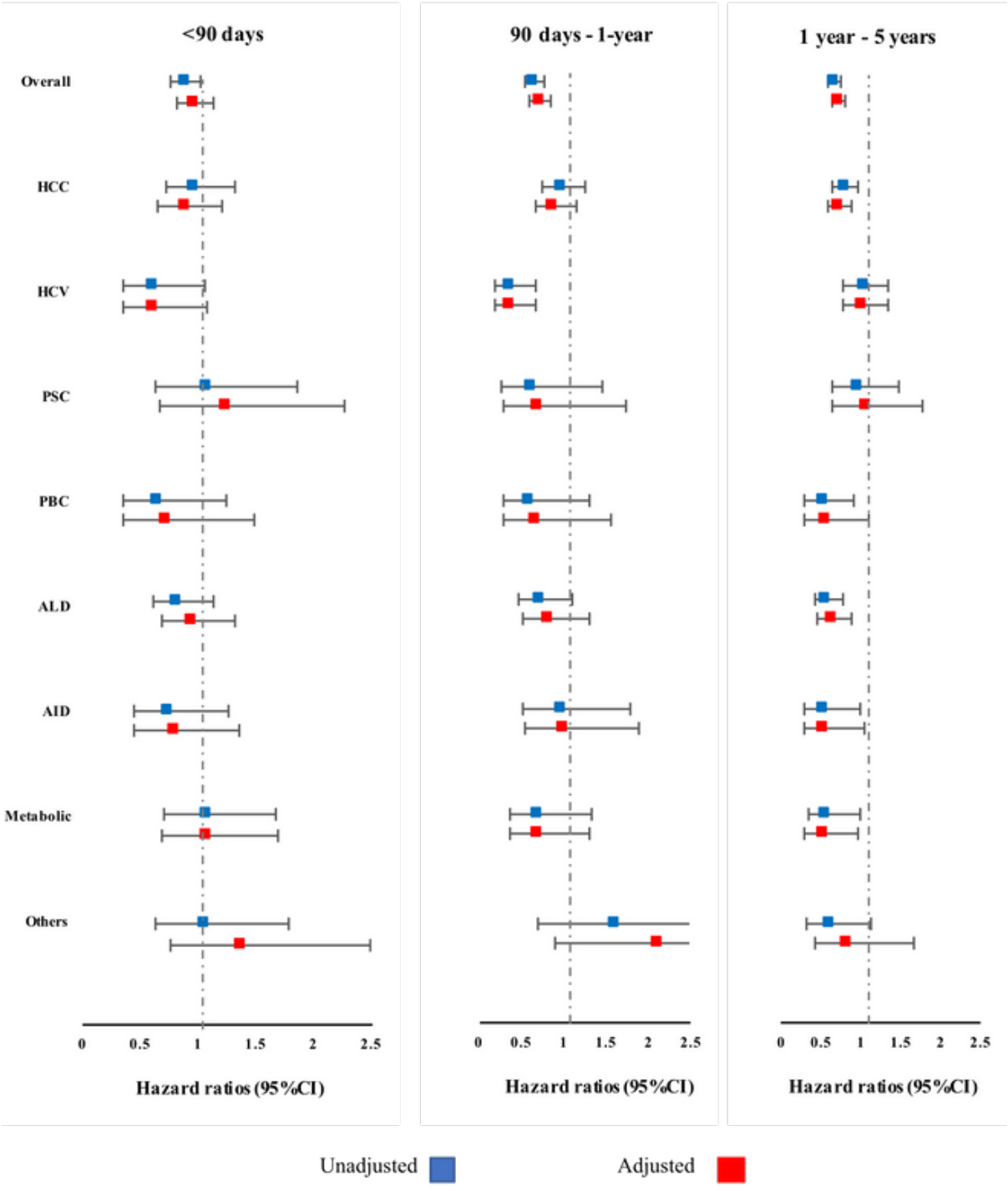
Table 1: A time-dependent comparison of 5-year patient mortality between the UK & Ireland and US in those receiving a deceased donor liver transplant.

	US COMPARED TO UK & IRELAND HAZARD RATIO (95% CI)			P-VALUE FOR TIME-DEPENDENCY
PRIMARY LIVER DISEASE	**0 – 3 MONTHS**	**3 MONTHS – 1-YEAR**	**1-YEAR to 5-YEARS**	
Overall				
- Unadjusted	0.88 (0.76-1.02)	0.65 (0.55-0.77)	0.66 (0.59-0.74)	0.0068
- Adjusted	0.96 (0.82-1.12)	0.71 (0.59-0.85)	0.71 (0.63-0.81)	0.004
HCC				
- Unadjusted	0.96 (0.71-1.31)	0.96 (0.74-1.24)	0.79 (0.65-0.96)	0.38
- Adjusted	0.88 (0.64-1.21)	0.87 (0.66-1.14)	0.71 (0.58-0.88)	0.35
Hepatitis C				
- Unadjusted	0.60 (0.34-1.06)	0.36 (0.19-0.66)	1.03 (0.78-1.35)	0.002
- Adjusted	0.60 (0.34-1.08)	0.35 (0.19-0.66)	1.01 (0.76-1.35)	0.0006
PSC				
- Unadjusted	1.08 (0.62-1.86)	0.61 (0.25-1.44)	0.96 (0.63-1.48)	0.52
- Adjusted	1.23 (0.67-2.26)	0.69 (0.28-1.72)	1.06 (0.64-1.76)	0.55
Hepatitis B				
- Unadjusted	1.73 (0.60-4.90)	Not enough events (UK)	Not enough events (UK)	N/A
- Adjusted	2.48 (0.72-2.26)	Not enough events (UK)	Not enough events (UK)	N/A
PBC				
- Unadjusted	0.65 (0.35-1.23)	0.60 (0.28-1.30)	0.53 (0.30-0.92)	0.88
- Adjusted	0.72 (0.35-1.49)	0.66 (0.28-1.55)	0.57 (0.30-1.10)	0.86
ALD				
- Unadjusted	0.82 (0.60-1.12)	0.71 (0.46-1.10)	0.56 (0.41-0.77)	0.23
- Adjusted	0.95 (0.68-1.32)	0.82 (0.52-1.29)	0.64 (0.45-0.89)	0.21
AID				
- Unadjusted	0.73 (0.43-1.26)	0.96 (0.52-1.78)	0.53 (0.28-1.00)	0.41
- Adjusted	0.79 (0.44-1.35)	1.00 (0.53-1.89)	0.54 (0.28-1.03)	0.38
Metabolic				
- Unadjusted	1.08 (0.70-1.66)	0.70 (0.37-1.32)	0.57 (0.33-0.99)	0.19
- Adjusted	1.07 (0.68-1.69)	0.68 (0.35-1.30)	0.54 (0.30-0.95)	0.14
Others				
- Unadjusted	1.05 (0.62-1.77)	1.59 (0.70-3.59)	0.61 (0.32-1.13)	0.16
- Adjusted	1.37 (0.75-2.48)	2.12 (0.89-5.07)	0.82 (0.41-1.65)	0.18

** Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), disease etiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal support, previous abdominal surgery.*

***Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m^2), cit, donor type (DCD/DBD), cause of death, abomatch, graft type.*

Figure 1: Unadjusted and adjusted HR's (and 95%CI) for mortality in the first 90 days, 90 days to 1-year and beyond the first year in the UK and Ireland (n=4 950) compared with US (n=42 874) by liver disease category.



Annual British Transplant Congress 2021

BTS NHSBT Live 24th – 25th February

Poster Presentation

P007

Post-transplantation outcomes after deceased donor liver transplantation: an international comparison between the United States and the United Kingdom & Ireland.

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Introduction: In the last decade, there has been considerable global variation in how deceased donor livers are utilised. However, no recent international comparison of outcomes following the use of brainstem death (DBD) or circulatory death (DCD) donors has been conducted. We evaluated the risk-adjusted short and long-term mortality of DBD and DCD liver transplant (LT) recipients in the UK & Ireland (UK&I) with recipients in the US.

Methods: The UK Liver Transplant Registry and the United Network Organ Sharing Dataset were combined and used to identify all adults (aged ≥18 years) who underwent a first elective deceased donor LT in the UK&I and US between 2008 and 2016. Time-dependent Cox-regression methods were used to estimate hazard ratio's (HR) that compared deceased donor specific risk adjusted mortality in the first 90 days after transplantation and between 90 days and 5-years.

Results: 4950 LT recipients from the UK and 42874 from the US were included. In the UK&I, the use of DCD donor livers increased from 15.7% to 30.6%, and in the US from 5.3% to 6.9%. In DCD recipients, 5-year patient survival was 79.1% (95%CI; 75.6%-82.2%) in the UK and 72.6% (70.1%-75.0%, p<0.001) in the US and in DBD recipients 82.7% (81.1%-84.2%) and 75.8% (75.2%-76.3%, p<0.001), respectively. Following risk-adjustment, no difference in short-term mortality was identified for either DCD (comparing the UK&I and US, HR: 0.89, 95%CI: 0.62-1.27) or DBD (HR: 1.06, 0.92-1.22) recipients. However, longer-term mortality was found to be significantly better in the UK&I for those who did receive a DCD (HR: 0.71, 0.54-0.95) and DBD (HR: 0.73, 0.65-0.83) LT.

Discussion: Longer-term mortality following deceased donor LT is superior in the UK&I compared to the US. International comparisons for deceased donor LT practice may help identify modifiable factors that can increase organ utilization and improve post-LT outcomes.

Table 1: A time-dependent comparison of 5-year patient mortality and graft failure between the UK and US in those receiving a DCD liver.

	UK compared to US Hazard ratio (95% CI)			P value time dependency*[2]
PATIENT MORTALITY	**Overall 5-yr survival**	**0 to 3 months**	**3 to 60 months**	
Unadjusted analysis	0·71 (0.60-0.85)	0·83 (0.61-1.13)	0·66 (0·53-0·83)	0·25
Adjusted for recipient characteristics*[1]	0·87 (0.69-1.08)	1·01 (0.72-1.42)	0·81 (0·62-1·05)	0·24
Adjusted for recipient and donor characteristics*[2]	0·76 (0.59-0.98)	0·89 (0.62-1.27)	0·71 (0·54-0·95)	0·25
GRAFT FAILURE				
Unadjusted analysis	0.86 (0.80-0.92)	1.27 (1.02-1.59)	0.71 (0.59-0.87)	<0.001
Adjusted for recipient characteristics*[1]	1.08 (0.90-1.30)	1.53 (1.19-1.97)	0.86 (0.68-1.07)	<0.001
Adjusted for recipient and donor characteristics*[2]	0.91 (0.74-1.12)	1.29 (0.98-1.69)	0.73 (0.57-0.93)	<0.001

** Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), disease etiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal support, previous abdominal surgery and era of transplant (2008-2011 and 2012-2016).*
***Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m^2), cit, cause of death, abomatch, graft type.*

Table 2: A time-dependent comparison of 5-year patient mortality and graft failure between the UK and US in those receiving a DBD liver.

	UK compared to US Hazard ratio (95% CI)			P value time dependency*[2]
PATIENT MORTALITY	**Overall 5-yr survival**	**0 to 3 months**	**3 to 60 months**	
Unadjusted analysis	0·68 (0.62-0.75)	0·83 (0.70-0.99)	0·64 (0·57-0·71)	0·01
Adjusted for recipient characteristics*[1]	0·88 (0.79-0.97)	1·08 (0.90-1.29)	0·82 (0·72-0·92)	0·008
Adjusted for recipient and donor characteristics*[2]	0·79 (0.77-0.88)	0·97 (0.81-1.16)	0·73 (0·65-0·83)	0·008
GRAFT FAILURE				
Unadjusted analysis	0.78 (0.72-0.84)	1.01 (0.88-1.16)	0.68 (0.62-0.76)	<0.001
Adjusted for recipient characteristics*[1]	0.94 (0.86-1.02)	1.22 (1.07-1.41)	0.82 (0.73-0.91)	<0.001
Adjusted for recipient and donor characteristics*[2]	0.81 (0.73-0.88)	1.06 (0.92-1.22)	0.70 (0.63-0.79)	<0.001

** Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), disease etiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal support, previous abdominal surgery and era of transplant (2008-2011 and 2012-2016).*
***Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m^2), cit, cause of death, abomatch, graft type.*

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Have changes in the utilisation of livers donated following circulatory death affected survival in patients undergoing liver transplantation for hepatocellular carcinoma?

David Wallace[1,2], Kate Walker[1], Susan Charman[1], Abid Suddle[2], Ian Rowe,[3] Thomas Cowling,[1] Nigel Heaton[2], Jan van der Meulen[1]

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Introduction: The rising incidence of hepatocellular carcinoma (HCC) has placed a considerable strain on liver transplantation services. In response, donated livers following circulatory death (DCD) are increasingly being utilised as clinicians strive to transplant patients with HCC in an acceptable oncological time-frame. We aimed to identify how post-transplantation survival in patients with HCC has changed over successive eras of liver transplantation and to what extent changes in survival can be explained by changes in both donor and recipient characteristics.

Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 1997 and 2016. We stratified the cohort into 4 eras of transplantation a)1997-2001 b) 2002-2006 c) 2007- 2011 and d) 2012-2016, and compared the change in the donor and recipient characteristics of HCC and non-HCC patients over eras. We used Kaplan-meier estimates to compare changes in 5-year patient survival and Cox regression to examine how, after adjustment for donor and recipient characteristics, the risk of undergoing liver transplantation for HCC successively changed from eras 1-3.

Results: 10,166 fist-time elective liver transplants were included. Across the entire study period, the utilisation of DCD livers disproportionately increased in HCC compared to non-HCC patients (32.7% vs 22.9%, $p<0.05$). 5-year patient survival improved from eras 1 to 3 in both HCC (59.9% to 73.2%) and non-HCC patients (74.8% to 83.4%, figure 1). Patient survival was consistently worse for HCC patients across all 3 eras of transplantation (log rank test $p<0.05$). This effect remained following adjustment for donor and recipient characteristics (table 1).

Discussion: Despite the increasing utilisation of DCD livers, survival for patients transplanted for HCC has improved considerably over last decade. However, in comparison to patients transplanted for non-HCC indications patients with HCC still have significantly worse long-term post-transplant outcomes.

BASL 2018 Annual Meeting

University of York 18th – 21st September 2018

Poster Presentation

99

Time-dependent impact of hepatocellular carcinoma on mortality after liver transplantation: a national cohort study.

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Introduction: Historic studies have shown that patients with hepatocellular carcinoma (HCC) have favourable outcomes in the first 3 months following liver transplantation, but higher mortality thereafter. It had previously been argued that the introduction of the Milan criteria would reduce rates of tumour recurrence and negate this negative effect of HCC. We aimed to address this important research question by performing an updated analysis that identified the prognostic impact of HCC on mortality at different periods of follow-up time after liver transplantation.

Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 2007 and 2016. We compared the donor and recipient characteristics of HCC and non-HCC patients and used Kaplan-Meier methods to compare patient survival. We used Cox regression to examine the prognostic impact of HCC status on mortality at three separate periods of follow-up time: 0-90 days, 90 days-2 years and 2 years-5 years.

Results: 5780 first-time adult elective liver transplants were included. Patients transplanted for HCC had lower UKELD scores but were more likely to receive segmental grafts and grafts from circulatory death donors ($P<0.05$). No difference in 90-day mortality between HCC (n=1397) and non-HCC (n=4383) groups was identified (HR 0.82, 95% CI 0.58-1.15, $p=0.25$). HCC was associated with a statistically significant increased risk of mortality from 90 days-2 years (1.77, 1.32-2.38 and 1.55, $P<0.001$) and from 2 years - 5 years (1.58, 1.18-2.05, $P<0.01$). The effect of HCC was found to vary significantly across the three periods of follow-up time (p for interaction=0.0006).

Discussion: HCC remains a significant risk factor for mortality after 3 months of follow-up time. Despite the implementation of the Milan criteria we are still transplanting patients who are at risk of early tumour recurrence and death

BASL 2018 Annual Meeting

University of York 18th – 21st September 2018

Poster Presentation

104

The impact of pre-transplantation performance status on hospital resource use following liver transplantation

David Wallace[1], Abid Suddle,[2] Jan van der Meulen,[1] Thomas Cowling[1], Nigel Heaton[2], William Bernal[2]

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Introduction: The impact of frailty and compromised performance status (PS) on hospital resource use following liver transplantation (LT) has had limited characterisation. In this study, we linked the United Kingdom LT registry to a national administrative dataset and examined the impact of Pre-LT PS on hospital resource use.

Methods: 7940 patients with cirrhotic CLD who received a first LT between 1995-2016 were studied. Pre-LT PS was assessed using a 5-point scale (modified Eastern Cooperative Oncology Group (ECOG) score). We compared the prevalence of post-operative complications according to ECOG status and used linear regression techniques to examine the association between PS and length of hospital stay (LOS) in the initial transplantation admission and at 1, 2 and 3 years' post-transplantation (excluding initial admission).

Results: Recipients with increasingly impaired PS had an increased risk of renal failure, post-operative haemorrhage, biliary tract leak, CMV infection and sepsis ($P<0.05$). Compared to those able to carry out normal activity (ECOG PS1), recipients with ECOG PS5 had increased LOS during the initial post-LT admission (adj mean: 25.6 days 95%CI: 18.5, 32.6, $p<0.01$) but no statistically significant increased LOS at 1,2 or 3-years following LT ($p>0.05$). ECOG PS5 recipients also required longer post-operative ventilation (adj mean: 2.1 days 95%CI: 0.6,3.7) and had significantly longer ITU LOS (adj mean: 3.2 95%CI:1.3, 5.1).In contrast, patients with ECOG PS3 and 4 had no increased LOS after initial LT but longer LOS in the 3-years following LT (PS3; adj mean 9.8 days 95%CI:1.3,18.4 and PS4; adj mean 12.3 days 95%CI:2.8,21.8).

Discussion: LT recipient PS assessed using a simple measure was independently predictive of post-LT hospital resource use. Overall, poorer PS at the time of LT was associated with increased post-LT complications and prolonged ITU and Hospital LOS admission, with increased hospitalisation seen up to 3-years following surgery.

AASLD The Liver Meeting

San Francisco 6th – 8th March

Poster Presentation

Reference: Hepatology. October 2018; 68(S1); 673A. https://doi.org/10.1002/hep.30257

1164
Changes in Performance Status after Liver Transplantation; A National Cohort Study

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Background: Frailty and compromised functional status are independent determinants of mortality in patients with chronic liver disease (CLD) and associated with worse post-liver transplant (LT) survival and higher resource use. How impaired performance status (PS) changes after LT is less well characterised. In a national cohort of LT recipients with CLD we examine changes in PS in the first 12 months after LT.

Methods: Utilising the National Database United Kingdom NHS Blood and Transplant, 7053 adult recipients with CLD of defined etiology undergoing first elective LT in the United Kingdom 1994-2016 were studied. Those with malignancy or with critical care support at LT were excluded. Pre-LT PS was prospectively assessed using a modified Eastern Cooperative Oncology Group Score, rating ability to perform personal care or work-related activities on a 5-point scale, where 1=no restriction and 5=completely reliant on nursing/medical care. PS was re-assessed at follow-up at 3 and 12 months post LT.

Results: Median recipient age was 53 years (Interquartile rage 46-60) and MELD 16 (13-20). 3925 (56%) of recipients were ECOG status 3 (capable of self-care but unable to work), 1021 (14%) recipients were status 4 (only capable of limited self-care, mostly confined to bed or chair) and 232 (3%) status 5 (fully dependent). As compared to recipients with status 1-3, status 4-5 had higher pre-LT MELD scores (19 (15-24) vs. 16 (13-19), p<0.001). 90-day post-LT patient survival was 94.4% in status 1-3 recipients and 90.9% in status 4-5 (p<0.001). Overall, median recipient ECOG status improved from 3 (IQR 2-3) pre-LT to 2 (1-3) at 3- and 1 (1-2) at 12 months post-LT (p<0.001). At 12 months 84% of recipients had improved PS, 12% were unchanged and 3% worsened (p<0.001). The proportion dependent upon others for selfcare (ECOG 4-5) fell from 17.7% pre-LT to 4.7% at 3- and 12-months follow-up (p<0.001). Of 1122 recipients of Pre-LT ECOG status 4-5, at 3 months post LT 91% showed improved PS, 6% no change and 3% worsened (p<0.001). At 12 months 98% had improved, 1.3% were unchanged and 0.7% worsened. Compared to recipients who had improved PS at 3 months, those who failed to improve or worsened showed only slight differences in standard pre-LT recipient or donor characteristics.

Conclusions: Impaired recipient PS improves rapidly after LT, even in those hospitalised or dependent upon others for self-care at the time of surgery. Identification of those whose improvement is delayed may require measures other than those currently standard to assess CLD severity. We thank NHS Blood and Transplant for the provision of data.

AASLD The Liver Meeting

San Francisco 6th – 8th March

Poster Presentation

Award Winner: AASLD Liver Transplant Surgical Fellow Travel Award 2018

Reference: Hepatology. October 2018; 68(S1); 687A. https://doi.org/10.1002/hep.30257

1188

The impact of pre-transplantation performance status on hospital resource use following liver transplantation

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1. *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
2. *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*

Introduction: The impact of frailty and compromised performance status (PS) on hospital resource use following liver transplantation (LT) has had limited characterisation. In this study, we linked the United Kingdom LT registry to a national administrative dataset and examined the impact of Pre-LT PS on hospital resource use.

Methods: 7940 patients with cirrhotic CLD who received a first LT between 1995-2016 were studied. Pre-LT PS was assessed using a 5-point scale (modified Eastern Cooperative Oncology Group (ECOG) score). We compared the prevalence of post-operative complications according to ECOG status and used linear regression techniques to examine the association between PS and length of hospital stay (LOS) in the initial transplantation admission and at 1, 2 and 3 years' post-transplantation (excluding initial admission).

Results: Recipients with increasingly impaired PS had an increased risk of renal failure, post-operative haemorrhage, biliary tract leak, CMV infection and sepsis ($P<0.05$). Compared to those able to carry out normal activity (ECOG PS1), recipients with ECOG PS5 had increased LOS during the initial post-LT admission (adj mean: 25.6 days 95%CI: 18.5, 32.6, $p<0.01$) but no statistically significant increased LOS at 1,2 or 3-years following LT ($p>0.05$). ECOG PS5 recipients also required longer post-operative ventilation (adj mean: 2.1 days 95%CI: 0.6,3.7) and had significantly longer ITU LOS (adj mean: 3.2 95%CI:1.3, 5.1).In contrast, patients with ECOG PS3 and 4 had no increased LOS after initial LT but longer LOS in the 3-years following LT (PS3; adj mean 9.8 days 95%CI:1.3,18.4 and PS4; adj mean 12.3 days 95%CI:2.8,21.8).

Discussion: LT recipient PS assessed using a simple measure was independently predictive of post-LT hospital resource use. Overall, poorer PS at the time of LT was associated with increased post-LT complications and prolonged ITU and Hospital LOS admission, with increased hospitalisation seen up to 3-years following surgery.

AASLD The Liver Meeting

San Francisco 6th – 8th March

Poster Presentation

Reference: Hepatology. October 2018; 68(S1); 688A. https://doi.org/10.1002/hep.30257

1190

Have changes in the utilisation of livers donated following circulatory death affected survival in patients undergoing liver transplantation for hepatocellular carcinoma?

David Wallace[1,2], Kate Walker[1], Susan Charman[1], Abid Suddle[2], Ian Rowe,[3] Thomas Cowling,[1] Nigel Heaton[2], Jan van der Meulen[1]

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Introduction: The rising incidence of hepatocellular carcinoma (HCC) has placed a considerable strain on liver transplantation services. In response, donated livers following circulatory death (DCD) are increasingly being utilised as clinicians strive to transplant patients with HCC in an acceptable oncological time-frame. We aimed to identify how post-transplantation survival in patients with HCC has changed over successive eras of liver transplantation and to what extent changes in survival can be explained by changes in both donor and recipient characteristics.

Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 1997 and 2016. We stratified the cohort into 4 eras of transplantation a)1997-2001 b) 2002-2006 c) 2007- 2011 and d) 2012-2016, and compared the change in the donor and recipient characteristics of HCC and non-HCC patients over eras. We used Kaplan-meier estimates to compare changes in 5-year patient survival and Cox regression to examine how, after adjustment for donor and recipient characteristics, the risk of undergoing liver transplantation for HCC successively changed from eras 1-3.

Results: 10,166 fist-time elective liver transplants were included. Across the entire study period, the utilisation of DCD livers disproportionately increased in HCC compared to non-HCC patients (32.7% vs 22.9%, $p<0.05$). 5-year patient survival improved from eras 1 to 3 in both HCC (59.9% to 73.2%) and non-HCC patients (74.8% to 83.4%, figure 1). Patient survival was consistently worse for HCC patients across all 3 eras of transplantation (log rank test $p<0.05$). This effect remained following adjustment for donor and recipient characteristics (table 1).

Discussion: Despite the increasing utilisation of DCD livers, survival for patients transplanted for HCC has improved considerably over last decade. However, in comparison to patients transplanted for non-HCC indications patients with HCC still have significantly worse long-term post-transplant outcomes.

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Poster Presentation

Reference: Hepatology. October 2018; 68(S1); 698A. https://doi.org/10.1002/hep.30257

1208

Time-dependent impact of hepatocellular carcinoma on mortality after liver transplantation: a national cohort study.

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Introduction: Historic studies have shown that patients with hepatocellular carcinoma (HCC) have favourable outcomes in the first 3 months following liver transplantation, but higher mortality thereafter. It had previously been argued that the introduction of the Milan criteria would reduce rates of tumour recurrence and negate this negative effect of HCC. We aimed to address this important research question by performing an updated analysis that identified the prognostic impact of HCC on mortality at different periods of follow-up time after liver transplantation.

Methods: We used the UK liver transplant registry to select a cohort of first-time adult recipients of elective liver transplants performed between 2007 and 2016. We compared the donor and recipient characteristics of HCC and non-HCC patients and used Kaplan-Meier methods to compare patient survival. We used Cox regression to examine the prognostic impact of HCC status on mortality at three separate periods of follow-up time: 0-90 days, 90 days-2 years and 2 years-5 years.

Results: 5780 first-time adult elective liver transplants were included. Patients transplanted for HCC had lower UKELD scores but were more likely to receive segmental grafts and grafts from circulatory death donors (P<0.05). No difference in 90-day mortality between HCC (n=1397) and non-HCC (n=4383) groups was identified (HR 0.82, 95% CI 0.58-1.15, p=0.25). HCC was associated with a statistically significant increased risk of mortality from 90 days-2 years (1.77, 1.32-2.38 and 1.55, P<0.001) and from 2 years - 5 years (1.58, 1.18-2.05, P<0.01). The effect of HCC was found to vary significantly across the three periods of follow-up time (p for interaction=0.0006).

Discussion: HCC remains a significant risk factor for mortality after 3 months of follow-up time. Despite the implementation of the Milan criteria we are still transplanting patients who are at risk of early tumour recurrence and death

International Liver Transplant Society Annual Congress 2019

Toronto May 15th – 18th

Concurrent Oral Abstract Session: Short and Long-term Patient and Allograft Outcomes

Award Winner: ILTS Young Investigator Award 2019

O-107

The impact of performance status at the time of transplantation on outcomes following liver transplantation: a national cohort study in the United Kingdom and Ireland

David Wallace[1, 2], Mark McPhail[2], Sarah Brown[2], Varuna Aluvihare[2], Abid Suddle[2], Georg Auzinger[2], Michael Heneghan[2], Julia Wendon[2], Nigel Heaton[2], Jan van der Meulen[2], William Bernal[2]

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Introduction In the setting of liver transplantation (LT) the impact of frailty and compromised performance status (PS) on post-transplant outcomes are not well characterised in patients with chronic liver disease (CLD). In a national cohort of patients with CLD we examined the association of pre-LT PS on post-LT patient survival.

Methods: 7285 patients with cirrhotic CLD who received a first LT between 1997 and 2016 were studied. Pre-LT PS was assessed using a 5-point scale (modified Eastern Cooperative Oncology Group (ECOG) score). We used stratified cox-regression methods to estimate hazard ratios (HR) that compared post-transplantation mortality for ECOG status in three post-transplantation time-periods (epochs): 0 to 90 days, 90 days to 1-year and 1 year to 5-years, and across different eras of transplantation (1995 to 2005 and 2006 to 2016).

Results: 5-year post-LT patient survival was 84.6% in patients able to carry out normal activity without restriction (ECOG PS1) decreasing to 71.0% in those completely reliant on nursing and medical care (ECOG PS5; p <0.001). With adjustment for donor and recipient characteristics, the impact of ECOG PS5 on mortality was significantly poorer in the first 90-days (HR: 2.14 95%CI: 1.43-3.20), but not significantly worse thereafter (90 days to 1-year: HR 1.59, 0.84-3.01; 1-year to 5-years: HR 0.82, 0.46-1.47). Over era, survival improved for patients in all ECOG status (PS1: 0.65, 0.31-1.37; PS2: 0.54, 0.41-0.70, PS3: 0.57, 0.48-0.68, PS4: 0.67, 0.50-0.90 and PS5 0.51, 0.30-0.89), however the effect of era did not different between ECOG status (p for interaction 0.81).

Conclusions: LT recipient PS assessed using a simple measure is independently predictive of post-transplant mortality with strongest association in those with greatest compromise. In these patients, its impact is most marked in the first 3-months after surgery. Over time, mortality has decreased by at least one third for patients in each ECOG category.

International Liver Transplant Society Annual Congress 2019

Toronto May 15th – 18th

Concurrent Oral Abstract Session: Short and Long-term Patient and Allograft Outcomes

O-108

The impact of transarterial chemoembolization on complications and survival after liver transplantation: a national study using linked healthcare data.

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5. *Department of Transplantation, Renal Unit, Guy's Hospital, London, United Kingdom*

Introduction: The impact of transarterial chemoembolisation (TACE) on early and late post-transplantation outcomes has never been identified in a representative cohort of recipients with hepatocellular carcinoma (HCC). We linked the UK Standard National Liver Transplant registry to a hospital administrative dataset and assessed the impact of TACE on post-operative complications and mortality following liver transplantation.

Methods: We identified a population-based cohort of HCC recipients of a liver transplant (aged ≥ 16 years) between 2006 and 2016. We stratified our cohort according to HCC recipients who had received TACE on the transplant waitlist and used Cox regression to compare mortality and estimate hazard ratios (HR), adjusted for relevant donor and recipient characteristics.

Results: 385 TACE and 583 non-TACE recipients were included. 5-year post-transplant survival was 75.2% (95%CI: 68.8% to 80.5%) in patients who received TACE and 75.0% (95%CI: 70.5% to 78.8%) in those who did not. With adjustment for donor and recipient characteristics, no significant differences in mortality (HR 0.96, 95%CI: 0.67-1.38, p=0.82) or graft survival were identified (HR: 1.01, 95%CI: 0.73-1.40, p=0.96). Also, the impact of TACE on mortality did not differ according to the number of TACE treatments (≥2 TACE treatments HR: 0.97, 95%CI: 0.61-1.55, p=0.90), the time-period after transplantation (p for interaction = 0.29) or the use of circulatory death donors (p for interaction = 0.97). The incidence of hepatic artery thrombosis was lower in those who received TACE (1.3% vs 2.5%, respectively, p=0.09).

Discussion: The use of TACE on HCC patients on the liver transplant waitlist does not increase the risk of early post-operative complications or graft failure nor does it improve long-term patient survival or rates of tumour recurrence.

International Liver Transplant Society Annual Congress 2020

Istanbul May 6th – 9th

Plenary Session I

Oral Presentation

O-066
Time-trends in patient mortality and graft survival of patients receiving a DCD or DBD liver transplantation in the UK and Ireland between 2008 and 2016.

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Introduction: Internationally, the UK is the primary exponent in the transplantation of livers from controlled donation after circulatory death (DCD). However, concerns exist in the efficacy of these grafts. We evaluated the mortality, graft failure and post-operative complications of DCD and DBD donor liver transplantation in successive eras between 2008 and 2016.

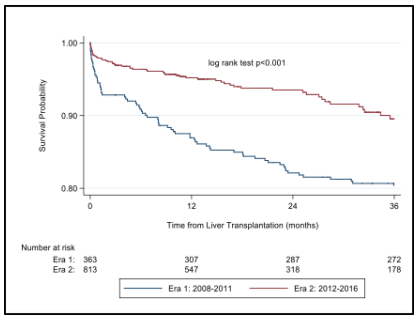
Methods: All first-time elective adult liver transplant recipients in the UK were identified and hazard ratios comparing the impact of era (2008-2011 and 2012-2016) on post-transplant mortality, graft failure and complications were estimated.

Results: 1 176 DCD recipients and 3 749 DBD recipients were included. The use of livers from DCD donors increased from 19.3% in era 1 to 26.7% in era 2. 3-year patient mortality decreased markedly from 19.6% in era 1 to 10.4% in era 2 (aHR:0.43, 95%CI: 0.30-0.62) for DCD recipients but only decreased from 12.8% to 11.3% (aHR:0.96, 0.78-1.19) in DBD recipients. Between eras no improvements in overall 3-year graft failure were observed for DCD (aHR:0.80, 0.61-1.05, p=0.11) or DBD recipients (aHR:0.95, 0.79-0.60, p=0.60) but the rate of re-transplantation increased from 7.2% to 10.1% in DCD recipients (p=0.14) and decreased from 4.8% to 3.7% in DBD recipients (p=0.01). In era 2, there was no difference in mortality between those receiving a DCD or DBD liver (aHR: 0.78, 0.56-1.09, p=0.14) however the incidence of biliary tract strictures increased for both cohorts (5.0% to 6.9% and 3.8% to 4.8%, respectively).

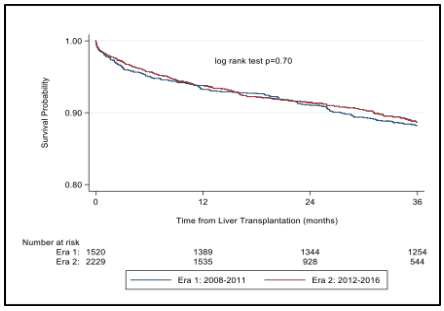
Conclusion: Between 2008 and 2016, mortality more than halved in those who received a DCD donor liver. In the UK, mortality following liver transplantation now appears to be comparable for patients receiving DCD and DBD donor livers.

Figure 1: 3-year patient survival across different eras of transplantation (2008-2011 and 2012-2016) in recipients receiving DCD or DBD livers (n=4 925).

a; DCD (n=1 176)



b; DBD (n=3 749)



International Liver Transplant Society Annual Congress 2020

Istanbul May 6th – 9th

Poster Round II (Viewing sessions 1,2 and 3)

Poster Presentation

P-502

Post-transplantation outcomes after deceased donor liver transplantation; an international comparison between the United States and the United Kingdom & Ireland.

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Background: In the last decade, there has been considerable global variation in how deceased donor livers are utilised. However, no recent international comparison of outcomes following the use of brainstem death (DBD) or circulatory death (DCD) donors has been conducted. We evaluated the risk-adjusted short and long-term mortality of DBD and DCD liver transplant (LT) recipients in the UK and Ireland (UK&I) with that in the US.

Methods: The Standard National Liver Transplant Registry and the United Network Organ Sharing Dataset were combined and used to identify all adults who underwent a first elective deceased donor LT in the UK&I and US between 2008 and 2016. Time-dependent Cox-regression methods were used to estimate hazard ratio's (HR) that compared deceased donor specific risk adjusted mortality in the first 90 days after transplantation and between 90 days and 5-years.

Results: 4 950 LT recipients from the UK and 42 874 from the US were included. In the UK&I, the use of DCD livers increased from 15.7% to 30.6%, and in the US from 5.3% to 6.9%. In DCD recipients, 5-year patient survival was 79.1% (95%CI; 75.6%-82.2%) in the UK and 72.6% (70.1%-75.0%, p<0.001) in the US and in DBD recipients 82.7% (81.1%-84.2%) and 75.8% (75.2%-76.3%, p<0.001), respectively. Following risk-adjustment, no difference in short-term mortality was identified for either DCD (comparing the UK&I and US, HR: 0.89, 95%CI: 0.62-1.27) or DBD (HR: 1.06, 0.92-1.22) recipients however longer-term mortality was found to be significantly better in the UK for those who did receive a DCD (HR: 0.71, 0.54-0.95) and DBD (HR: 0.73, 0.65-0.83) LT.

Discussion: Longer-term mortality following deceased donor LT is superior in the UK&I compared to the US. International comparisons for deceased donor LT practice may help identify modifiable factors that can increase organ utilization and improve post-LT outcomes.

APPENDIX E – TRAINING HISTORY

Course	Location
Year 1	
Reviewing the literature	LSHTM
Statistical Methods in Epidemiology (SME)	LSHTM
Advanced Statistical Methods in Epidemiology (ASME)	LSHTM
Advanced Analysis of Linked Health Care Data	University of Swansea
Advanced Statistical Methods in Epidemiology	University of Southampton
ONS Researcher Accreditation Course	Southampton
Evidence and Values in Clinical Education	University of Warwick
Research Methods in Clinical Education	University of Warwick
ATLS Instructor Course	The Royal College of Surgeons
Year 2	
Introductory Analysis of Linked Health Care data	University of Swansea
MA Medical Education Project Launch	University of Warwick