POST-OPERATIVE LIVER DECOMPENSATION EVENTS FOLLOWING PARTIAL HEPATECTOMY AMONG PATIENTS WITH CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

by

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ABSTRACT

Background

Partial hepatectomy, or liver resection, is a potentially-curative therapy for patients diagnosed with hepatocellular carcinoma (HCC). Because the majority of patients with HCC have pre-existing cirrhosis, pre-operative decision-making must consider severity of liver dysfunction to mitigate adverse liver-related post-operative outcomes.

Objectives

The goals of this thesis were: 1) to critically appraise currently available prognostic models for predicting the risk of post-operative liver decompensation events (POLDEs), and 2) to identify patient-level, pre-operative predictors of POLDEs among individuals with cirrhosis and HCC undergoing liver resection.

Methods

A systematic review of the literature was performed to identify multivariable prognostic models predicting the risk of POLDEs following liver resection. Study details regarding patients, outcomes, predictors, methodology, statistical analyses were abstracted. Studies were qualitatively assessed for risk of bias. A population-based retrospective cohort study was also conducted, of patients with cirrhosis and incident HCC diagnosed between 2007-2017 in the province of Ontario. Cox proportional hazards regression was used to identify independent predictors of POLDE-free survival, and cause-specific hazards for POLDEs and death.

Results

In total, 36 multivariable prognostic modelling studies were identified; 25 focused on model development, 3 performed development and external validation, and 8 validated pre-existing models. Commonly used predictors in these models were serum bilirubin, platelet count, and indocyanine green retention rate at 15 minutes ($ICGR_{15}$). Due to statistical and methodologic concerns, all studies were assessed a high risk of bias. In the population study, the cohort comprised 611 patients with cirrhosis and incident HCC, who subsequently underwent liver resection. Of these, 160 (26.2%) experienced at least 1 POLDE within 2 years of resection and 189 (30.9%) died in the same timeframe. Independent predictors of inferior POLDE-free survival were presence of diabetes, major liver resection, and previous non-malignant decompensation. In contrast, hepatitis B cirrhosis etiology appeared to be protective. In cause-specific analysis, the same risk factors were associated with POLDEs, except for planned extent of liver resection. Age (per year) and history of previous non-malignant decompensation were cause-specific predictors of death.

Conclusions

Currently available multivariable prognostic models for predicting the risk of post-operative liver decompensation events following liver resection have limited validity and applicability for routine clinical use. We have identified patient and disease-related factors associated with POLDE-free survival and POLDEs, which can be used for improved patient selection and to develop prognostic tools, with the aim of improving post-operative outcomes among patients with cirrhosis and HCC.

CO-AUTHORSHIP

This thesis document reflects the original work of Zuhaib M. Mir, who designed and conducted the studies herein, performed all data analyses, and produced the final document. Supervisory oversight relating to methodology, analyses, and editorial input for final write-up was provided by Patti A. Groome, Jennifer A. Flemming, and Sulaiman Nanji. The search strategy for the systematic review was designed and executed in collaboration with Sandra McKeown. Screening of references, data abstraction, and qualitative assessment of included studies was conducted with assistance from Haley Golding. Creation of the study cohort of patients was performed by Maya Djerboua.

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LIST OF ABBREVIATIONS

AFP – Alpha-Fetoprotein
ALD – Alcohol-related Liver Disease
AUC – Area Under Receiver Operating Characteristic Curve
BCLC – Barcelona Clinic Liver Cancer staging classification
BSC – Best Supportive Care
DAD – Discharge Abstract Database
CHARMS – Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
CIHI – Canadian Institute for Health Information
CT – Computed Tomography
CTP – Child-Turcotte-Pugh score
EPV – Events per Predictor Variable
HBV – Hepatitis B Viral infection
HCC – Hepatocellular Carcinoma
HCV – Hepatitis C Viral infection
ICD – International Classification of Diseases
ICG – Indocyanine Green
$ICGR_{15}$ – Indocyanine Green Retention rate at 15 minutes
INR – International Normalized Ratio
ISGLS – International Study Group of Liver Surgery
LI-RADS – Liver Imaging Reporting and Data System
LR – Liver Resection
LT – Liver Transplantation
MELD – Model for End-stage Liver Disease score
MRI – Magnetic Resonance Imaging
MWA – Microwave Ablation
NACRS – National Ambulatory Care Reporting System
NAFLD – Non-Alcoholic Fatty Liver Disease
NASH – Non-Alcoholic Steatohepatitis
OCR – Ontario Cancer Registry
OHIP – Ontario Health Insurance Plan
OLIS – Ontario Laboratories Information System
PHLF – Post-Hepatectomy Liver Failure
POLDE – Post-Operative Liver Decompensation Event
PROBAST – Prediction Model Risk of Bias Assessment Tool
RFA – Radiofrequency Ablation
RPDB – Registered Persons Database
SDS – Same Day Surgery database
SES – Socioeconomic Status
TACE – Transarterial Chemoembolization
TRIPOD – Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement
UCSF – University of California San Francisco

CHAPTER 1

INTRODUCTION

1.1. Introduction

Among primary malignancies of the liver, hepatocellular carcinoma (HCC) is the most common, and is challenging to treat from a surgical perspective given that it typically occurs in patients with cirrhosis (1, 2). This disease represents an important public health concern, with both its incidence and mortality on the rise (3). Partial hepatectomy, or liver resection, represents one of the potentially-curative surgical modalities for HCC (1-3). However, patient selection for resection is complex, as underlying cirrhosis impairs the functional and regenerative capabilities of the liver (4, 5). Therefore, an important aspect of pre-operative decision-making is accurately determining the risk of adverse liver-related outcomes following surgery. Specifically, post-operative liver decompensation events (POLDEs) encompass several clinical conditions that occur due to inadequate organ functions of the remnant liver after resection (6, 7). This thesis aims to critically evaluate current prognostic tools developed to predict the risk of post-operative decompensation following liver resection, with a view to determine their validity for routine clinical use. Furthermore, it provides a population level analysis of POLDEs among patients with cirrhosis and HCC following liver resection, in order to identify key predictors of such adverse events.

1.2. Thesis outline

This thesis is divided into 5 chapters. This first chapter serves as a brief introduction to the clinical problem. Chapter 2 provides a more detailed review of the literature as it relates to HCC, POLDEs, and prognostic research. The rationale for this work is provided and formal objectives of this thesis are also listed therein. Chapter 3 is a manuscript describing a systematic review of the literature, with critical appraisal of prognostic modelling studies of POLDEs following partial hepatectomy. Chapter 4 is a manuscript describing a population-based analysis of potential prognostic factors for POLDEs after partial hepatectomy in patients with cirrhosis and incident HCC, with consideration of the competing risk of death. Lastly, Chapter 5 provides a synthesis of the key findings of this thesis, their potential impact, and possible directions for future research.

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CHAPTER 2

LITERATURE REVIEW, RATIONALE, & OBJECTIVES

2.1. Hepatocellular carcinoma: definitions, risk factors, diagnosis, & staging

2.1.1. Definitions

Hepatocellular carcinoma (HCC) is the most common primary malignant lesion of the liver, representing 80-95% of all primary malignant liver masses (1). It arises from cells known as hepatocytes and chiefly occurs in the setting of cirrhosis due to chronic liver disease (2). The resultant pro-inflammatory state is thought to be crucial for the malignant transformation of hepatocytes over time (3). Therefore, an understanding of chronic liver disease and resultant cirrhosis is crucial to understanding the pathophysiology of HCC.

Cirrhosis is considered to be the end-result of multiple chronic liver diseases, with some common aberrations noted at the cellular level, regardless of etiology (2). These include activation of Kupffer cells (liver macrophages) and hepatic stellate cells, leading to apoptosis (programmed cell death) of hepatocytes and fibrosis of the liver parenchyma, respectively (2, 4). The diagnosis of cirrhosis is definitively made on histopathology, where the degree of fibrosis is graded from 0 to 4, with grade 4 being indicative of cirrhosis (5).

An important consequence of the loss of hepatocytes is the subsequent decrease in important organ functions of the liver, such as synthesis of proteins (eg. coagulation factors, albumin), glucose homeostasis, bilirubin degradation, and removal of fat-soluble toxins from the circulation. Due to parenchymal remodeling, there are also changes in blood flow to the liver that lead to portal hypertension, which results in circulatory system changes, the development of ascites, and an increased risk of gastrointestinal bleeding complications (6). The most common causes of cirrhosis are non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease

(ALD), chronic hepatitis C infection (HCV), and chronic hepatitis B infection (HBV) (7, 8). Other recognized, rarer causes include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hereditary hemochromatosis, Wilson disease and alpha-1 anti-trypsin deficiency (8). Because roughly 80-90% of all HCC patients have underlying cirrhosis, it is important to consider the degree of liver dysfunction when deciding on a management strategy for HCC (9, 10).

Patients with cirrhosis can be broadly classified into 2 groups based on its severity: compensated or decompensated (7). Compensated cirrhosis, in simple terms, is clinically asymptomatic cirrhosis. Therefore, while the liver demonstrates histopathologic changes of cirrhosis, the clinical sequelae of liver failure are not apparent. In contrast, decompensated cirrhosis refers to clinically symptomatic cirrhosis, where there is evidence of liver failure, including ascites, jaundice, gastrointestinal variceal bleeding, coagulopathy, portal hypertension, hepatorenal syndrome, and hepatic encephalopathy (11). The occurrence of HCC can be considered a malignant decompensation of cirrhosis. Approximately 5-7% of patients with compensated cirrhosis progress to decompensated cirrhosis on an annual basis, and the associated median survival times for both conditions are 12 and 2 years, respectively (12, 13). The Child-Pugh and MELD scores are important clinical prognostication tools for hepatic dysfunction in this patient population (14-16). The Child-Pugh scores uses 5 parameters to assess prognosis among patients with cirrhosis; these include serum bilirubin, albumin, and international normalized ratio (INR), as well as the presence/absence of ascites and hepatic encephalopathy. In contrast, the MELD scores uses laboratory investigations only, including serum bilirubin, INR, creatinine, and sodium. Importantly, the incidence of HCC among patients with cirrhosis of any kind ranges from < 1% to over 5% per year, and this risk is associated with both patient demographics and liver disease factors (17).

2.1.2. Risk factors & screening

The presence of multiple risk factors appears to have a synergistic effect on the carcinogenesis of HCC (18). In addition to cirrhosis, other risk factors for the development of HCC include (17-20):

- Advanced age
- Non-white race
- Male sex
- Tobacco use
- Diabetes and obesity
- Cirrhosis etiology/cause
- Severity of liver dysfunction
- Alcohol abuse

In contrast, factors associated with a lower risk of developing HCC include (21-24):

- Increased physical activity
- Aspirin use
- Coffee consumption
- Statin use

Current HCC screening guidelines from specialty societies recommend routine (every 6 months) abdominal ultrasonography in patients with cirrhosis of any cause (25, 26). For patients with HBV, screening is also recommended in the absence of cirrhosis due to direct hepatocyte DNA damage leading to carcinogenesis (25-27). Despite these recommendations, there are several controversies relating to HCC screening. The first is a lack of randomized studies evaluating screening effectiveness, although pooled observational data does show a clear association with improved patient outcomes (28). There is also evidence suggesting the addition of biomarkers such as alpha-fetoprotein (AFP) to ultrasound screening may improve HCC detection, but this remains an area of equipoise (27, 29, 30). Lastly, barriers resulting from numerous patient, provider, and system level factors continue to limit access to HCC screening among at-risk patients (31, 32).

2.1.3. Diagnosis

Following the screening or incidental detection of a suspicious liver lesion, further work-up with a contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) is needed to establish the diagnosis of HCC (33). Characteristic radiological findings include:

- Arterial phase hyper-enhancement
- Non-peripheral venous/delayed phase washout
- Enhancing capsule
- Threshold growth

In high-risk patients (i.e. those with cirrhosis, chronic hepatitis B, or positive family history of HCC), these findings are usually highly specific for the diagnosis HCC (27, 30). The Liver Imaging Reporting and Data System (LI-RADS) provides a standardized and comprehensive method of reporting and interpreting such radiographic findings (34). It categorizes liver lesions into diagnostic groups that predict their likelihood of malignancy (35, 36):

- LR-1 = definitely benign (100% certainty of non-malignant observation)
- LR-2 = probably benign (high probability of non-malignant observation, but <100%)
- LR-3 = intermediate (moderate probability of malignant or non-malignant observation)
- LR-4 = probably HCC (high probability of HCC, but <100%)
- LR-5 = definitely HCC (100% certainty of HCC)

While imaging and associated LI-RADS category are typically sufficient for diagnosis, biopsy is reserved for patients that are not high-risk but whose imaging demonstrates the abovementioned characteristic findings, for patients pre-disposed to non-malignant liver lesions that appear similar to HCC, or for high-risk patients with suspicious lesions that do not show the features listed above (25). There is also a non-negligible risk of malignant seeding of the needle track after biopsy (37).

Once the diagnosis of HCC is suspected, further investigations are required to complete extra-hepatic staging of the disease. These include contrast-enhanced CT or MRI of the chest, abdomen, and pelvis, with bone scans as needed in the setting of skeletal symptoms (27).

2.1.4. Staging

There are numerous HCC staging systems that have been developed for prognostication of patients and to guide treatment decisions (38, 39). These reflect the diversity of disease pathophysiology, patient populations, and treatment options/availability used to develop them. Importantly, such systems must consider disease characteristics and underlying liver dysfunction.

One of the most widely-used staging systems is the Barcelona Clinic Liver Cancer (BCLC) staging classification, which was first proposed in 1999 (40, 41). It separates patients into 4 groups: stage A (early), B (intermediate), C (advanced), and D (terminal/end-stage). Classification is based on tumour burden, overall performance status, and severity of liver dysfunction. Ultimately, this grouping determines the treatment modalities that may be offered to a patient, as well as associated prognoses. While the BCLC classification has been updated, recent studies suggest there may be room to expand indications for curative-intent surgical therapy (30, 40, 42).

For liver transplantation specifically, the Milan criteria (single tumour ≤5 cm in diameter, or up to 3 tumours each ≤3 cm in diameter) are widely used to determine patient eligibility (43, 44). Because some consider these indications to be too restrictive, numerous expanded criteria have also been developed for patient selection, but they must balance increased patient eligibility with higher risk of cancer recurrence (43). The University of California San Francisco (UCSF) criteria (single tumour ≤6.5 cm, or up to 3 tumours each ≤4.5 cm with total tumour diameter ≤8 cm) are one of the commonly-used expanded transplantation criteria for patients with HCC (43, 45).

2.2. Epidemiology

2.2.1. Global epidemiology of HCC

Hepatocellular carcinoma ranks as the sixth-most common cancer with respect to global incidence, and the second-highest cause of cancer deaths (3). The 5-year overall survival is roughly 18%, although among surgically-managed HCC patients (i.e. liver transplantation or liver resection), survival improves to between 50-80% (3). There is a strong predilection for males, with the male-to-female ratio of incidence ranging between 2:1–4:1 (46). Furthermore, recent studies have shown that both the incidence and mortality due to HCC continue to increase in North America (46, 47).

Globally, the highest incidence of HCC is seen in sub-Saharan Africa and East Asia (48). Specifically, China has been found to account for >50% of global HCC incidence, with age-standardized incidence rates as high as 35.2 per 100,000 among men and 13.3 per 100,000 among women. In these high-rate regions, by far the most common etiology of HCC is HBV cirrhosis, with historic causes being aflatoxin exposure and liver flukes. That being said, public health campaigns promoting hepatitis vaccination in newborns, as well as strategies aimed at decreasing ingestion of contaminated foods, have started to decrease the incidence of HCC in these regions. More recently, however, cirrhosis due to alcohol use and non-alcoholic fatty liver disease (NAFLD) have been on the rise (49).

In contrast, low-incidence regions such as the Americas, Europe, and Oceania have age-standardized HCC incidence rates of less than 5.0 per 100,000 (48). In these areas, incidence has increased over time predominantly due to chronic hepatitis C infection. However, with recent improvements in the prevention and medical management of hepatitis C, increased rates of cirrhosis and HCC are attributed to a growing burden of NAFLD (47, 50, 51).

2.2.2. HCC in Canada

Several epidemiologic studies of HCC have been conducted in Canada, all using routinely-collected administrative health and cancer registry data (Table 1). Secular trends from the Canadian Cancer Registry showed sustained increases in the age-standardized incidence rates of HCC for both males and females from the 1970s into the early 2000s, with almost a tripling in incidence among men (52-54). Similar trends were also seen with mortality rates, and projections suggested that these trends would continue into 2015 (53). Indeed, the most recent Canadian Cancer Statistics corroborate these findings, and while HCC incidence rates are stabilizing in males (+0.2% annual percent change), they continue to rise among females (+2.7% annual percent change) (55). In Canada, the management of HCC has evolved over time due to the realization of volume-outcome relationships in hepatobiliary and pancreatic surgery, development and success of percutaneous ablative techniques, establishment of surgical quality control benchmarks, and advances in living-donor liver transplantation (56-59).

Table 1. Epidemiologic studies of hepatocellular carcinoma in Canada

Author	Year	Study Design	Scope
ElSaadany et al. (52)	2002	Retrospective cohort	Age-standardized HCC incidence and mortality rates Geographic distribution of HCC disease burden
Pocobelli et al. (53)	2008	Retrospective cohort	Incidence trends by birth cohort and calendar period
Jembere et al. (60)	2012	Retrospective cohort	HCC survival by socioeconomic status
De et al. (54)	2013	Retrospective cohort	HCC incidence and mortality trends
Thein et al. (61)	2013	Retrospective cohort	HCC attributable healthcare costs
Thein et al. (62)	2015	Retrospective cohort	Screening and survival in viral hepatitis-induced HCC
Thein et al. (63)	2015	Retrospective cohort	Relative survival trends
Anyiwe et al. (64)	2016	Retrospective cohort	HCC incidence and stage at diagnosis by SES
Thein et al. (65)	2016	Case control	HCC healthcare utilization and costs of care
Aravinthan et al. (66)	2017	Retrospective cohort	Survival after LT in advanced HCC
Thein et al. (67)	2017	Retrospective cohort	Cost-effectiveness of curative modalities for HCC
Thein et al. (68)	2017	Retrospective cohort	Cost-effectiveness of palliative HCC therapy

HCC: hepatocellular carcinoma, LT: liver transplantation.

2.3. Overview of HCC treatment

Left untreated, the 5-year survival of patients with HCC is typically less than 10% (69, 70). The different treatment options for HCC are listed below (27, 71, 72):

Table 2. Treatment modalities for the management of HCC.

Curative	**Non-curative**
Surgical	Chemotherapy/immunotherapy
Liver transplant (LT)	Radiation therapy
Liver resection (LR)	Transarterial chemoembolization (TACE)
Percutaneous ablation	Best supportive care

Evaluating comorbidities is essential when considering a patient's ability to withstand invasive therapies such as liver transplant or resection. Among these, understanding the degree of liver dysfunction cannot be overstated in selecting management strategies for patients with HCC. This is because the remnant, non-cancerous liver does not function as well as a healthy, non-cirrhotic liver. Therefore, the optimal treatment selection for each patient requires careful consideration of benefits and harms, typically necessitating multi-disciplinary input from sub-specialty radiologists, hepatologists, oncologists, and surgeons.

Liver transplantation for HCC offers patients the best opportunity for cure by addressing both their tumour and their chronically-diseased liver, the latter being an important risk factor for the former (43). As a result, 75% of patients are expected survive to 4 years following transplant, with cancer recurrence rates below 15% (73). The limitations of this approach relate to the availability of compatible organs, although the use of living-donor liver transplantation aims to mitigate some of these issues (59).

Percutaneous ablation comprises several potentially-curative loco-regional therapeutic modalities for HCC, relying on tissue destruction, with radiofrequency ablation (RFA) being the reference standard because it is the most studied (74). In early-stage HCC (i.e. less than 2-3 cm), randomized trials comparing RFA to liver resection have demonstrated similar long-term oncologic outcomes, with potentially fewer short-term adverse events after RFA, owing to its less invasive approach (57). As the entire breadth of percutaneous ablative modalities (eg. microwave ablation, cryoablation, electroporation, etc.) are increasingly studied, their emerging roles as bridging measures to liver transplantation and in the management of recurrent HCC continue to be clarified (74, 75).

Outside of liver transplantation, liver resection offers the best opportunity for cure from HCC, with patient survival as high as 80% at 5 years, though roughly 10-15% of patients present with both resectable disease and sufficient liver function to withstand surgery (70). Nonetheless, significant improvements in outcomes from liver resection have been achieved for this group of patients. The risk of post-operative mortality has dropped from about 20% to less than 5%, and instead, the focus has shifted towards mitigating other major complications, which include hemorrhage, venous thromboembolism, bile leak, and post-hepatectomy liver failure (76).

2.4. Post-operative liver decompensation

Liver decompensation refers to the inability of the liver to adequately perform its routine organ functions (11). Clinical manifestations of liver decompensation include: jaundice, ascites, coagulopathy, bleeding gastroesophageal varices, portal hypertension, hepatorenal syndrome, and hepatic encephalopathy (11, 77). Often referred to as post-hepatectomy liver failure (PHLF) in the surgical literature, decompensation is an important and worrisome complication that may develop following liver resection in any patient, but especially among those with underlying liver dysfunction (78, 79). Reported to range between 1–35%, accurately quantifying the occurrence of PHLF is challenging due to the heterogeneity of definitions for this outcome (79-81). In an effort to standardize reporting and research of PHLF, the International Study Group of Liver Surgery (ISGLS) proposed a consensus definition and grading system in 2011 (81). They define

PHLF as “a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions.” These functions are measured by specific laboratory values for the INR and serum bilirubin on or after post-operative day 5. In this classification, PHLF is further divided into 3 categories: grade A requires no change in management, grade B requires non-invasive management, and grade C requires invasive management.

The ISGLS and other definitions of post-operative liver decompensation detect hepatic insufficiency in the early post-operative period (i.e. within days of resection) with identification typically relying on abnormal bloodwork parameters (81, 82). Limitations of these approaches include the inability to capture patients that do not undergo routine investigations after surgery, patients that are discharged early, or events that occur on a delayed timeline following resection. As well, such definitions of post-operative decompensation/failure treat the outcome in a binary manner, without providing details regarding clinical presentation and types of decompensation events.

We have outlined how percutaneous ablative modalities have limited and specific roles as potentially-curative therapies, while liver transplantation, though preferred, is not widely or immediately available. Disease progression while on transplant waiting lists is an important concern (75, 83). With liver resection a viable alternative, pre-operative decision-making is very important to properly identify the subset of patients with HCC who are most likely to benefit from a resection. While oncologic outcomes following resection have been studied, the aforementioned definitions of post-operative liver decompensation events do not allow adequate analysis of liver-related outcomes beyond the immediate post-operative period for appropriate consideration of benefit (84). In addition to considering the curability of the cancer, when offering resection for HCC, it is important for surgeons to determine a patient's long-term risk of non-malignant hepatic decompensation when making treatment recommendations.

2.5. Prognostic research

Prognostic research in the medical sciences deals with accurately predicting the risk of developing an outcome of interest over time, given a-priori information regarding certain predictors (85). One surgical application is in pre-operative risk stratification of patients with respect to development of post-operative complications. Developing prognostic models utilizes multivariable modelling techniques as it is rare for a single variable to be the sole predictor of an outcome (85) and the statistical techniques for multivariable prediction modelling studies are typically based on regression, classification, or neural networks (86). Prognostic research, however, is much more than multivariable modelling with studies grouped into 5 general categories based on their objective: predictor-finding, model development only, model development and external validation, external validation (with or without model updating), and model impact assessment (87).

Formal guidance for conducting multivariable prognostic research is well-described in authoritative literature on this topic (86, 88). More recently, tools to standardize the reporting and appraisal of such studies have also been published. These include the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement, the Quality in Prognostic Studies (QUIPS) tool, the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS), and the Prediction Model Risk of Bias Assessment Tool (PROBAST) (87, 89-91). Previously published series have aimed to disseminate the key concepts of prognostic research to clinical audiences (85, 92-98). However, a need to solidify understanding still exists among clinical researchers given that most prognostic modelling studies published in high impact medical journals retain methodologic and analytic concerns (87).

2.6. Rationale & objectives

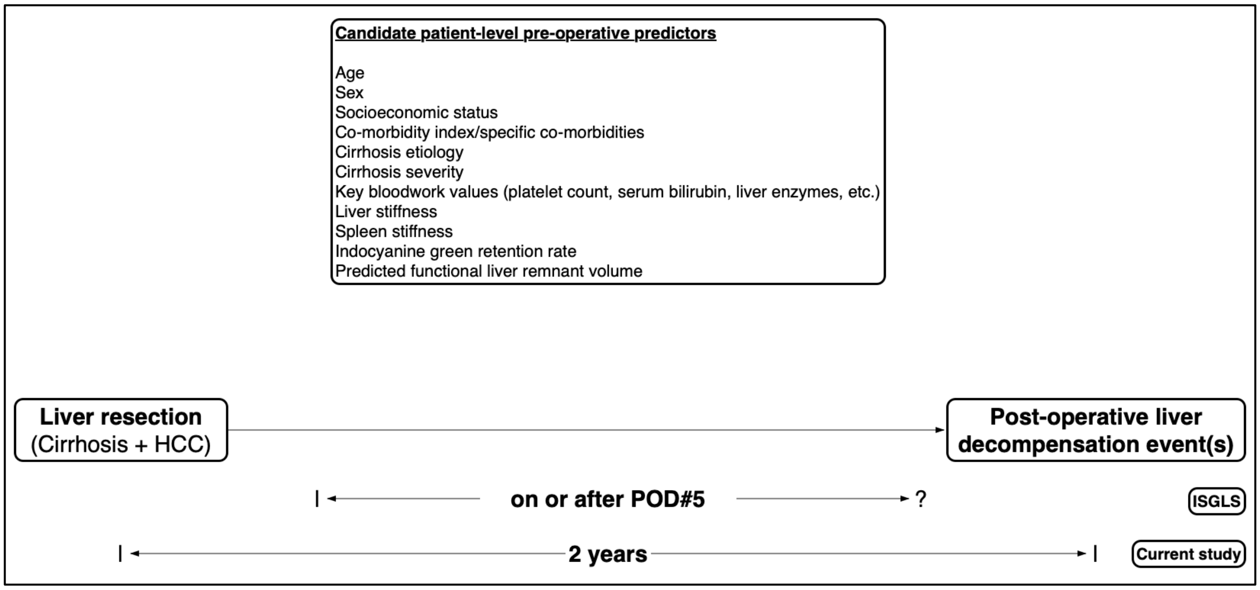
The validity of current prognostic models for predicting the risk of adverse liver-related outcomes following liver resection is unknown. Traditionally-used outcome definitions also preclude the description of adverse liver-related events beyond the early post-operative period. A comprehensive description of adverse liver-related post-operative events and their predictors in a contemporary cohort of patients following resection of HCC is critically needed because HCC management has significantly evolved over the past several decades due to advances in percutaneous interventional techniques, improvements in the management of patients with cirrhosis, and the regionalization of surgical therapy.

The objectives of this MSc thesis are:

1) To perform a systematic review of multivariable prognostic risk models for POLDEs following partial hepatectomy, in order to critically appraise their development/validation and document the predictors used within them.

2) To describe post-operative outcomes and identify independent, pre-operative, patient-level predictors of POLDEs occurring within 2 years of liver resection for HCC.

2.7. Conceptual framework



The conceptual framework for the research contained in this thesis is presented above. Among patients with underlying cirrhosis and incident HCC who undergo liver resection, a proportion will experience at least one post-operative liver decompensation event. Current surgical research focuses on early decompensation (i.e. ISGLS definition of PHLF), without a definite endpoint to capture these events. In contrast, we aim to use a broader definition and timeframe to identify POLDEs. Candidate patient-level, pre-operative predictors of these decompensation events are listed in the framework above, identified through review of background literature and clinical insight (80, 99). Given the variable reporting of bloodwork results into provincial databases, these parameters will likely not be available for analysis.

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CHAPTER 3

APPRAISAL OF MULTIVARIABLE PROGNOSTIC MODELS PREDICTING POST-OPERATIVE LIVER DECOMPENSATION FOLLOWING PARTIAL HEPATECTOMY: A SYSTEMATIC REVIEW

3.1. Abstract

3.1.1. Background

The systematic evaluation of prognostic modelling studies in the clinical literature is a relatively new area of research, with few studies assessing prognostic tools used for surgical decision-making. In liver surgery, post-operative decompensation is a potentially-lethal complication of resection, especially among patients with underlying cirrhosis. Currently, there is no systematic review of prognostic models of hepatic dysfunction following partial hepatectomy.

3.1.2. Objective

The objective of this systematic review was to describe and critically appraise studies that have developed or validated multivariable prognostic models for post-operative liver decompensation events following partial hepatectomy.

3.1.3. Methods

This study was designed using the CHARMS checklist. We performed a comprehensive search of the literature across multiple databases, without any time or language restrictions. Two reviewers independently screened studies for inclusion and abstracted relevant study details. Qualitative assessment of included studies was performed using the PROBAST tool.

3.1.4. Results

We identified 36 prognostic modelling studies; 25 focused on development only, 3 developed and validated models, and 8 validated pre-existing models. No studies assessed the

impact of routine clinical use of a prognostic model on patient outcomes. Most studies employed single-institution, retrospective cohort designs, and were conducted in Eastern populations. Commonly identified pre-operative predictors used were $ICGR_{15}$, platelet count, and serum bilirubin. In total, we noted 15 different outcome definitions for post-operative liver decompensation events. Statistical concerns surrounding model overfitting, performance assessment, and internal validation, led to all studies having a high risk of bias on qualitative assessment.

3.1.5. Conclusions

Current prognostic modelling studies for post-operative liver decompensation following partial hepatectomy may not be valid for routine clinical practice due to design and methodologic concerns. Landmark resources and recently-published reporting guidelines such as the TRIPOD statement can assist researchers, and additionally, model impact assessment studies represent opportunities for future research.

3.2. Introduction

The majority of published prognostic modelling studies in major clinical journals have several methodologic issues, raising concerns regarding their clinical utility (1, 2). This underscores the importance of conducting systematic appraisals of such prognostic modelling studies for specific clinical uses. Extensive guidance and education for conducting prognostic research is available, but may not be readily accessible to clinician-researchers (3, 4). To address this, numerous publications have outlined prognostic research methodology specifically for clinical audiences (5-12). These are also supplemented by the recently-developed “transparent reporting of a multivariable prediction model for individual prognosis or diagnosis” (TRIPOD) statement (13). While many prognostic models for post-operative outcomes after liver surgery exist, there has in fact been little appraisal of the studies that constructed or tested these tools in the hepatobiliary and pancreatic surgical literature (14-17).

Post-operative liver decompensation is a potentially-lethal complication of partial hepatectomy, with incidence ranging between 0.7–34% in some series (18). This large variation is in part explained by equipoise surrounding the exact definition of this outcome, since it actually encompasses several clinical conditions (18-20). Nonetheless, any decision to perform a liver resection must weigh the risk of decompensation against the intended benefits of the procedure. Central to this decision is considering the presence of underlying liver dysfunction and any additional comorbidities. Well-established prognostic models of hepatic dysfunction such as the Child-Pugh and model for end-stage liver disease (MELD) scores are often used in surgical decision-making, but they were not originally developed or validated for such widespread applications (21, 22). Others have attempted to develop new models specifically for predicting post-operative liver decompensation events using pre-operative variables, however, the rigour of development and performance of those models is unknown (23, 24).

The objective of this systematic review was to compile, summarize, and critically appraise the literature relating to the development and validation of multivariable prognostic models for post-operative liver decompensation following partial hepatectomy. Through this, we hope to provide an understanding of what prognostic models are currently available to clinicians, what predictors they use, and how well they have been constructed and validated.

3.3. Methods

3.3.1. Study design

We performed a systematic review of the literature to identify studies that developed and/or validated multivariable risk prediction models for the occurrence of post-operative liver decompensation events following liver resection. The review was designed and reported in accordance with the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (25).

3.3.2. Search strategy

A comprehensive literature search was carried out in order to identify published studies, using a 3-step approach as outlined in the Joanna Briggs Institute Reviewer's Manual (26). This included a preliminary search in Ovid Embase using a combination of text words and subject headings, followed by an analysis of relevant citations to identify other relevant text words and subject headings. The "Ingui" search filter with "Geersing" optimization, both of which have been developed and validated for searching prognostic modelling studies in MEDLINE, were adapted and incorporated into the Ovid Embase search (27).The optimized Ovid Embase search strategy was then adapted for Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. All databases were searched from their inception until November 2019, without any language or date restrictions. The complete search strategies for all databases are presented in Appendix A. Cited references were also examined to ensure no modelling studies were missed. The total number of records obtained from all databases using both search strategies was 8032, all of which were uploaded into Covidence systematic review software for screening.

3.3.3. Inclusion and exclusion criteria

Studies were considered if they expressed the intention to develop and/or validate a multivariable prognostic model for determining the risk of post-operative liver decompensation events using at least one pre-operative predictor. Similar to previous work from our group, studies were excluded for the following a-priori exclusion criteria (28, 29): if their objective was predictor-finding, if they only assessed the prognostic value of a single factor (unless adding to a pre-existing multivariable model), if they had an inapplicable analytic purpose (eg. multivariable modelling not aimed at prognostication, development of novel statistical methods), if their outcome(s) did not include a post-operative liver decompensation event, or if they were a duplicate study not initially screened out.

3.3.4. Screening

Screening was carried out by 2 reviewers independently (ZMM and HG). Any discordances regarding inclusion/exclusion were resolved via discussion and independent input from a third reviewer (PAG).

3.3.5. Data abstraction

Data abstraction from the final set of included studies was carried out by 2 reviewers independently (ZMM and HG). A standardized table of domains and items to be abstracted was developed a-priori using the CHARMS checklist.

3.3.6. Quality assessment

The risk of bias and applicability of participants, predictors, outcomes, and analysis within each included study were assessed using the prediction model risk of bias assessment tool (PROBAST) (30). Decisions of low concern, high concern, or unclear concern regarding risk of bias and applicability were made by both reviewers independently, with discrepancies resolved via discussion. The presence of a high or unclear concern assessment in any sub-domain resulted in the assignment of the same for the overall domain.

3.4. Results

3.4.1. Search results

Our search results yielded 8,032 studies, of which 3,110 were removed as duplicates (figure 1). Two reviewers then independently screened the remaining 4,922 abstracts for relevance, identifying 192 studies for full-text review. Ultimately, 36 studies were included for analysis; 25 of these developed a novel multivariable risk prediction model for post-operative liver decompensation, 3 developed and performed formal external validation of their model, and 8 studies aimed to validate pre-existing prognostic models. Full details on each study are provided in tables 1 and 2.

Among the 28 total studies that developed new multivariable models, the earliest was published in 1984. We noted an increasing number of such publications over time, especially after the year 2012, with 7 models developed each year in 2018 and 2019 (figure 2). The majority of prediction models (26 out 28) were developed from single-centre studies predominantly conducted in populations from Japan (12 studies) and China (8 studies). Almost unanimously (32 out of 36), study designs were retrospective in nature. In the 8 validation-only studies, the pre-existing models analyzed included: eFLRF, MELD, E-PASS, mE-PASS, P-POSSUM, APRI, ALBI, ALICE, and the Child-Pugh scores (31-38).

3.4.2. Patients, outcomes, and predictors

Across all included studies, sample sizes ranged between 28 and 1868 patients, with 7 studies analyzing more than 500 patients (table 1). The indications for partial hepatectomy varied between studies, though most often, resection was performed for hepatocellular carcinoma. Other indications included liver metastases (colorectal or otherwise), cholangiocarcinoma/bile duct carcinomas, and gallbladder carcinomas. Liver resection for benign lesions was rare. Cirrhosis presence and severity were also variably reported.

In total, 15 different outcome definitions were used for post-operative liver decompensation (Appendix B). The most common of these was the International Study Group of Liver Surgery (ISGLS) definition of post-hepatectomy liver failure, which was used in 18 out of 36 studies (19). In addition, only 6 studies explicitly specified a timeframe for follow-up, during which outcomes were recorded. On balance, the occurrence of post-operative decompensation events varied considerably across all studies, ranging between 1.7% and 43.4%.

3.4.3. Predictors of post-operative decompensation

The predictors from newly-developed multivariable models were abstracted and catalogued (table 1). Of these, we categorized pre-operative predictors into 4 groups: demographics/co-morbidities, bloodwork, functional/volumetric/imaging measures, and indocyanine green (ICG) based measures (figure 3). The most commonly-used pre-operative predictors were: indocyanine green retention rate at 15 minutes ($ICGR_{15}$), platelet count, and serum bilirubin, which were each found in 4 different predictive models. The largest contributing category was functional/volumetric/imaging measures, accounting for 23 predictors.

3.4.4. Statistical considerations

We documented the statistical methods used for model development and evaluation in the included studies (tables 1 and 2). The majority of development-only studies (21 of 25) performed multivariable logistic regression to generate their final models (figure 4). Other techniques included multiple linear regression (2 studies), Cox proportional hazards regression (2 studies), and linear discriminant analysis (1 study). One study did not report the modelling method used, and 1 study reported both linear and logistic regression in different parts of their manuscript. For all studies, it was unclear if all modelling assumptions had been explicitly satisfied for the statistical technique that was utilized.

Typically during model development, a large number of candidate predictors were considered, although the numbers of all candidate predictors prior to modelling were not consistently reported across studies. Among the development-only studies that did report these metrics, we calculated that 17 had a ratio of events-to-predictor variable (EPV) >10 for their final predictive models following predictor selection. When all candidate predictors prior to selection were considered, only 2 studies had EPV >10. Candidate predictor selection for statistical modelling was predominantly based on univariate significance, while predictor selection during multivariable modelling was inconsistently described (table 2).

Following model development, model performance through calibration and discrimination was not routinely assessed in the included studies (table 2). Only 12 of the 36 studies performed calibration of their multivariable predictive models, while 28 out of 36 studies assessed model discrimination. The latter was predominantly evaluated by comparing area under receiver operating characteristic curve (AUC) values, sometimes with formal statistical testing (eg. DeLong test). Formal internal validation of prognostic models occurred in 12 out of 28 development studies, through either splitting of the patient sample, or through the use of data resampling techniques such as bootstrapping, cross-validation, or jack-knifing.

3.4.5. Risk of bias and applicability

The qualitative appraisal of each study using the PROBAST tool is presented in Table 3. Contemporary studies had fewer domains with high or unclear concern for risk of bias or applicability, when compared to older studies. Universally, all studies assessed were deemed to have a high risk of bias in their statistical analysis methods; reasons for this included low event rates, low event-to-predictor variable ratios, lack of details provided regarding missing data and their handling, predictor selection for modelling on the basis of univariate significance only, and/or absence of formal internal validation of models. Other concerns included applicability of outcome definitions

3.5. Discussion

The critical appraisal of multivariable prognostic risk models for clinical practice is a relatively new area of research, facilitated by resources such as the CHARMS checklist, the TRIPOD statement, and the PROBAST tool (13, 30, 39). In the hepatobiliary and pancreatic surgical literature, such evaluative studies are still few in number, with only a handful of reports all published within the last 3 years (14-17). Our aim was to systematically review studies that developed and/or validated multivariable prognostic models for predicting the occurrence of post-operative liver decompensation events following liver resection. To that end, we performed a comprehensive search of the literature using validated search terms and filters for identifying clinical prognostic modelling studies, with sensitivities of >90% (27). After screening, we found 36 studies in total, with 25 focusing on development only, 3 performing development and external validation, and 8 conducting external validation of pre-existing models.

Almost all the studies we identified had a single-centre, retrospective cohort design. This is an obvious choice due to feasibility considerations such as cost, simplicity, and convenience, often utilizing routinely-collected health or registry data (1, 4). However, there are important drawbacks to such methods when the goal is to develop useful prognostic models. Analysis of retrospective data limits the ability to specify what information is collected, how patients are selected for inclusion, if candidate predictors are recorded consistently and reliably, and how much data is missing (4, 12). For these reasons, the potential for misclassification and information bias exists in all these studies. Additionally, the lack of multi-centre data may lead to referral bias, sample size constraints, and lack of generalizability of the models developed. Therefore, prospective, multi-centre studies specifically for the purposes of developing multivariable prognostic models should be considered by researchers, though recognizing that such approaches are typically more expensive, time-consuming, and tedious to carry out (1, 4, 12).

We identified 15 different outcome definitions used to develop and validate prediction models for post-operative liver decompensation. To a degree, this variation reflects the breadth of potential clinical presentation of patients, including jaundice, ascites, coagulopathy, bleeding varices, hepatorenal syndrome, hepatic encephalopathy, or portal hypertension. Despite efforts to put forward a consensus definition for post-hepatectomy liver failure, our results suggest that uptake in the surgical literature has not been uniform (19). Along with consistent outcome definitions, it is also crucial to explicitly specify the timeframe during which the outcome of interest is ascertained, which we found most studies did not perform. Together, these limitations reduce the useability of the prognostic models we assessed. Variable outcome definitions also pose difficulties for future work aimed at validating or updating prognostic tools.

There were also several statistical concerns among the studies we analyzed. The first was the number of candidate predictors considered for model development. Most of the included studies assessed a large set of predictors in relation to sample size and number of outcome events. This resulted in low EPV ratios, which often produces biased regression coefficients after regression modelling (40, 41). Candidate predictor selection for multivariable modelling was also an issue, as predictors were usually selected for model development based on univariate significance alone. Together, these two approaches to predictor selection increase the chance of deriving an overfitted model, resulting in a prediction model that is falsely expected to perform well when applied to a real-world population, on the basis of its performance in the development sample (2, 4, 41). A widely-accepted rule-of-thumb to guide investigators in prediction modelling research is to maintain a ratio of 10 to 20 events-per-predictor variable (4, 12). Furthermore, predictor selection should not focus on univariate significance alone, as this incorrectly equates the statistical significance of a covariate to its predictive ability and can exclude predictors that become significant on adjusted analysis (4, 10).

Another statistical issue relates to the use of multivariable logistic regression as a modelling technique; we found at least 21 studies that utilized this method. While it is commonly-used in the medical literature and can incorporate predictors robustly, it is crucial that the underlying assumptions of logistic regression are satisfied. For the cohort studies we analyzed, this means there can be no censored observations in order for the derived models to be valid (42). However, lack of information regarding the completeness of patient follow-up in most of the studies we assessed precludes verification of this criterion. When planning prognostic modelling studies, clinician-researchers must allow the type of outcome (i.e. continuous, binary, ordinal, etc.), the underlying assumptions of a statistical technique, and the nature of the data on-hand to guide the appropriate statistical modelling approach (3, 4).

Lastly, few studies formally assessed model performance or conducted internal validation. Model performance assessment requires calibration and discrimination; the former compares agreement between observed and predicted outcomes, whereas the latter focuses on whether the model can distinguish an event from a non-event (4, 10, 11, 39). We noted that many studies assessed model discrimination with AUC measures, however, calibration was less consistently examined. Internal validation, which explores the reproducibility of results within the study population, was also rarely (12 out of 28 development studies) carried out. Performance and validation assessments are crucial in corroborating the modelling methods employed before moving to estimation in the broader target population (9, 11). Without them, a prognostic model cannot be considered for clinical use, as its ability to predict outcomes outside of the development sample with consistency is unknown. Thus, model performance and validation both represent areas in need of attention within future prognostic modelling studies.

Our work is the first systematic review of multivariable prognostic modelling studies for predicting post-operative liver decompensation following hepatic resection. It provides an important overview of this body of the literature, outlining key predictors, outcome definitions, published models, and their limitations. Strengths of our study include the comprehensive search strategy we employed, which was conducted with minimal restrictions, utilizing validated and sensitive search strings for the identification of modelling studies. Furthermore, we provide a detailed examination of each study's design and appraisal of their statistical methodology based on authoritative published guidelines, highlighting important points for investigators to consider when engaged in such research. An important limitation of our work is the lack of quantitative synthesis of results; this was not possible due to the heterogeneity of patients, indications for resection, and outcome definitions between studies.

In conclusion, we have identified several studies focused on developing and/or validating multivariable prognostic models for predicting post-operative liver decompensation events after partial hepatectomy. Common predictors included $ICGR_{15}$, platelet count, and serum bilirubin, however, studies broadly suffered from methodologic and design issues, thereby undermining their validity and precluding adoption of any particular model into routine clinical practice. Future work on prognostic modelling should apply rigorous methodology outlined in authoritative literature, as well as adhering to published reporting recommendations, referenced herein.

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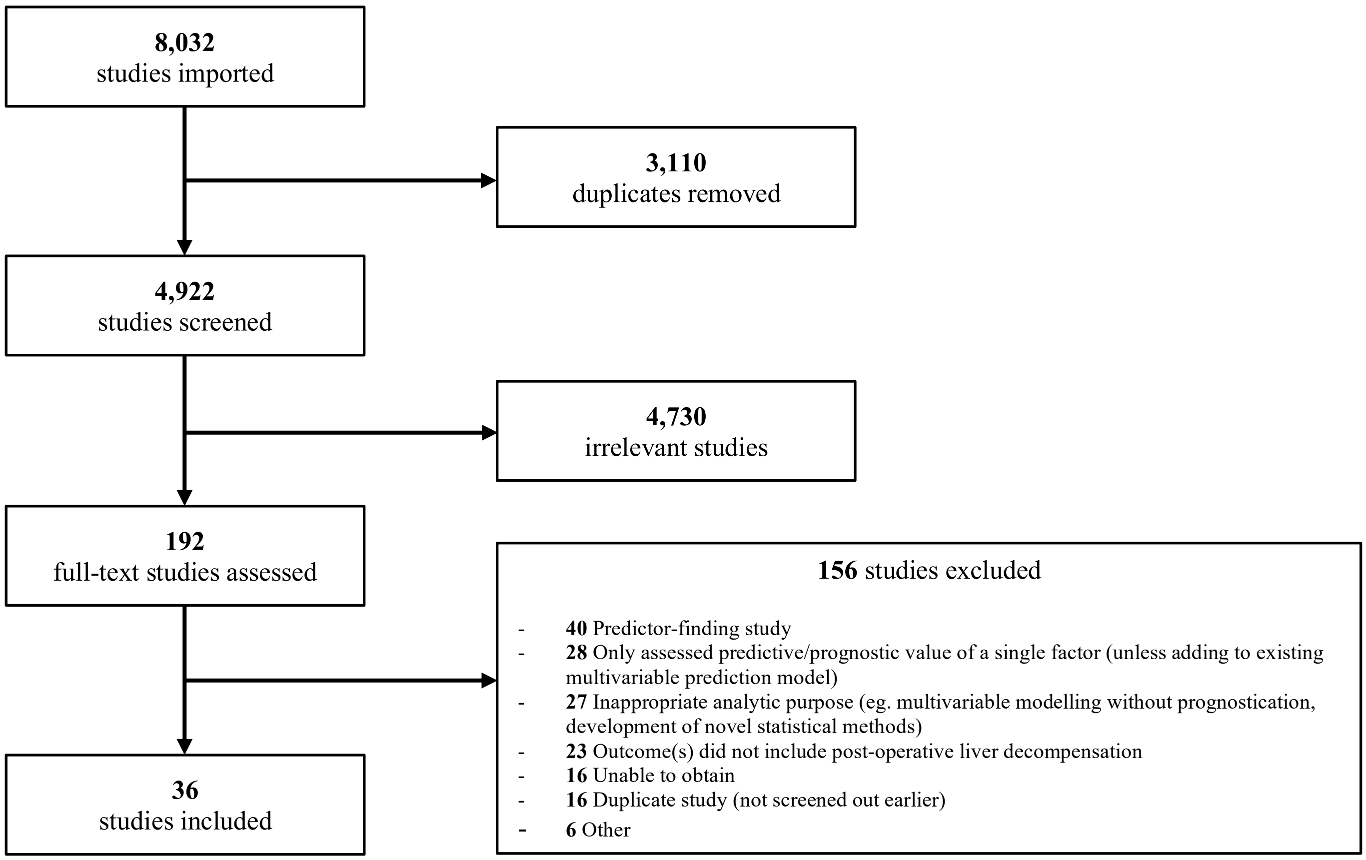

Figure 1. Flow diagram of study selection for analysis.

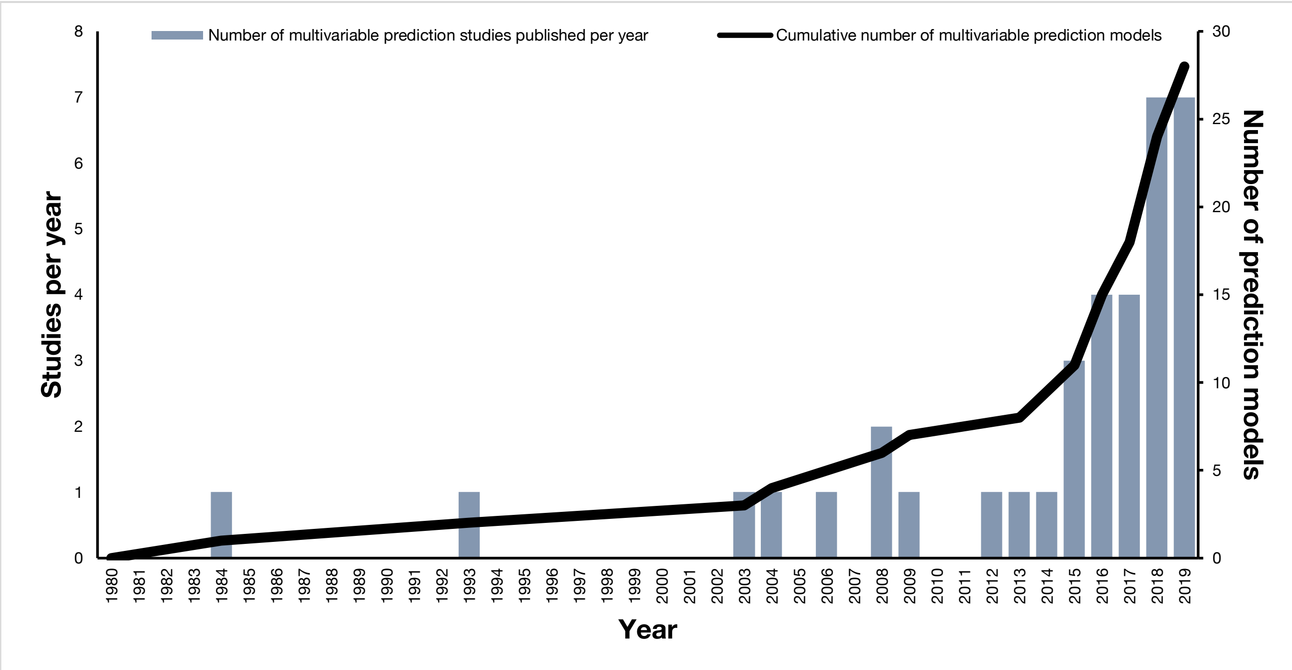

Figure 2. Prognostic modelling studies of post-operative liver decompensation published over time.

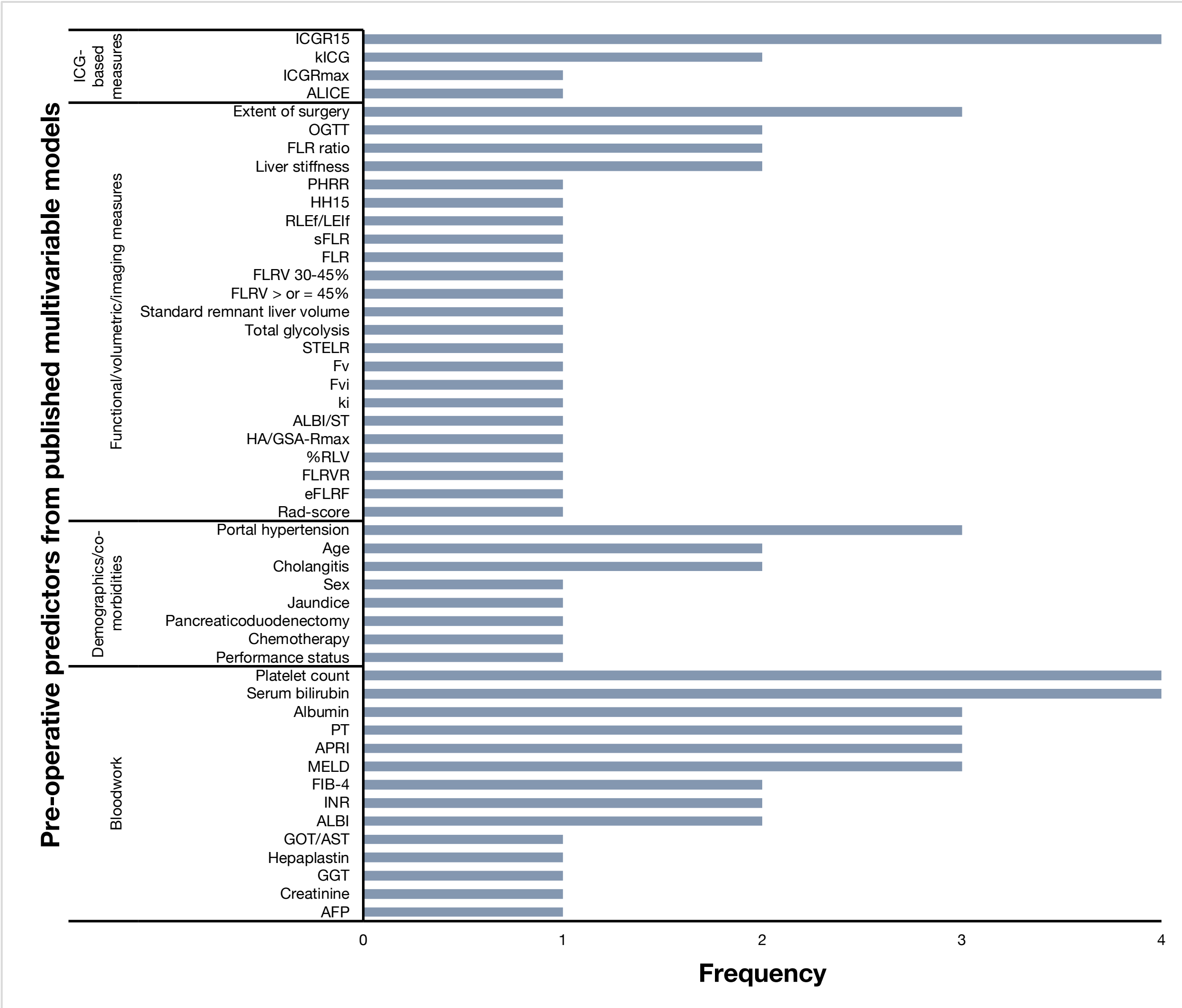

Figure 3. Frequency of pre-operative predictors used in the development of various multivariable models.

$ICGR_{15}$: indocyanine green retention rate at 15 minutes; kICG: indocyanine disappearance rate; $ICGR_{max}$: maximal removal rate of indocyanine green; ALICE: albumin-indocyanine green evaluation grade; OGTT: oral glucose tolerance test; FLR: future liver remnant; PHRR: parenchymal hepatic resection rate; HH_{15}: clearance index of 99mTc-galactosyl human serum albumin; RLEf/LEIf: relative liver enhancement normalized to fat/liver enhancement index normalized to fat; sFLR: standardized future liver remnant; FLRV: future liver remnant volume; STELR: standardized estimated liver remnant; k_i: k-value of the planned residual liver of the i^{th} voxel of interest; F_{vi}: planned residual functional liver volume of the i^{th} voxel of interest; F_v: preoperative total functional liver volume; ALBI/ST: ; HA/GSA-R_{max}: ratio of serum hyaluronic acid to the maximum removal rate of technetium-99m diethylenetriaminepentaacetic acid galactosyl human serum albumin; %RLV: ratio of remnant liver volume to total liver volume; FLRVR: future liver remnant volume ratio; eFLRF: estimated future liver remnant function; PT: prothrombin time; APRI: aspartate transaminase to platelet ratio index; MELD: model for end-stage liver disease; FIB-4: fibrosis-4 score; INR: international normalized ratio; ALBI: albumin-bilirubin grade; GOT/AST: glutamic oxaloacetic transaminase/aspartate transaminase; GGT: gamma-glutamyl transferase; AFP: alpha-fetoprotein.

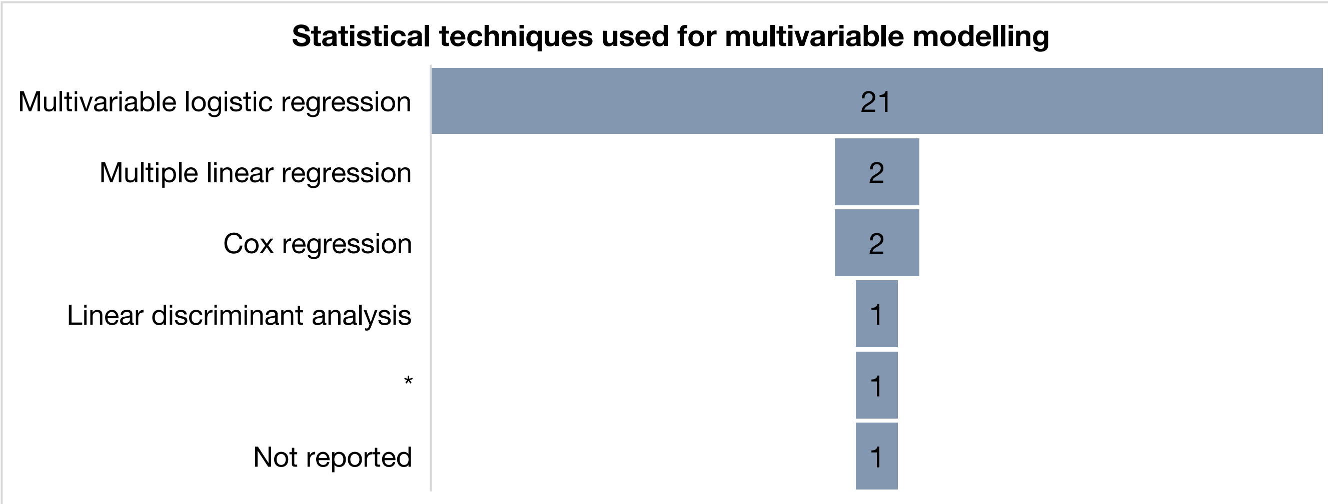

Figure 4. Statistical techniques used in developing multivariable prediction models for post-operative liver decompensation.

Table 1. Details of studies included for analysis.

Author	Publication year	Study years	Study Design	Sites	Country	Patients with cirrhosis	Indication(s) for resection	Sample Size	Outcome(s)	Follow-up details	Event number (%)	Predictors considered (EPV)	Predictors in final model (EPV)	Predictor list
Model development only														
Cai et al.	2019	2008-2016	RC	S	China	Y	HCC	112	PHLF-ISGLS[1]	NR	40 (35.7)	18 (2.2)	9 (4.4)	- MELD score - Performance status - Rad-score (7 variables)
Chapelle et al.	2016	2008-2010	RC	S	Belgium	Y	CRLM: 48 HCC: 12 BLT: 10 non-CRLM: 8 ICC: 5 PHCC: 5	88	PHLF-ISGLS	NR	12 (13.6)	5 (2.4)	1 (12.0)	- eFLRF
Chin et al.	2018	2001-2013	RC	S	Singapore	Y	HCC	157	1) 50-50 criteria[2] 2) PHLF-ISGLS 3) MSKCC criteria[3]	NR	50-50: 11 (7.0) PHLF-ISGLS: 65 (41.4) MSKCC: 44 (28.0)	14 (0.8)	3 (3.7)	- Platelet count - MELD score - AFP
Cho et al.	2017	2005-2014	RC	S	Korea	Y	HCC	149	Serum bilirubin >5 mg/dL for the first 5 post-operative days or death in the absence of other causes	NR	7 (4.7)	7 (1.0)	2 (3.5)	- APRI - Total glycolysis
Citterio et al.	2016	2000-2013	RC	S	Italy	Y	HCC	543	Liver decompensation[4]	Every 4 months for first 2 years, then every 6 months till 2015	108 (19.9)	13 (8.3)	3 (36.0)	- Major hepatectomy - Portal hypertension - MELD score >9
Costa et al.	2018	2010-2013	RC	S	Canada	Y	CRLM: 46 HCC: 13 CC: 2 Metastatic NET: 2 Hepatic cyst: 1 Hepatoma: 1	65	PHLF-ISGLS	NR	9 (13.8)	Unclear	7 (1.3)	- Age - Sex - Previous chemotherapy - FLR ratio - RLE_f/LEI_f - IOT - EBL

Dasari et al.	2019	2008-2016	RC	S	UK	NR	CRLM: 791 Other malignant: 156 Benign: 116 HCC: 111 CC: 69 Liver donor: 26	1180	PHLF-ISGLS	NR	154 (13.1)	47 (3.3)	8 (19.3)	- Extent of surgery - Creatinine - $\log_2$ bilirubin - INR
Dong et al.	2015	2006-2012	RC	S	China	Y	HCC: 330 CC: 8	338	PHLF-ISGLS	NR	14 (4.1)	16 (0.9)	2 (7.0)	- FLRVR - FIB-4
Furuyama et al.	2016	2000-2012	RC	S	Japan	Y	HCC	385	1) ELF: 50-50 criteria 2) MLF: PT <40% or total bilirubin >85 umol/L	NR	ELF: 24 (6.2) MLF: 18 (4.7)	ELF: 24 (1.0) MLF: 24 (0.75)	ELF: 2 (12.0) MLF: 2 (9.0)	- Prothrombin time - Direct bilirubin
Hu et al.	2018	2015-2016	RC	S	China	Y	HCC	216	PHLF-ISGLS	NR	64 (29.6)	23 (2.8)	5 (12.8)	- Platelet count - ElastPQ values (kPa) - Serum bilirubin - Portal hypertension - Serum GGT
Ichikawa et al.	2009	1994-2004	RC	S	Japan	Y	HCC	366	Post-operative hepatic failure[5]		30 (8.2)	33 (0.9)	1 (30.0)	- APRI
Iguchi et al.	2015	2004-2012	RC	S	Japan	NR	HCC	265	PHLF-ISGLS	NR	105 (39.6)	11 (9.5)	4 (26.3)	- %RLV - Platelet count - Prothrombin time - Albumin
Kaibori et al.	2008	2000-2006	NR*	S	Japan	Y	HCC	191	Liver failure[5]	> 1 year after hepatectomy	16 (8.4)	19 (0.8)	1 (16.0)	- HA/GSA-R_{max}
Lee et al.	2018	2001-2013	RC	S	Korea	N	PHCC	143	PHLF-ISGLS	NR	62 (43.4)	8 (7.8)	3 (20.7)	- FLR ratio - Operative blood loss - Prothrombin time
Lei et al.	2017	2015 (May-September)	NR*	S	China	Y	HCC	247	PHLF[6]	NR	37 (15.0)	27 (1.4)	2 (18.5)	- LSM (kPa) - INR
Li et al.	2015	2010-2014	RC	S	China	Y	HCC: 256 CC: 54	310	50-50 criteria	1 month after liver resection	44 (14.2)	8 (5.5)	3 (14.7)	- $ICGR_{15}$ - Operative bleeding - Standard remnant liver volume

Nagino et al.	1993	1980-1990	NR*	S	Japan	NR	BDC: 55 GBC: 29	84	Hepatic failure[7]	NR	25 (29.8)	18 (1.4)	4 (6.3)	- OGTT pattern - Cholangitis - kICG - PD
Nanashima et al.	2013	2001-2013	RC	S	Japan	Y	HCC: 197 Metastases: 123 IHCC: 44 GBC: 18 BDC: 40 Other: 20	442	Hepatic failure[8]	NR	23 (5.2)	22 (1.0)	2 (11.5)	- HH_{15} (>0.6) - Operative time
Olthof et al.	2017	1997-2014	RC	M	Netherlands USA	NR	PHCC	217	PHLF-ISGLS	NR	52 (24.0)	9 (5.8)	6 (8.7)	- Jaundice - Cholangitis - FLRV ≥ 45% - FLRV 30-45% - Bilirubin > 50
Qian et al.	2018	2005-2014	RC	S	China	Y	HCC	181	Post-operative ascites[9]	NR	62 (34.2)	14 (4.4)	4 (15.5)	- Platelet count - RBC transfusion - FFP transfusion - FLR
Shirata et al.	2019	2002-2014	RC	S	Japan	Y	HCC	1025	1) Large volume ascites[10] 2) PHLF-ISGLS	NR	LA: 142 (13.9) PHLF: 38 (3.7)	LA: 8 (17.8) PHLF: 8 (4.8)	LA: 4 (35.5) PHLF: 3 (12.7)	LA: - ALICE - Major hepatectomy - Portal hypertension - Blood loss >800 mL PHLF: - ALICE - Major hepatectomy - Portal hypertension
Yamanaka et al.	1984	1980-1982	RC	S	Japan	Y	HCC: 27 BTC: 5 BLT: 2 Metastases: 2	36	NR	NR	8 (22.2)	17 (0.47)	4 (2.0)	- PHRR - $ICGR_{15}$ - Age - $ICGR_{max}$
Zou et al.	2018	2015-2017	RC	S	China	Y	HCC	229	PHLF-ISGLS	1 month after discharge, then every 3 months; end date of March 15, 2017	21 (9.2)	15 (1.4)	2 (10.5)	- ALBI - sFLR

Satoh et al.	2003	NR	NR	S	Japan	NR	HCC: 33 CC: 9 GBC: 7 Metastases: 8	57	NR	NR	5 (8.7)	Unclear	3 (1.7)	- k_i - Fvi - Fv
Wakabayashi et al.	2004	1996-2001	RC	S	Japan	NR	HCC	120	Post-operative liver dysfunction[11]	NR	24 (20.0)	2 (12.0)	2 (12.0)	- $ICGR_{15}$ - STELR
Model development and external validation														
Uchiyama et al.	2008	1981-1989	NR*	S	Japan	Y	HCC	28	Intractable ascites[12]	NR	4 (14.3)	5 (0.8)	11 (0.4)	- Albumin - Hepaplastin - GOT/AST - kICG - OGTTLI - Weight of resected liver
Kokudo et al.	2016	1989-2014	RC	M	Japan Switzerland and UK	Y	HCC	1868	1) Ascites (> Clavien-Dindo grade 2) 2) Liver failure (not defined) 3) Any death within 90 days (survival was primary outcome)	NR	84 (4.4)	13 (6.5)	2 (42.0)	- $ICGR_{15}$ - Albumin
Zhang et al.	2019	2010-2017	RC	S	China	Y	HCC	932	PHLF-ISGLS	NR	69 (7.4)	11 (6.3)	2 (34.5)	- ALBI - ALBI/ST - APRI - FIB-4
External validation of pre-existing model														
Chapelle et al.	2017	2012-2016	RC	S	Belgium	NR	CRLM	140	PHLF-ISGLS	NR	21 (15.0)	–	–	- eFLRF
Cucchetti et al.	2006	1997-2004	RC	S	Italy	Y	HCC	154	Irreversible liver failure[13]	1 year	11 (7.1)	–	–	- MELD score
Haga et al.	2012	2000-2007	RC	M	Japan	NR	HCC: 736 Metastases: 187 CC: 30 Other: 7	960	Post-operative liver failure[14]	NR	16 (1.7)	–	–	- E-PASS - mE-PASS - P-POSSUM
Mai et al.	2019	2013-2016	RC	S	China	Y	HCC	1044	PHLF-ISGLS	1 month after hepatectomy, then every 2-3 months for 1 year, then every 3-6 months from the second year; no end date specified	213 (20.4)	–	–	- APRI - ALBI - MELD score - Child-Pugh
Miyazaki et al.	2019	2000-2016	RC	S	Japan	NR	IHCC: 84 PHCC: 62 GBC: 20	166	1) 50-50 criteria 2) PHLF-ISGLS 3) Mullen's criteria		50-50: 7 (4.2) Mullen's: 13 (7.8) PHLF: 32 (19.3)	–	–	- ALICE

Russolilo et al.	2019	2005-2016	RC	M	Italy	Y	HCC	400	1) All complications 2) PHLF-ISGLS	NR	Ascites: 68 (17.0) Liver failure: 82 (20.5) Deaths: 5 (1.3)	–	–	- ALICE - ALBI
Tanaka et al.	2014	2001-2012	RC	S	Japan	Y	HCC	457	Modification of ISGLS and 50-50 criteria[15]	NR	19 (4.2)	–	–	- APRI
Zhang et al.	2018	2010-2014	RC	S	China	Y	HCC	338	PHLF-ISGLS	1 month after discharge, then every 3 months for year 1, then every 6 months until end date of December 31, 2017	26 (7.7)	–	–	- ALBI - Child-Pugh - Major hepatectomy

EPV: events-per-predictor variable; NR: not reported; NR*: not reported, likely retrospective cohort; RC: retrospective cohort; S: single-centre; M: multi-centre; HCC: hepatocellular carcinoma; CRLM: colorectal cancer liver metastases; BLT: benign liver tumours; CC: cholangiocarcinoma; ICC: intra-hepatic cholangiocarcinoma; PHCC: perihilar cholangiocarcinoma; NET: neuroendocrine tumour; BDC: bile duct cancer; GBC: gallbladder carcinoma; PHLF: post-hepatectomy liver failure; ISGLS-International Study Group for Liver Surgery, MSKCC: Memorial-Sloan Kettering Cancer Centre, ELF: early liver failure; MLF: mortality due to recurrence-free liver failure; LA: large volume ascites.

MELD: model for end stage liver disease; eFLRF: estimated future liver remnant function; AFP: alpha-fetoprotein; FLR: future liver remnant; RLEf/LEIf: relative liver enhancement normalized to fat/liver enhancement index normalized to fat; IOT: intra-operative transfusion; EBL: estimated blood loss; INR: international normalized ratio; FLRVR: future liver remnant volume ratio; FIB-4: fibrosis-4 score; kPa: kilopascals; GGT: gamma-glutamyl transferase; APRI: aspartate transaminase to platelet ratio index; %RLV: ratio of remnant liver volume to total liver volume; HA/GSA-R_{max}: ratio of serum hyaluronic acid to the maximum removal rate of technetium-99m diethylenetriaminepentaacetic acid galactosyl human serum albumin; LSM: liver stiffness measurement; $ICGR_{15}$: indocyanine green retention rate; OGTT: oral glucose tolerance test; kICG indocyanine green disappearance rate; PD: pancreaticoduodenectomy; HH_{15}: clearance index of 99mTc-galactosyl human serum albumin; RBC: red blood cell; FFP: fresh frozen plasma; ALICE: albumin-indocyanine green evaluation grade; PHRR: parenchymal hepatic resection rate; ICGRmax: ; ALBI: albumin-bilirubin grade; sFLR: standardized future liver remnant; k_i: k-value of the planned residual liver of the i-th voxel of interest; F_{vi}: planned residual functional liver volume of the i-th voxel of interest; F_v: preoperative total functional liver volume; OGTTLI: oral glucose tolerance test linearity index ; STELR: standardized estimated liver remnant; ALBI/ST: albumin-bilirubin grade to splenic thickness ratio.

1-15: the various outcome definitions are listed in Appendix B.

Table 2. Description of model development, performance, and evaluation within included studies.

Author	MODEL DEVELOPMENT								MODEL PERFORMANCE					MODEL EVALUATION		
	Blinded predictor assessment	Missing Data	If yes, number of participants with missing data and handling of missing data	Statistical modelling method	Modelling assumptions satisfied	Predictor selection for modelling	Predictor selection during modelling	Shrinkage of predictor weights or regression coefficients?	Model calibration performed	Model discrimination assessment	Confidence intervals for performance assessment	Classification measures	A-priori cutpoints	Internal validity assessment	External validity assessment	Final model/existing models tested
Development only																
Cai et al.	NR	NR	NR	MLR	Not clear	Predictors with non-zero correlation coefficients	Backward	Yes	Yes, calibration curve and HL test	Yes, AUC with DeLong test	Yes	No	Yes	Yes, CV and bootstraps (1000 re-samples)	–	Nomogram
Chapelle et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR	No	No	Yes, AUC only	No	Yes	No	No	–	eFLRF with cut-off value 2.3%/min/m^2
Chin et al.	NR	NR	NR	MLR	Not clear	Univariate association	Stepwise	No	No	Yes, AUC only	No	Yes	No	No	–	3-point MAP score
Cho et al.	NR	NR	NR	MLR	Not clear	Univariate association	Stepwise	No	No	Yes, AUC with Delong test	Yes	Yes	Yes	Yes, bootstraps (1000 re-samples) with c-index	–	Regression equation with beta and intercept values
Citterio et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR; random forest variable important	No	No	Yes, Harrell's C-index with Cis	Yes	No	No	Yes, CV (10-fold)	–	Classification tree
Costa et al.	NR	NR	NR	MLR	Not clear	Variables with high individual AUC	Forward	No	No	Yes, AUC only	Yes	No	No	No	–	Variables in model only
Dasari et al.	NR	Yes	Outcome only available for 1180/1269 patients Excluded from analysis	MLR	Not clear	Univariate association and no missing data > 20%	Forward	No	Yes, Brier score	Yes, AUC only	No	Yes	Yes	Yes, CV	–	14-point PHLF risk score
Dong et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR	No	No	Yes, AUC only	Yes	Yes	No	No	–	Variables in model only
Furuyama et al.	NR	NR	NR	MLR	Not clear	Univariate association	Forward	No	No	Yes, AUC only	Yes	Yes	Yes	Yes, split sample	–	DBPTRI

Hu et al.	NR	Yes	6 patients with inconclusive liver stiffness measurement Excluded from analysis	Cox regression	Not clear	Univariate association	Backward	No	No, labelled ROC curves as calibration curves	Yes, AUC and concordance index	Yes	No	No	Yes, bootstraps (1000 re-samples)	State validation set was internal at one point and external at another	Nomogram
Ichikawa et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR	No	No	No	No	Yes	No	No		APRI with cut-off value 10
Iguchi et al.	NR	Yes	239 (234 without volumetric data; 5 without kICG/ICGR$_{15}$ data) Excluded from analysis	MLR	Not clear	Univariate association	NR	No	No	Yes, AUC only	No	Yes	No	No	–	Risk score with %RLV limits
Kaibori et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR	No	No	No	No	Yes	No	No	–	HA/GSA-Rmax ratio with cut-off value 500 mg/min/dL
Lee et al.	NR	Yes	NR	MLR	Not clear	Univariate association	Backward	No	Yes, calibration plot and HL test	Yes, AUC only	Yes	No	Yes	Yes, bootstraps (1000 re-samples)	–	10-point risk score
Lei et al.	Yes	NR	NR	MLR	Not clear	Univariate association	Forward	No	No	Yes, AUC with unspecified test	Yes	Yes	No	No	–	LSM-INR index with equation and cut-off value -1.9
Li et al.	NR	NR	NR	MLR	Not clear	Univariate association	Forward	No	Yes, scatter plot	Yes, AUC only	Yes	Yes	Yes	Yes, split sample	–	PLFEI equation with cut-off value -2.16 for POLD and -1.97 for FLF

Nagino et al.	NR	NR	NR	MLR	Not clear	18 pre-specified candidate predictors; all included	Stepwise	No	Yes, scatter plot	No	Yes	Yes	No	Yes, split sample and jack-knifing for all 84 patients	–	Discriminant score and equation
Nanashima et al.	NR	NR	NR	MLR*	No	Univariate association	Forced entry (text) Stepwise (figure)	No	No	Yes, AUC only	No	No	No	No	–	Equations presented with cut-offs
Olthof et al.	NR	Yes	19 cases Full case analysis	MLR	Not clear	Univariate association	Backward	No	Yes, crosstab and HL test	Yes, AUC only	Yes	No	No	Yes, bootstraps (200 re-samples)	–	8-point risk score
Qian et al.	NR	NR	NR	MLR	Not clear	NR	Backward	No	No	Yes, AUC only	Yes	Yes	No	No	–	14-point risk score
Shirata et al.	NR	NR	NR	MLR	Not clear	8 clinically significant variables from those with univariate association	Backward	No	No	Yes, AUC only	Yes	No	No	No	–	Decision tree
Yamanaka et al.	NR	NR	NR	MLiR	Not clear	Correlation between predictor and score for early prognosis	Stepwise	No	Yes, comparison of prediction score and outcome	No	No	No	No	Yes, split sample	–	Prediction score with cut-off value 50 points
Zou et al.	NR	NR	NR	MLR	Not clear	Not reported	NR	No	No	Yes, AUC with unspecified test	No	Yes	No	No	–	ALBI x sFLR
Satoh et al.	NR	NR	NR	NR	Not clear	Not reported	NR	No	No	No	No	Yes	No	No	–	PRI with cut-off value 0.38
Wakabayashi et al.	NR	NR	NR	LDA	Not clear	Not reported	NR	No	No	No	No	No	No	No	–	Two equations for $ICGR_{15}$ cut-off
Development and external validation																
Uchiyama et al.	NR	NR	NR	MLiR	Not clear	Not reported	NR	No	No	No	No	No	No	No	Different time period	Liver function score with cut-off value 50

Kokudo et al.	NR	Yes	NR	Cox regression	Not clear	Pre-specified risk factors	Backward	No	No	Yes, Harrell's C statistic and AUC	No	No	No	Yes, split sample	Multiple sites	ALICE grade 3 grades with cut-off values -2.2 and -1.39
Zhang et al.	NR	NR	NR	MLR	Not clear	Univariate association	NR	No	Yes, crosstab only	Yes, AUC with DeLong test	Yes	Yes	No	No	Different patient population	ALBI/ST ratio with cut-off value - 0.627
External validation of pre-existing model																
Chapelle et al.	NR	NR	NR	–	–	–	–	–	No	Yes, AUC only	No	No	No	–	Different patient population	eFLRF
Cucchetti et al.	NR	Yes	32 patients Excluded from analysis	–	–	–	–	–	No	Yes, AUC only	Yes	Yes	No	–	Different patient population	MELD score
Haga et al.	NR	Yes	174 patients without P-POSSUM data Excluded from analysis	–	–	–	–	–	Yes, HL test for mortality outcome	Yes, AUC only	Yes	No	No	–	Different patient population	- E-PASS - mE-PASS - P-POSSUM
Mai et al.	NR	NR	NR	–	–	–	–	–	Yes, bar graph only	Yes, AUC with unspecified test	Yes	Yes	No	–	Different patient population	- APRI - ALBI - MELD score - Child-Pugh
Miyazaki et al.	NR	NR	NR	–	–	–	–	–	Yes, bar graph only	Yes, AUC only	No	Yes	No	–	Different patient population	ALICE
Russolilo et al.	NR	Yes	NR Excluded from analysis	–	–	–	–	–	No	No	No	No	No	–	Different patient population	- ALICE - ALBI
Tanaka et al.	NR	NR	NR	–	–	–	–	–	No	Yes, AUC only	Yes	Yes	No	–	Different patient population	APRI
Zhang et al.	NR	NR	NR	–	–	–	–	–	Yes, bar graph only	Yes, AUC with DeLong test	Yes	Yes	No	–	Different patient population	ALBI

NR: not reported; MLR: multivariable logistic regression; MLR*: binomial logistic regression (text); multiple linear regression (figure) and abstract; MLiR: multiple linear regression; LDA: linear discriminant analysis; AUC: area under the receiver operating characteristic curve; HL: Hosmer-Lemeshow test of goodness-of-fit.

Table 3. Qualitative assessment of included studies using the prediction model risk of bias assessment tool.

Author	Publication Year	RISK OF BIAS				APPLICABILITY			OVERALL ASSESSMENT	
		Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of Bias	Applicability
Yamanaka et al.	1984	H	?	H	H	?	?	H	H	H
Nagino et al.	1993	H	?	L	H	?	?	?	H	?
Satoh et al.	2003	H	?	H	H	?	?	H	H	H
Wakabayashi et al.	2004	L	?	H	H	L	?	?	H	?
Cucchetti et al.	2006	H	L	H	H	?	L	H	H	H
Kaibori et al.	2008	L	L	?	H	L	L	?	H	?
Uchiyama et al.	2008	L	?	H	H	L	?	H	H	H
Ichikawa et al.	2009	L	L	?	H	L	L	?	H	?
Haga et al.	2012	H	L	?	H	?	?	?	H	?
Nanashima et al.	2013	H	L	L	H	?	L	?	H	?
Tanaka et al.	2014	L	L	L	H	L	L	?	H	?
Dong et al.	2015	L	L	L	H	L	?	L	H	?
Iguchi et al.	2015	H	L	L	H	?	L	L	H	?
Li et al.	2015	L	?	L	H	L	?	?	H	?
Chapelle et al.	2016	H	L	L	H	H	?	L	H	H
Citterio et al.	2016	L	L	L	H	L	L	L	H	L
Furuyama et al.	2016	L	L	?	H	L	L	?	H	?
Kokudo et al.	2016	L	L	H	H	L	L	H	H	H
Chapelle et al.	2017	L	L	L	H	L	?	L	H	?
Cho et al.	2017	L	L	H	H	L	L	H	H	H
Lei et al.	2017	L	?	?	H	L	?	?	H	?
Olthof et al.	2017	L	L	L	H	L	L	L	H	L
Chin et al.	2018	L	L	L	H	L	L	?	H	?
Costa et al.	2018	H	H	L	H	H	?	L	H	H
Hu et al.	2018	L	L	L	H	L	?	L	H	?
Lee et al.	2018	L	L	L	H	L	?	L	H	?
Qian et al.	2018	L	L	?	H	?	?	?	H	?
Zhang et al.	2018	L	L	L	H	L	L	L	H	L
Zou et al.	2018	L	?	L	H	?	?	L	H	?
Cai et al.	2019	L	L	L	H	L	?	L	H	?
Dasari et al.	2019	H	L	L	H	?	L	L	H	?
Mai et al.	2019	L	L	L	H	L	L	L	H	L
Miyazaki et al.	2019	H	L	L	H	?	L	?	H	?
Russolillo et al.	2019	L	L	L	H	L	L	L	H	L
Shirata et al.	2019	L	L	H	H	L	L	?	H	?
Zhang et al.	2019	L	L	L	H	L	L	L	H	L

H: high concern; L: low concern; ?: unclear concern.

CHAPTER 4

PREDICTORS OF POST-OPERATIVE LIVER DECOMPENSATION EVENTS FOLLOWING PARTIAL HEPATECTOMY IN PATIENTS WITH CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: A POPULATION-BASED STUDY

4.1. Abstract

4.1.1. Background

Appropriate patient selection for liver resection in hepatocellular carcinoma (HCC) is critical to mitigate major post-operative complications. Currently, no standard prognostic tool exists to assess the risk of post-operative liver decompensation events (POLDEs) following partial hepatectomy in patients with cirrhosis and hepatocellular carcinoma.

4.1.2. Objective

The objective of this study was to identify independent pre-operative predictors of POLDEs, for future development of prognostic tools to improve surgical decision-making.

4.1.3. Methods

This was a population-based, retrospective cohort study of patients with cirrhosis and incident HCC between 2007-2017, identified using routinely-collected administrative health data from Ontario, Canada. The proportion who experienced a POLDE (any one of jaundice, ascites, bleeding gastroesophageal varices, portal hypertension, hepatorenal syndrome, hepatic coma/encephalopathy, or hepatic failure) or died within 2 years from surgery was described. Multivariable Cox regression was used to identify independent predictors of POLDE-free survival, cause-specific hazards for POLDEs, and cause-specific hazards for death.

4.1.4. Results

Among 611 patients with cirrhosis and HCC who underwent liver resection, 160 (26.2%) experienced at least 1 POLDE and 189 (30.9%) died within 2 years of surgery. Presence of

diabetes, hepatitis B cirrhosis etiology, major liver resection, and previous non-malignant decompensation were independent predictors of POLDE-free survival. The same risk factors were associated with POLDEs in cause-specific analysis, except for planned extent of liver resection. In contrast, only age and history of previous non-malignant decompensation were independent predictors of death.

4.1.5. Conclusions

In patients with cirrhosis undergoing resection for HCC, patient and disease-related factors are associated with POLDEs and POLDE-free survival. This information can be used to refine clinical practice and for the development of pre-operative prognostic tools, which may lead to improved outcomes in this population.

4.2. Introduction

Hepatocellular carcinoma (HCC) represents the majority of primary malignancies of the liver, ranking 6th with respect to global cancer incidence and becoming increasingly common in the North American population (1-3). The main risk factor for the development of HCC is liver cirrhosis, which represents end-stage hepatic fibrosis as a consequence of multiple chronic liver diseases, and is the precursor for liver-related malignant and non-malignant decompensation events (2, 4). As such, roughly 80-90% of patients with newly-diagnosed HCC have underlying cirrhosis (5).

Liver resection, or partial hepatectomy, represents one of the potentially-curative options for patients with HCC, with the other modalities including percutaneous radiofrequency or microwave ablation (RFA/MWA), and liver transplantation (LT) for those meeting criteria (6, 7). There are, however, several considerations when deciding which therapy to pursue, including the severity of underlying liver dysfunction, the location and burden of oncologic disease in the liver, and the overall performance status of a patient to be able to withstand such an operation. While patients with HCC who undergo surgery do benefit from higher survival, only 10-20% of patients are eligible for resection at the time of presentation (7). Optimal patient selection for potentially-curative hepatectomy is critical in order to maximize survival while avoiding major adverse events.

An important complication following liver resection is post-operative liver decompensation (8, 9), which is defined as a state of inadequate function of the remnant liver that can result in a broad spectrum of clinical presentations, including jaundice, ascites, coagulopathy, bleeding gastroesophageal varices, hepatorenal syndrome, hepatic encephalopathy/coma, and portal hypertension (10, 11). The overall incidence of such post-operative complications has decreased over time, however, estimation of accurate rates is challenging due to variability in the definition of post-operative liver decompensation events (POLDEs) in the literature (12, 13). To that end, the International Study Group of Liver Surgery (ISGLS) published a consensus definition and severity grading of post-hepatectomy liver failure in 2011, which is characterized as abnormally elevated international normalized ratio and concomitant serum hyperbilirubinemia, both occurring on or after the 5th post-operative day (14). Since this relies on bloodwork parameters only, it is unclear whether all patients who experience POLDEs can be truly captured by the ISGLS approach. Furthermore, patients who experience delayed complications following discharge from hospital are also at risk of being missed, as they may not have routine bloodwork following discharge.

The objective of this study was to identify clinically-relevant, pre-operative predictors of POLDEs and POLDE-free survival with a view to use this information in future research to develop prognostic tools to risk-stratify and guide surgical decision-making among patients with cirrhosis being considered for partial hepatectomy.

4.3. Methods

4.3.1. Study design & patient population

This was a retrospective cohort study performed using routinely-collected linked administrative health data from Ontario, Canada, held at ICES (ices.on.ca). All Ontario adult patients with prior cirrhosis and an incident HCC diagnosis between January 1, 2007 and December 1, 2017 who underwent partial hepatectomy formed the study cohort. The maximum follow-up time for all patients in the study was 2 years after their partial hepatectomy, with a study end date of December 31, 2019.

To generate the cohort, we first identified patients with prevalent cirrhosis dating back to 1991 using a previously published and validated diagnostic algorithm (sensitivity 99%, specificity 79%) (15). From this pre-existing cohort of patients with cirrhosis, we identified incident cases of hepatocellular carcinoma using a validated diagnostic algorithm which uses both International Classification of Diseases (ICD) codes and linkage to the Ontario Cancer Registry (OCR) using topography and morphology codes (sensitivity 96%, specificity 98%) (15). Lastly, we focused on the subset of patients who underwent liver resection within 6 months of HCC diagnosis using procedure codes in the Ontario Health Insurance Plan (OHIP) billing claims and the Canadian Institute for Health Information (CIHI) in-patient discharge abstracts (Appendix C, I). Patients were excluded from the study if they did not have a unique ICES identifier, were aged < 18 years, underwent liver transplant before HCC diagnosis and/or liver resection, were not OHIP eligible at least 2 years prior to HCC diagnosis, or received a diagnosis of HCC prior to a diagnosis of cirrhosis.

This study was approved by the Health Sciences Research Ethics Board at Queen's University (Appendix H). The study was designed, analyzed, and reported in accordance with the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) and TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statements (16, 17).

4.3.2. Data sources and study variables

The province of Ontario has a single-payer, universal healthcare framework that is financially supported through OHIP. The healthcare services provided by physicians are reflected by their billing claims to OHIP, which are considered highly accurate regardless of the physician's practice type or specialty (18). The CIHI Discharge Abstract Database (CIHI-DAD) contains details regarding hospital admissions, diagnoses, surgical procedures, and complications. For cohort creation, we used the OHIP claims database, the OCR and the CIHI-DAD to identify patients with cirrhosis and HCC, as well as those that underwent partial hepatectomy (Appendix C, I).

Patient demographics and vital statistics were obtained from the OHIP Registered Persons Database (RPDB) and the Office of the Registrar General Vital Statistics Database (ORGD), respectively. Socioeconomic status was described as an area-level variable using income quintiles. Comorbidity for each patient was described in 2 different ways, using the CIHI same day surgery (CIHI-SDS), CIHI-DAD, and OHIP databases. First, the Elixhauser comorbidity index was calculated for each patient using previously-published methods (19). The 2 years immediately preceding HCC diagnosis were used to screen for relevant diagnoses. Second, we used ICES-validated algorithms to identify the presence of specific comorbidities for each patient, which included: asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes, and hypertension (20-24). Viral serology results were obtained from Public Health Ontario laboratory data, and using previously published and validated algorithms, individual patients' cirrhosis etiology was defined as any one of: Hepatitis C (HCV), Hepatitis B (HBV), alcohol-related disease (ALD), non-alcoholic fatty liver disease (NAFLD), or other (25).

The type of surgical procedure for each patient was determined using OHIP billing codes and procedure codes from the CIHI National Ambulatory Care Reporting System (NACRS). For each patient, the type of liver resection was classified as minor (<3 segments), major (≥3 segments), or unknown based on these codes. Information regarding the receipt of LT was obtained from OHIP billing codes and the Canadian Organ Replacement Register (CORR), bloodwork results were obtained from the Ontario Laboratory Information System (OLIS), and emergency department visits were determined from the CIHI NACRS.

The primary outcome for this study was the occurrence of the first post-operative liver decompensation event, which included any one of: jaundice, ascites, bleeding gastroesophageal varices, portal hypertension, hepatorenal syndrome, hepatic coma/encephalopathy, or hepatic failure. These were identified using OHIP and CIHI-DAD codes on the basis of previously published and validated algorithms (15). The timeframe for assessing this outcome was within 2 years after liver resection. The secondary outcome was overall mortality within 2 years after liver resection.

Candidate predictors for analysis of the abovementioned outcomes were selected on the basis of previous literature, clinical relevance, and plausibility. These included: age, sex, diabetes history, cirrhosis etiology, extent of liver resection, and history of previous non-malignant decompensation.

All information abstracted from the databases was linked to individual patients using unique ICES identifiers for each patient, with analysis performed at ICES Queen's.

4.3.3. Statistical analyses

Continuous variables were assessed for normality of distribution both graphically, as well as with the Kolmogorov-Smirnov test of normality. Normally-distributed continuous variables were compared using the t-test, whereas non-normal variables were compared with the Mann-Whitney U test. No continuous variables were categorized for analysis. Proportions for categorical variables were compared using Chi square tests.

POLDE-free survival was modelled using Cox proportional hazards regression and unadjusted survival curves were generated using the Kaplan-Meier method. The occurrence of POLDE or mortality were classified as events for this analysis, and the time was measured from date of resection to the date of occurrence of the first event. Patients who underwent liver transplant after resection or completed 2 years of post-operative follow-up were censored. In total, the covariates used resulted in 9 degrees of freedom and provided an event-to-predictor variable ratio of 17.7 for the analysis. All the candidate predictors were tested for univariate significance and all were included in the final multivariable regression model.

To account for competing risks, cause-specific hazards were also modelled using Cox regression, while sub-distribution hazards were modelled using Fine and Gray's method for competing risks (26, 27). For these analyses, only POLDEs were considered as events, whereas deaths were classified as competing events. The candidate predictors were handled in the same manner as previously described.

As per ICES policy, cells with counts <6 were suppressed and instead, reported as ranges to avoid risk of patient reidentification. All statistical tests were considered significant if p<0.05.

All analyses were performed using SAS™ Enterprise Guide software version 7.1 (SAS institute, Cary, NC).

4.3.4. Missing data

Any missing or unknown data for a variable is indicated in each descriptive table in the results. The only variable with missing data included in the regression analysis was the extent of liver resection, which had 21 unknown observations. These were classified as minor resections for all analyses. A separate sensitivity analysis was carried out with these observations classified as major resections (Appendix D). Due to the high proportion of missing bloodwork results in OLIS, bloodwork variables were summarized but not included in any analyses (Appendix G).

4.4. Results

4.4.1. Patient demographics

We identified 181,459 patients with prevalent cirrhosis, of which 9,731 were diagnosed with HCC between 2007-2017. After applying relevant exclusions, a total of 8,707 patients with incident HCC remained, of which 611 (7.0%) patients who underwent partial hepatectomy formed the final cohort. Patient selection and exclusion criteria are outlined in figure 1.

We first examined the baseline characteristics of all patients diagnosed with HCC (table 1). Compared to unresected individuals with HCC, those who received a liver resection tended to be younger (mean age: 64.1 years vs. 62.8 years, $p=0.01$), were of higher socioeconomic status (lowest income quintile: 25.2% vs. 20.5%, $p<0.0001$), had fewer comorbidities (Elixhauser comorbidity index >3: 26.0% vs. 8.2%, $p<0.0001$), comprised different cirrhosis etiology (Hepatitis B: 9.8% vs. 26.8%, $p<0.0001$), and far fewer had a history of non-malignant liver decompensation prior to their HCC diagnosis (40.3% vs. 10.0%, $p<0.0001$).

4.4.2. Perioperative events & post-operative outcomes

We then examined relevant peri-operative events and post-operative outcomes (table 2). Following HCC diagnosis, the average time to resection was 59.3 days (median: 50 days). Among the 611 resections, 360 (58.9%) were carried out at liver transplant centres and 335 (54.8%) patients underwent major resections. The average length of stay in hospital after surgery was 10.9 days (median: 7 days), while readmission rates were 1.1% (69 patients) at 30 days and 19.3% (118 patients) at 90 days.

Focusing on liver-specific outcomes, a total of 160 (26.2%) resected patients experienced at least 1 post-operative liver decompensation event within 2 years after surgery, the most common being ascites requiring percutaneous drainage (71.3%). The median time from resection to POLDE was 63.5 days, with 60 (37.5%) occurring within the first 30 days. Lastly, overall mortality among resected patients at the end of 2-year follow-up was 30.9% (189 patients).

4.4.3. Preliminary analysis of post-operative liver decompensation events

Table 3 presents the distribution of our candidate predictors and other descriptors, comparing patients who went on to develop POLDEs to those who did not. Among pre-operative characteristics, we did not find any significant differences in age or sex between the two groups. However, a greater proportion of patients with post-operative decompensation events had diabetes (33.9% vs. 44.4%, $p=0.02$), hypertension (54.3% vs. 65.6%, $p=0.01$), and a history of previous non-malignant decompensation (8.2% vs. 15.0%, $p=0.01$). Interestingly, patients with POLDEs did not significantly differ in the extent of liver resection they had received, but did have a larger percentage with hepatitis C or alcohol use as the etiology for their cirrhosis (hepatitis C: 18.4% vs. 23.8%, alcohol: 9.8% vs. 19.4%, $p<0.0001$).

Patients who experienced POLDEs were more likely to have had their resection at a non-transplant centre (37.7% vs. 50.6%, p=0.004). Patients with POLDEs also had significantly higher post-resection lengths of stay in hospital (mean: 9.3 days vs. 15.4 days, p<0.0001), more readmissions to hospital after discharge (5.3% vs. 28.1% at 30 days, p<0.0001), more emergency department visits after discharge (mean: 1.8 vs. 3.2, p<0.0001), and higher mortality at 2 years (23.9% vs. 50.6%, p<0.0001). There was no significant difference in post-operative liver transplantation rates between the groups.

4.4.4. POLDE-free survival

The occurrence of a POLDE or death was examined as a composite outcome using survival curves, as well as a Cox proportional hazards model to determine pre-operative predictors of POLDE-free survival following liver resection (figure 2 & table 4). In total, 265 (43.4%) resected patients experienced either a decompensation event or died within 2 years from their surgery. Among the candidate predictors, age, presence of diabetes, cirrhosis etiology, and history of previous non-malignant decompensation were significant on univariate analysis. After multivariable regression, where all candidate predictors were kept in the model, the independent predictors of inferior POLDE-free survival were diabetes (HR: 1.34 [1.03–1.74], p=0.03), major liver resection (HR: 1.42 [1.10–1.84], p=0.007), and history of previous non-malignant decompensation (HR: 2.09 [1.46–3.00], p<0.0001).

4.4.5. Cause-specific hazards for POLDEs and death

Because the outcome of POLDE-free survival included patients that died before decompensation or the end of the study, we also determined cause-specific hazards for POLDEs and death separately to see if the pre-operative predictors differed for these outcomes (table 5). Among the resected patients, 159 (26.0%) experienced POLDEs and 106 (17.3%) died within 2 years after surgery. Following multivariable regression, the independent cause-specific predictors of POLDEs were presence of diabetes (HR: 1.47 [1.06–2.06], p=0.02) and history of previous non-malignant decompensation (HR: 1.64 [1.04–2.58], p=0.03). Interestingly, HBV cirrhosis etiology was protective for POLDE (HR: 0.41 [0.25–0.69], p=0.001). In comparison, the independent cause-specific predictors of death were age (HR: 1.04 [1.00–1.04], p=0.02) and a history of previous non-malignant decompensation (HR: 2.04 [1.15–3.63], p=0.02).

4.4.6. Effect of institution transplant status

Since POLDE rates differed significantly between in patients treated at a transplant institution compared to the rest, we explored institution transplant status as an additional covariate in the multivariable models for POLDE-free survival and cause-specific hazards. This revealed that undergoing liver resection at a liver transplant centre had beneficial associations with POLDE-free survival (HR: 0.75 [0.58–0.96], p=0.02) and POLDEs (cause-specific HR: 0.62 [0.45–0.86], p=0.004), but no significant association with death (cause-specific HR: 0.99 [0.66–1.48], p=0.95). On this basis, we performed a stratified analysis to assess for the presence of effect modification of our candidate predictors by institution transplant status (table S3).

The independent predictors of POLDE-free survival were largely the same, although presence of diabetes lost significance in the non-transplant centres (HR: 1.36 [0.91–2.04], p=0.13). An intriguing exception we observed was the opposite, non-significant effect for the association between ALD cirrhosis and POLDE-free survival (non-transplant centre HR: 1.58 [0.83–3.00], p=0.16; transplant centre HR: 0.79 [0.43–1.47], p=0.46. When institution transplant status was included as an interaction term with cirrhosis etiology in the multivariable model, there was a significant interaction noted with ALD cirrhosis was (p=0.03), but not with the cirrhosis etiology variable overall (p=0.10).

Applying the same stratification by institution to cause-specific hazards (table S5), we saw that presence of diabetes (HR: 1.84 [1.12–3.02], p=0.02) and HBV cirrhosis etiology (HR: 0.24 [0.08–0.76], p=0.001) remained independent cause-specific predictors of POLDEs in non-transplant centres, while a history of previous decompensation was no longer significant (HR: 1.57 [0.77–3.22], p=0.22). Now, major liver resection was found to be a predictor of decompensation in non-transplant institutions (HR: 1.62 [1.02–2.59], p=0.04). In liver transplant centres, the independent cause-specific predictors of post-operative liver decompensation events were HBV cirrhosis etiology (HR: 0.48 [0.27–0.87], p=0.02) and history of previous decompensation (HR: 2.00 [1.08–3.72], p=0.03). The only independent predictor of death was major liver resection performed in liver transplant centres (HR: 1.84 [1.04–3.23], p=0.04). When added to the cause-specific model for POLDE, institution transplant status had a statistically significant interaction with cirrhosis etiology as a group (p=0.004) and with ALD cirrhosis specifically (p=0.001). In the cause-specific model for death, no significant interaction between institution transplant status and cirrhosis etiology as a group was noted (p=0.86).

4.4.7. Competing risks for POLDE

Lastly, we determined the sub-distribution hazards for candidate predictors of post-operative decompensation by utilizing Fine and Gray’s method to account for POLDEs and death as competing events (table S6). With this analysis, similar to the cause-specific hazards, the independent risk factors for POLDEs were presence of diabetes (HR: 1.47 [1.05–2.07], p=0.03) and history of previous non-malignant decompensation (HR: 1.64 [1.02–2.64], p=0.04). Again, HBV cirrhosis etiology was found to have an inverse association with post-operative decompensation (HR: 0.41 [0.24–0.70], p=0.001).

4.5. Discussion

Among patients with cirrhosis and HCC, the pre-operative determination of liver decompensation risk following partial hepatectomy is crucial, as a potentially-curative resection may be compromised by potentially-lethal liver-related complications (28, 29). While many studies have focused on post-hepatectomy liver failure, their outcomes and analyses tend to rely on abnormal bloodwork parameters measured in the early post-operative period (13). In contrast, we have presented a contemporary analysis of post-operative liver decompensation events occurring up to 2 years following liver resection in patients with cirrhosis and HCC. We found that 160 (26.2%) patients from our cohort experienced a POLDE after partial hepatectomy. These included 114 (71.3%) patients with ascites requiring percutaneous drainage, 21 (13.1%) with bleeding gastroesophageal varices requiring intervention, and 25 (15.6%) with any one of jaundice, hepatic failure, hepatic encephalopathy, and hepatorenal syndrome. Our definition of POLDEs captures a broader range of clinically-significant liver-related complications, relying on routinely-collected administrative health data instead of specific bloodwork or imaging parameters. As such, this represents a novel and encompassing approach to the description of post-operative liver decompensation in the surgical literature, with the potential to further refine patient selection for surgery.

Presence of diabetes was found to be an independent predictor of inferior POLDE-free survival (HR: 1.34 [1.03–1.74], p=0.03). Deconstruction of this relationship by cause-specific hazards showed it was driven by POLDEs (cause-specific HR: 1.47 [1.06–2.06], p=0.02) as opposed to mortality (cause-specific HR: 1.03 [0.66–1.55], p=0.9). Diabetes is known to increase the general risk of perioperative morbidity and mortality, and some studies have demonstrated an association with post-hepatectomy liver failure (13). Among patients with cirrhosis, diabetes is linked to progression of hepatic dysfunction and decreased survival (30, 31). Our findings confirm this relationship with adverse liver-related outcomes following partial hepatectomy. Importantly, not only is the presence of diabetes a potential predictor in future prognostic models, it also represents a modifiable patient factor where improved pre-operative glycemic control may result in decreased risk of post-operative liver decompensation.

The relationship between underlying cirrhosis etiology and adverse liver-related events following resection is not well-characterized in the literature. In unadjusted analyses using HCV as the reference group, patients with HBV cirrhosis appeared to have better POLDE-free survival, while those with ALD and other causes of cirrhosis (i.e. hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis) did worse. Upon multivariable regression, we found that HBV cirrhosis etiology had a non-significant protective association with POLDE-free survival (HR: 0.73[0.50–1.07], p=0.11), but a clear protective association with POLDEs (cause-specific HR: 0.41[0.25–0.69], p=0.001). We know that HCC can develop in patients with HBV infection without significant inflammation or hepatic dysfunction, due to direct DNA damage within hepatocytes (32). Thus, patients with HBV-related cirrhosis may present with less severe liver dysfunction. In contrast, some forms of HCV are associated with hepatic steatosis, leading to increased fibrosis and inflammation of the liver, thereby decreasing its functional and regenerative capacity (33-35). Among the remaining causes of cirrhosis, none were shown to have a clear relationship with POLDE-free survival, POLDEs, or mortality on adjusted analyses.

For the other candidate predictors, major extent of liver resection and a previous history of non-malignant decompensation were both associated with inferior POLDE-free survival (HR: 1.42[1.10–1.84], p=0.007 and HR: 2.09[1.46–3.00], p<0.0001). The latter was also associated with POLDEs (cause-specific HR: 1.64[1.04–2.58], p=0.03) and death (cause-specific HR:

2.04[1.15–3.63], p=0.02). Predictably, age was associated with a slightly increased risk of death as well (cause-specific HR: 1.02[1.00–1.04], p=0.02). These findings are not surprising as major liver resection and a history of previous decompensation both reflect situations of decreased hepatic reserve, while increasing age confers a greater risk of dying from any cause. Given these observations, stricter patient selection regarding previous decompensation history, along with a lower threshold to pursue liver transplantation over resection may be considered during pre-operative decision-making.

The role of institution transplant status was explored, first as a main effect, where undergoing resection at a liver transplant centre was associated with increased POLDE-free survival (HR: 0.75 [0.58–0.96], p=0.02) and a decreased cause-specific hazard of POLDEs (cause-specific HR: 0.62 [0.45–0.86], p=0.004). Given these relationships, we conducted stratified analyses to determine if predictor findings differed between the two institution types. Although more resections were carried out at liver transplant centres (n=251 vs. n=360), the incidence of POLDEs was significantly higher in non-transplant centres (32.3% vs. 21.9%, p=0.004). On adjusted analyses, there was no clear effect modification of most predictors as they retained similar associations with POLDE-free survival in both non-transplant and transplant institutions (diabetes presence: 1.36 [0.91–2.04] vs. 1.44 [1.01–2.04]; extent of liver resection: 1.46 [1.00–2.14] vs. 1.51 [1.06–2.16]; history of previous non-malignant decompensation: 1.92 [1.09–3.39] vs. 2.44 [1.51–3.94]). The lack of statistical significance for the former 2 predictors in non-transplant institutions is likely the result of a loss in power from smaller sample size. Similar results were also seen for the cause-specific hazards of POLDEs, where effect estimates of the abovementioned predictors were again comparable, though not always statistically significant.

Interestingly, the only predictor that showed potential for effect modification by institution transplant status was cirrhosis etiology, specifically among patients with ALD cirrhosis. We noted opposite associations for POLDE-free survival (1.58 [0.83–3.00], p=0.16 vs. 0.79 [0.43–1.47], p=0.46) and cause-specific hazards for POLDEs (1.75 [0.86–3.55], p=0.12 vs. 0.54 [0.24–1.24], p=0.15) in non-transplant and liver transplant institutions respectively. While these relationships were not statistically significant, the possibility of effect modification by institution transplant status may be a consequence of referral bias and potentially-modifiable factors. Some studies have explored outcomes in patients with cirrhosis by institution transplant status, however, these compared critically-ill, non-surgical patients (36). A recent population-level study of patients with autoimmune hepatitis demonstrated differential access to sub-specialty hepatology by institution transplant status (37). Patients in that study also experienced a wider range of treatment options and novel therapies in liver transplant centres. Whether such institutional differences existed in our work is unknown, but they should be characterized as patients with alcoholic cirrhosis have specific perioperative considerations and benefit from pre-operative optimization (38). It is possible that these differences arose from differential referral of patients to transplant vs. non-transplant centres among individuals with ALD cirrhosis. Nonetheless, understanding institutional differences driving disparate patient outcomes represents an important direction for future research.

Our study is unique in the use of an encompassing definition and lengthier timeframe of post-operative liver decompensation events to report population-level outcomes and predictors in a cohort of patients with cirrhosis and HCC. The analysis of POLDE-free survival represents a novel approach in the surgical literature, as decompensation-free survival has only been reported in a handful of non-surgical studies thus far (39, 40). We utilized a large, multi-centric cohort of

611 patients, thereby minimizing selection bias from geographic and institutional factors. Lastly, we took particular care to avoid the pitfalls of insufficient power and model overfitting by ensuring an adequate event-to-predictor variable ratio and appropriate handling of candidate predictor variables as per published guidelines (17, 41).

Limitations of our work arise predominantly due to the nature of linked, routinely-collected administrative health data. We were unable to ascertain disease burden for each patient, including tumour characteristics such as size, multifocality, or location within the liver. Their relationships with outcomes was not directly evaluated, though some aspects are captured within the extent of resection variable. Examining the role of cirrhosis severity in predicting outcomes was also not possible. A high proportion of missing bloodwork data (39.4%) resulted in exclusion of potentially important predictors from the analyses, such as the model for end-stage liver disease (MELD) score (Appendix G). Lastly, our data is also susceptible to miscoding of diagnostic and procedure codes, which were used to assign exposure and outcome status. This is expected to be non-differential misclassification as it would affect all patients in the cohort, leading to more conservative effect estimates.

In conclusion, we have identified independent predictors of POLDE-free survival and POLDEs following partial hepatectomy for HCC in patients with cirrhosis. Factors such as diabetes and alcoholic-cirrhosis etiology may be amenable to pre-operative optimization, while those such as age, HBV cirrhosis etiology, and history of previous decompensation may provide basis for stricter patient selection for resection. Ultimately, these risk factors can be used to develop a multivariable prognostic model for post-operative liver decompensation in this patient population in order to refine surgical decision-making.

4.6. References

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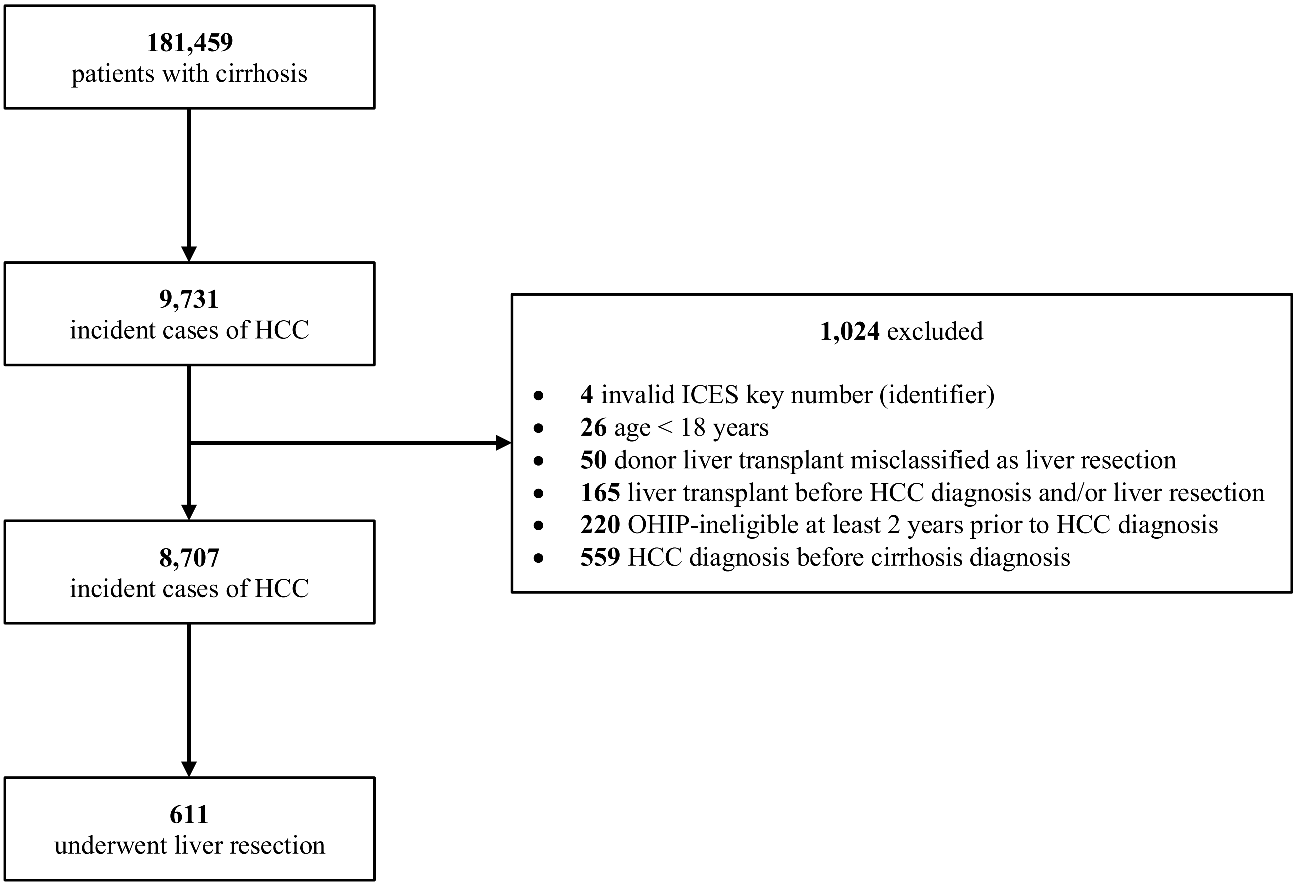
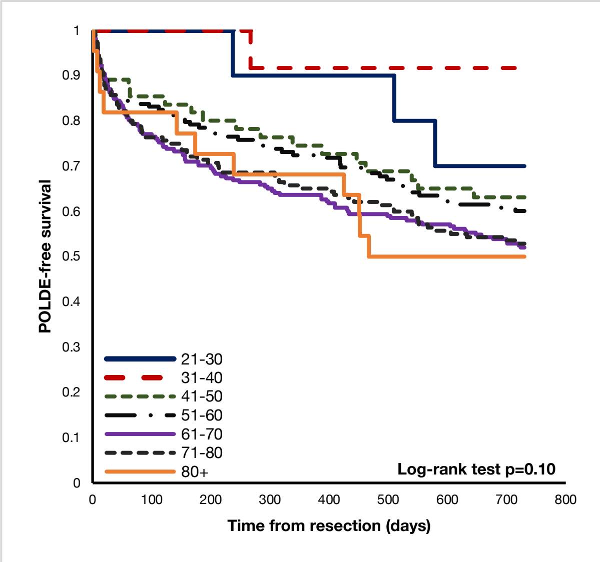
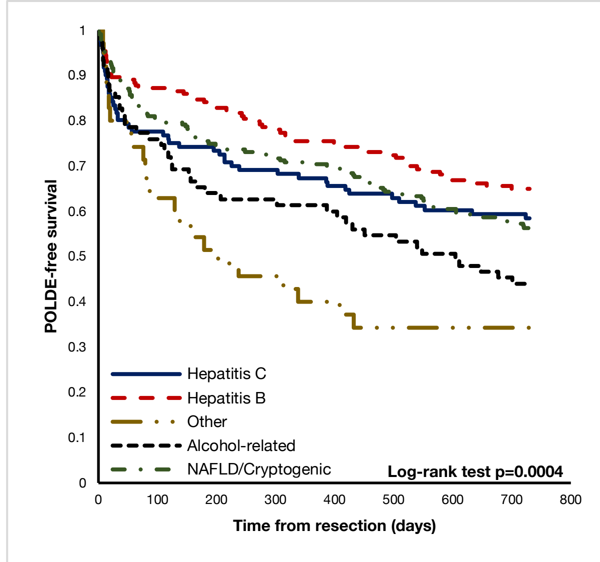
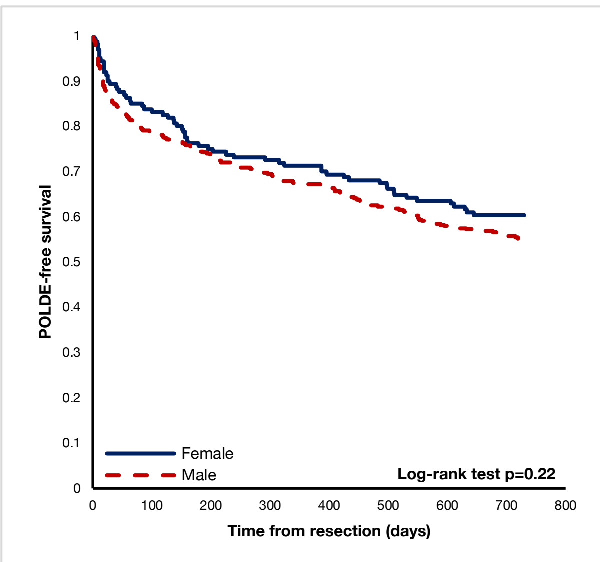
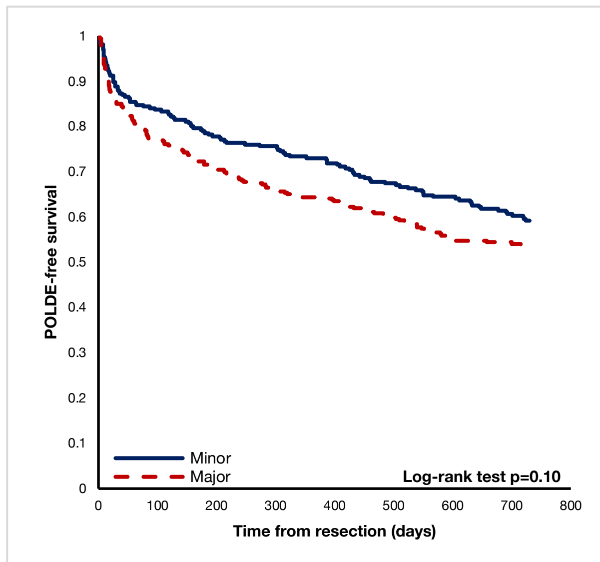


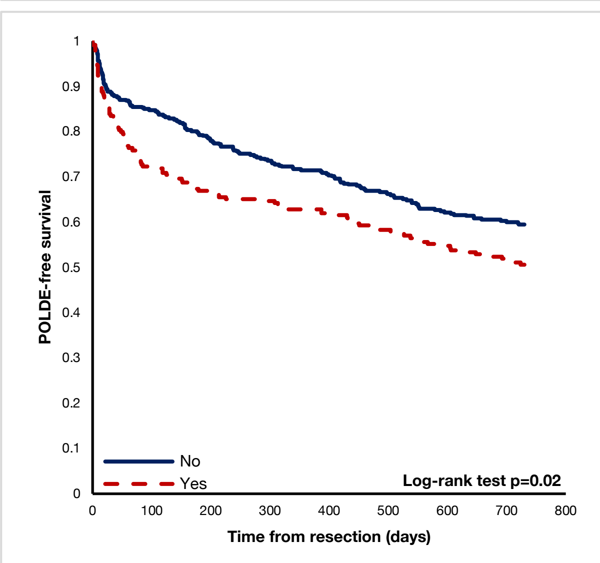
Figure 1. Flow diagram of patient selection for inclusion in study.
HCC: hepatocellular carcinoma, OHIP: Ontario health insurance plan.


POLDE-free survival
Time from resection (days)
21-30
31-40
41-50
51-60
61-70
71-80
80+
Log-rank test p=0.10


POLDE-free survival
Time from resection (days)
Hepatitis C
Hepatitis B
Other
Alcohol-related
NAFLD/Cryptogenic
Log-rank test p=0.0004


POLDE-free survival
Time from resection (days)
Female
Male
Log-rank test p=0.22


POLDE-free survival
Time from resection (days)
Minor
Major
Log-rank test p=0.10


POLDE-free survival
Time from resection (days)
No
Yes
Log-rank test p=0.02

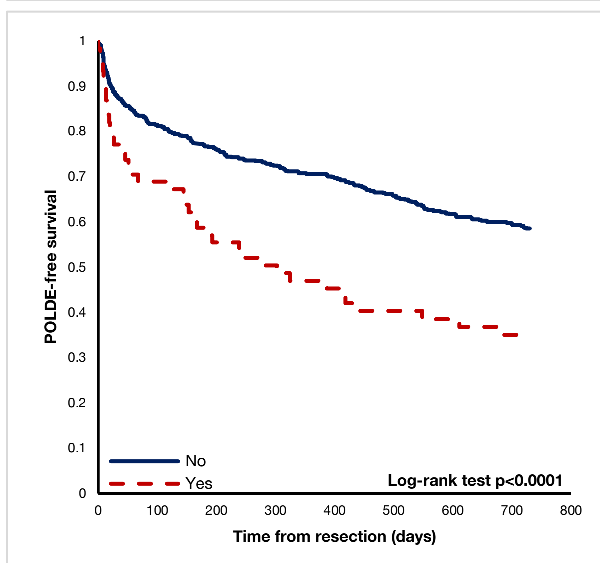

POLDE-free survival
Time from resection (days)
No
Yes
Log-rank test p<0.0001

Figure 2. Unadjusted survival curves of POLDE-free survival within 2 years after liver resection, stratified by candidate predictors: age (by decade; left-upper), sex (left-middle), presence of diabetes (left-lower), cirrhosis etiology (right-upper), extent of liver resection (right-middle), previous non-malignant decompensation history (right-lower).

Table 1. Characteristics of patients diagnosed with hepatocellular carcinoma in Ontario (2007-2017).

	All patients (n=8707) Value (%)	Unresected (n=8096) Value (%)	Resected (n=611) Value (%)	p-value
Age				
Mean / SD	64.0 / 12.5	64.1 / 12.6	62.8 / 11.4	0.01
Median / IQR	64.0 / 17.0	64.0 / 17.0	63.0 / 15.0	
Sex				
Male	6361 (73.1)	5910 (73.0)	451 (73.8)	0.66
Female	2346 (26.9)	2186 (27.0)	160 (26.2)	
Income quintile				
1	2167 (24.9)	2042 (25.2)	125 (20.5)	<0.0001
2	1960 (22.5)	1829 (22.6)	131 (21.4)	
3	1730 (19.9)	1603 (19.8)	127 (20.8)	
4	1477 (17.0)	1364 (16.8)	113 (18.5)	
5	1339 (15.4)	1228 (15.2)	111 (18.2)	
Missing / Unknown	34 (0.4)	30 (0.4)	4 (0.7)	
Elixhauser comorbidity index				
0-3	2999 (34.4)	2812 (34.7)	187 (30.6)	<0.0001
4-6	1727 (19.8)	1685 (20.8)	42 (6.9)	
7+	430 (4.9)	422 (5.2)	8 (1.3)	
No hospitalization data*	3551 (40.8)	3177 (39.2)	374 (61.2)	
Specific comorbidities				
Asthma	1166 (13.4)	1087 (13.4)	79 (12.9)	0.73
CHF	942 (10.8)	913 (11.3)	29 (4.7)	<0.0001
COPD	2146 (24.6)	2043 (25.2)	103 (16.9)	<0.0001
Diabetes	3639 (41.8)	3415 (42.2)	224 (36.7)	0.01
Hypertension	5087 (58.4)	4737 (58.5)	350 (57.3)	0.55
Cirrhosis etiology				
Hepatitis B	2262 (26.0)	790 (9.8)	164 (26.8)	<0.0001
Hepatitis C	954 (11.0)	2141 (26.4)	121 (19.8)	
Alcohol	1916 (22.0)	1841 (22.7)	75 (12.3)	
NAFLD / Cryptogenic	2917 (33.5)	2701 (33.4)	216 (35.4)	
Other	658 (7.6)	623 (7.7)	35 (5.7)	
History of non-malignant decompensation				
Yes	3327 (38.2)	3266 (40.3)	61 (10.0)	<0.0001
No	5380 (61.8)	4830 (59.7)	550 (90.0)	

SD: standard deviation, IQR: interquartile range, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, NAFLD: non-alcoholic fatty liver disease, HCC: hepatocellular carcinoma.
*within 2 years preceding HCC diagnosis.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.

Table 2. Perioperative events and post-operative outcomes following partial hepatectomy (n=611 resected patients).

	Value (%)
Time from HCC diagnosis to liver resection (days)	
Mean / SD	59.3 / 48.0
Median / IQR	50.0 / 72.0
Extent of liver resection	
Major	335 (54.8)
Minor	255 (41.7)
Unknown	21 (3.4)
Institution of liver resection	
Liver transplant centre	360 (58.9)
Non-transplant centre	251 (41.1)
Length of stay (days)	
Mean / SD	10.9 / 12.7
Median / IQR	7.0 / 6.0
Missing / Unknown	8 (1.3)
Readmission to hospital	
30-day	69 (1.1)
90-day	118 (19.3)
Post-operative liver transplant	
Yes	17 (2.8)
No	594 (97.2)
POLDE (n=160)	
Ascites	114 (71.3)
Bleeding gastroesophageal varices	21 (13.1)
Other*	25 (15.6)
Post-operative mortality	
30-day	26 (4.3)
90-day	55 (9.0)
2-year	189 (30.9)

HCC: hepatocellular carcinoma, SD: standard deviation, IQR: interquartile range, POLDE: post-operative liver decompensation event.
*Other POLDE includes: Jaundice, hepatic failure, hepatic encephalopathy, hepatorenal syndrome.

Table 3. Patient descriptors, candidate predictors of POLDE, and surgical outcomes in resected patients stratified by POLDE status (n=611 resected patients).

	POLDE – **(n=451)** Value (%)	**POLDE+** **(n=160)** Value (%)	**p-value**
Age			
Mean / SD	62.5 / 11.9	63.5 / 9.8	0.36
Median / IQR	63.0 / 16.0	64.0 / 13.5	
Sex			
Male	328 (72.7)	123 (76.9)	0.31
Female	123 (27.3)	37 (23.1)	
Specific comorbidities			
Asthma	59 (13.1)	20 (12.5)	0.85
CHF	17 (3.8)	12 (7.5)	0.06
COPD	72 (16.0)	31 (19.4)	0.32
Diabetes	153 (33.9)	71 (44.4)	0.02
Hypertension	245 (54.3)	105 (65.6)	0.01
Cirrhosis etiology			
Hepatitis B	139 (30.8)	25 (15.6)	<0.0001
Hepatitis C	83 (18.4)	38 (23.8)	
Alcohol	44 (9.8)	31 (19.4)	
NAFLD / Cryptogenic	164 (36.3)	52 (32.5)	
Other	21 (4.7)	14 (8.8)	
History of non-malignant decompensation			
Yes	37 (8.2)	24 (15.0)	0.01
No	414 (91.8)	136 (85.0)	
Perioperative events and post-operative outcomes			
Time from HCC diagnosis to liver resection (days)			
Mean / SD	59.0 / 48.2	60.2 / 47.5	0.72
Median / IQR	50.0 / 74.0	50.5 / 74.0	
Extent of liver resection			
Major	248 (55.0)	87 (54.4)	0.97
Minor	188 (41.7)	67 (41.9)	
Unknown	15 (3.3)	6 (3.8)	
Institution of liver resection			
Liver transplant centre	281 (62.3)	79 (49.4)	0.004
Non-transplant centre	170 (37.7)	81 (50.6)	
Length of stay (days)			
Mean / SD	9.3 / 10.5	15.4 / 16.7	<0.0001
Median / IQR	6.0 / 4.0	9.0 / 12.0	
Missing / Unknown	6 (1.3)	2 (1.3)	
Readmission to hospital			
30-day	24 (5.3)	45 (28.1)	<0.0001
90-day	54 (12.0)	64 (40.0)	<0.0001
Number of ED visits after discharge			
Mean / SD	1.8 / 2.9	3.2 / 3.5	<0.0001
Median / IQR	1.0 / 2.0	2.0 / 4.0	
Number of hospitalizations after discharge			
Mean / SD	1.0 / 1.4	2.0 / 2.2	<0.0001
Median / IQR	0.0 / 1.0	1.0 / 3.0	
Post-operative liver transplant*			
Yes	10–14 (2.2–3.1)	<6 (<3.8)	0.78
No	437–441 (97.0–97.8)	153–157 (95.6–98.1)	

Post-operative mortality*			
30-day	19–23 (4.2–5.1)	<6 (<3.8)	0.50
90-day	32 (7.1)	23 (14.4)	0.006
2-year	108 (23.9)	81 (50.6)	<0.0001

SD: standard deviation, IQR: interquartile range, POLDEs: post-operative liver decompensation event, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, NAFLD: non-alcoholic fatty liver disease, HCC: hepatocellular carcinoma, ED: emergency department.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Ranges reported to in order to suppress counts <6 as per ICES small-cell policy.

Table 4. Univariate and multivariable Cox regression of candidate predictors of POLDE-free survival (n=611 resected patients).

	Univariate regression			Multivariable regression		
	HR	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**
Age (per year)	1.01	1.003–1.03	0.01	1.01	1.00–1.02	0.11
Sex						
Female	Reference			Reference		
Male	1.19	0.90–1.58	0.22	1.21	0.90–1.62	0.21
Diabetes						
No	Reference			Reference		
Yes	1.35	1.06–1.73	0.02	1.34	1.03–1.74	0.03
Cirrhosis etiology			0.001[a]			0.02[a]
Hepatitis C	Reference			Reference		
Hepatitis B	0.76	0.52–1.11	0.15	0.73	0.50–1.07	0.11
Alcohol-related	1.43	0.95–2.16	0.09	1.18	0.77–1.80	0.44
NAFLD or Cryptogenic	1.00	0.71–1.41	1.00	0.95	0.66–1.36	0.76
Other	1.97	1.21–3.26	0.007	1.64	0.99–2.73	0.06
Extent of liver resection						
Minor*	Reference			Reference		
Major	1.22	0.96–1.56	0.20	1.42	1.10–1.84	0.007
History of previous non-malignant decompensation						
No	Reference			Reference		
Yes	2.0	1.42–2.81	<0.0001	2.09	1.46–3.00	<0.0001

PODLE: post-operative liver decompensation event, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.
[a]: indicates p-value for type 3 test.

Table 5. Multivariable cause-specific hazards of candidate predictors of POLDE and death (n=611 resected patients).

	POLDE (n=159)			Death (n=106)		
	HR	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**
Age (per year)	1.00	0.98–1.01	0.80	1.02	1.00–1.04	0.02
Sex						
Female	Reference			Reference		
Male	1.18	0.81–1.73	0.39	1.21	0.76–1.90	0.42
Diabetes						
No	Reference			Reference		
Yes	1.47	1.06–2.06	0.02	1.03	0.66–1.55	0.90
Cirrhosis etiology			0.001[a]			0.53[a]
Hepatitis C	Reference			Reference		
Hepatitis B	0.41	0.25–0.69	0.001	1.56	0.80–3.10	0.19
Alcohol-related	1.18	0.72–1.93	0.51	1.42	0.62–3.26	0.41
NAFLD or Cryptogenic	0.66	0.43–1.03	0.07	1.62	0.83–3.14	0.15
Other	1.12	0.59–2.11	0.73	2.14	0.87–5.24	0.10
Extent of liver resection						
Minor*	Reference			Reference		
Major	1.25	0.90–1.74	0.19	1.51	1.00–2.29	0.05
History of previous non-malignant decompensation						
No	Reference			Reference		
Yes	1.64	1.04–2.58	0.03	2.04	1.15–3.63	0.02

POLDE: post-operative liver decompensation event, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.
[a]: indicates p-value for type 3 test.

CHAPTER 5

GENERAL DISCUSSION

5.1. Key findings

The overall aim of this thesis was to explore how prognostication of adverse post-operative outcomes is performed for patients undergoing liver resection. Specifically, we were interested in individuals with underlying cirrhosis and incident HCC, as they may experience liver decompensation events either as a consequence of aggressive resection or due to progression of underlying liver dysfunction. In this subset of patients with HCC, it is crucial to accurately estimate the benefits of potentially-curative resection with the risks of adverse liver-related complications, as the latter can dramatically impair quality of life and decrease survival independent of cancer prognosis.

We first searched the published literature for currently available clinical prognostication tools of POLDEs following hepatic resection. A systematic review of the multivariable prognostic modelling literature yielded 36 studies for analysis; 25 developed novel prognostication tools, 3 developed and externally validated them, and 8 externally validated pre-existing models. We abstracted study details and critically appraised each study's methodology and statistical analyses. Common pre-operative predictors were serum bilirubin, platelet count, and $ICGR_{15}$; each were used in 4 different models. All studies were assessed as having a high risk of bias due to analytic and design concerns. Contributing factors were their selection and handling of candidate predictor variables, low event-to-predictor variable ratios, missing patient follow-up details, and lack of internal validation. Applicability of prognostic models was also a concern due to heterogeneous outcome definitions and pre-dominantly Eastern cohorts used for model development. Together, these findings suggest that currently available multivariable prognostic models for POLDEs may not be valid or broadly applicable for clinical use.

To better understand the predictors of post-operative liver decompensation following resection, we then conducted a population-based retrospective cohort study of patients in the province of Ontario. Specifically, we examined patients with underlying cirrhosis who then developed HCC between 2007-2017 and underwent liver resection. In this cohort of 611 patients, 160 (26.2%) experienced at least one POLDE within 2 years following hepatic resection, with 60 (37.5%) occurring within 30 days of surgery. On adjusted analyses, independent predictors of inferior POLDE-free survival were presence of diabetes (HR: 1.34 [1.03–1.74]), major liver resection (HR: 1.42 [1.10–1.84]), and history of previous decompensation (HR: 2.09 [1.46–3.00]). Cause-specific predictors of POLDEs were presence of diabetes (HR: 1.47 [1.06–2.06]), HBV cirrhosis etiology (0.41 [0.25–0.69]), and history of previous decompensation (1.64 [1.04–2.58]). These factors, along with those identified in our systematic review, can be used to inform pre-operative patient selection prior to partial hepatectomy.

5.2. Strengths

No previous work has critically appraised published prognostic modelling studies of adverse post-operative outcomes following liver resection. Therefore, this thesis provides the first insight into the validity and applicability of such models for current clinical practice. In addition, we utilized a comprehensive and validated search strategy across several databases to identify studies for screening, without time or language restrictions. We followed a structured approach to the abstraction of key study details and to qualitatively assess each study for risk of bias, based on the CHARMS checklist and the PROBAST tool.

Our population-based analyses of POLDE-free survival and cause-specific hazards of POLDEs represent novel analytic approaches in the surgical literature. Such outcomes have only previously been studied using narrow definitions of post-hepatectomy liver failure. Furthermore, utilization of patient data from across the province of Ontario mitigated the biases from geographic and institutional factors typically seen in single-centre studies. Lastly, we focused on key patient and disease-level candidate predictors not previously described in this clinical context.

5.3. Limitations

We were unable to perform a meta-analysis of results from the systematic review due to the heterogeneity of patients, surgical indications, and outcomes across included studies. The commonly-used predictors identified in the systematic review were not studied at the population level due to the high proportion of missing bloodwork data from administrative datasets. Other important limitations included the lack of cirrhosis severity data for patients within the resected cohort, as well as potential for misclassification of diagnostic codes used to assign exposure and outcome status.

5.4. Impact and future research

Appropriate and informed clinical decision-making for patients with HCC is crucial to achieving the best possible outcomes for individuals with this disease. Due to underlying cirrhosis and the limited availability of liver transplantation, patients with resectable disease can be provided a unique opportunity for cure, although this must be weighed against the risk of worsening their liver dysfunction with invasive surgery. This thesis provides an important analysis of prognostic research in the field of liver surgery, specifically as it relates to predicting the risk of post-operative liver decompensation. Through the systematic review and critical appraisal, we have shown that currently available prognostic models for post-operative liver decompensation following liver resection are not valid for routine clinical use and also suffer from lack of generalizability. Thus, there is still a need for well-developed prognostic models to assist with pre-operative decision-making in this clinical context. The second portion of this thesis provides the foundation for prognostic model development, by identifying key predictors of POLDEs following liver resection among patients with cirrhosis and HCC.

There are several important avenues for future research arising from this work. First, the predictors identified herein can be utilized in a future study to develop prognostic models for POLDEs. Following model development, validation studies across multiple clinical settings (i.e. geographic and temporal) should also be pursued. To determine whether clinical outcomes actually improve with the use of such prognostic models, impact assessment studies may compare patient outcomes between routine clinical practice and clinical practice aided by these tools. Lastly, exploring differences in patient outcomes between transplant and non-transplant institutions represents an important health services research question, aimed at highlighting and understanding any disparities in the provision of health care.

Appendix A. Complete systematic review search strategy

Embase Classic+Embase (1947 to Present)

1 liver resection/
2 hemihepatectomy/
3 liver lobectomy/
4 partial hepatectomy/
5 ((liver or hepatic) adj3 (resection or lobectomy)).mp.
6 hepatectom*.mp.
7 hemihepatectom*.mp.
8 or/1-7
9 predict*.ti.
10 rule*.af.
11 validat*.af.
12 prediction/
13 predictive value/
14 predictive validity/
15 "prediction and forecasting"/
16 nomogram/
17 nomogram*.mp.
18 statistical model/
19 (predict* and (outcome* or risk* or model*)).af.
20 ((predict* or model* or decision* or identif* or prognos*) and (history or variable* or criteria or scor* or characteristic* or finding* or factor*)).af.
21 (decision* and (model* or clinical*)).af.
22 (stratification or discrimination or discriminate or "c-statistic" or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).af.
23 exp area under the curve/
24 receiver operating characteristic/
25 (predict* adj4 value*).mp.
26 or/9-25
27 8 and 26
28 liver failure/ or acute liver failure/ or acute on chronic liver failure/ or chronic liver failure/ or end stage liver disease/ or fulminant hepatic failure/ or hepatic encephalopathy/ or mild hepatic impairment/ or moderate hepatic impairment/ or severe hepatic impairment/
29 ((hepatic or liver) adj2 (fail* or insufficien* or impair*)).mp.
30 decompensated liver cirrhosis/
31 decompensat*.mp.
32 postoperative complication/
33 (postoperative adj3 complication*).mp.
34 (post-operative adj3 complication*).mp.
35 (complication* adj4 (after* or following) adj4 (surgery or resection)).mp.
36 jaundice/ or eye jaundice/ or obstructive jaundice/
37 jaundice.ti,ab,kw.
38 exp ascites/

39 paracentesis/
40 paracentesis.ti,ab,kw.
41 varicosis/
42 esophagus varices bleeding/
43 esophagus varices/
44 ascites.ti,ab,kw.
45 varicosis.ti,ab,kw.
46 varices.ti,ab,kw.
47 variceal.ti,ab,kw.
48 encephalopathy.ti,ab,kw.
49 exp brain disease/
50 or/28-49
51 8 and 26 and 50
52 limit 51 to conference abstract
53 51 not 52
54 limit 53 to "review"
55 53 not 54

Ovid MEDLINE(R), Ovid MEDLINE(R) Daily and Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 to Present)

1 Hepatectomy/
2 ((liver or hepatic) adj3 (resection* or lobectom*)).mp.
3 hepatectom*.mp.
4 hemihepatectom*.mp.
5 1 or 2 or 3 or 4
6 predict*.ti.
7 "Predictive Value of Tests"/
8 logistic models/
9 nomograms/
10 nomogram*.mp.
11 (predict* adj4 value*).mp.
12 (Predict$ and (Outcome$ or Risk$ or Model$)).af.
13 ((Predict$ or Model$ or Decision$ or Identif$ or Prognos$) and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$)).af.
14 (Decision$ and (Model$ or Clinical$)).af.
15 (Stratification or Discrimination or Discriminate or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable").af.
16 ROC Curve/
17 validat*.af.
18 rule$.af.
19 or/6-18
20 exp Liver Failure/
21 exp Liver Cirrhosis/
22 ((hepatic or liver) adj2 (fail* or insufficien* or impair*)).mp.
23 decompensat*.mp.

24 Postoperative Complications/
25 (postoperative adj3 complication*).mp.
26 (post-operative adj3 complication*).mp.
27 (complication* adj4 (after* or following) adj4 (surgery or resection)).mp.
28 exp Jaundice/
29 jaundice.mp.
30 Chylous Ascites/ or Ascites/
31 exp Paracentesis/
32 exp Varicose Veins/
33 "Esophageal and Gastric Varices"/
34 exp Brain Diseases/
35 paracentesis.mp.
36 ascites.mp.
37 varicosis.mp.
38 varices.mp.
39 variceal.mp.
40 encephalopathy.mp.
41 or/20-40
42 5 and 19 and 41
43 limit 42 to "review"
44 42 not 43

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials

1 Hepatectomy/
2 ((liver or hepatic) adj3 (resection* or lobectom*)).mp.
3 hepatectom*.mp.
4 hemihepatectom*.mp.
5 1 or 2 or 3 or 4
6 predict*.ti.
7 "Predictive Value of Tests"/
8 logistic models/
9 nomograms/
10 nomogram*.mp.
11 (predict* adj4 value*).mp.
12 (Predict$ and (Outcome$ or Risk$ or Model$)).af.
13 ((Predict$ or Model$ or Decision$ or Identif$ or Prognos$) and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$)).af.
14 (Decision$ and (Model$ or Clinical$)).af.
15 (Stratification or Discrimination or Discriminate or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable").af.
16 ROC Curve/
17 validat*.af.
18 rule$.af.
19 or/6-18
20 exp Liver Failure/

21 exp Liver Cirrhosis/
22 ((hepatic or liver) adj2 (fail* or insufficien* or impair*)).mp.
23 decompensat*.mp.
24 Postoperative Complications/
25 (postoperative adj3 complication*).mp.
26 (post-operative adj3 complication*).mp.
27 (complication* adj4 (after* or following) adj4 (surgery or resection)).mp.
28 exp Jaundice/
29 jaundice.mp.
30 Chylous Ascites/ or Ascites/
31 exp Paracentesis/
32 exp Varicose Veins/
33 "Esophageal and Gastric Varices"/
34 exp Brain Diseases/
35 paracentesis.mp.
36 ascites.mp.
37 varicosis.mp.
38 varices.mp.
39 variceal.mp.
40 encephalopathy.mp.
41 or/20-40
42 5 and 19 and 41

Web of Science Core Collection

#1 TS= (((liver or hepatic) NEAR/3 (resection* or lobectom*))) OR TS=(hepatectom*) OR TS=(hemihepatectom*)
#2 TS=(((hepatic or liver) NEAR/2 (fail* or insufficien* or impair*))) OR TS=(decompensat*) OR TS=((postoperative NEAR/3 complication*)) OR TS=((post-operative NEAR/3 complication*)) OR TS=((complication* NEAR/4 (after* or following) NEAR/4 (surgery or resection))) OR TS=(jaundice) OR TS=(paracentesis) OR TS=(ascites) OR TS=(varicosis) OR TS=(varices) OR TS=(variceal) OR TS=(encephalopathy)
#3 TS=(validat* OR rule*) OR TS=((Predict* and (Outcome* or Risk* or Model*))) OR TS=(((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) and (Predict* or Model* or Decision* or Identif* or Prognos*))) OR TS=((Decision* and (Model* or Clinical*))) OR TS=((Stratification or Discrimination or Discriminate or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable"))
#4 TI=(predict*) OR TS=(nomogram*) OR TS=(predict* NEAR/4 value*)
#5 #4 OR #3
#6 #5 AND #2 AND #1
#7 #6 **Refined by: DOCUMENT TYPES:** (ARTICLE OR LETTER OR NOTE OR CORRECTION OR RETRACTED PUBLICATION OR PROCEEDINGS PAPER OR EARLY ACCESS OR BOOK CHAPTER)

Appendix B. Study outcome definitions for post-operative liver decompensation

1) PHLF-ISGLS
   - A post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after post-operative day 5 (increased INR and hyperbilirubinemia are defined according to the normal range of cut-off levels of the local laboratory)

2) 50-50 criteria
   - The conjunction of PT <50% and serum bilirubin >50 umol/L on post-operative day 5

3) MSKCC criteria
   - CT findings of low correlation (linear dependency of gray levels on neighboring pixels) and high entropy (randomness of brightness variation)

4) Liver decompensation
   - Refractory ascites causing a delay in the removal of surgical drains and/or requiring paracentesis (grade 2 or grade 3a complication)
   - Increase of bilirubin levels to more than 3 mg/dL
   - Alteration of coagulation factors requiring fresh-frozen plasma infusion with an international normalized ratio of more than 1.50 (in the absence of serum bilirubin levels >12 mg/dL)
   - Renal impairment, defined as a serum urea nitrogen level of more than 2.00 g/L (to convert to millimoles per liter, multiply by 0.357) and/or increase of serum creatinine level to more than 2 mg/dL (to convert to micromoles per liter, multiply by 88.4) requiring dopamine hydrochloride or terlipressin therapy or dialysis.

5) Post-operative hepatic failure/liver failure
   - Occurrence of any of the following:
     - Encephalopathy associated with hyperbilirubinemia (a total bilirubin level >5 mg/dl for more than 5 days) after surgery
     - Intractable pleural effusion or ascites (requiring diuretics, thoracocentesis, or abdominal paracentesis on two or more occasions, or continuous drainage)
     - Variceal bleeding

6) PHLF
   - The presence of at least one of the following variables
     - Occurrence of refractory ascites causing a delay in the removal of surgical drainages and/or postoperative drainage exceeding 500 ml/day
     - A continuous elevation of total serum bilirubin concentration (≥60umol/ l) beyond post-operative day 7
     - Alteration of coagulation factors requiring fresh frozen plasma infusion with an International Normalized Ratio (INR) of more than 1.50

7) Hepatic failure
   - Increased serum total bilirubin level above 10 mg/dL

8) Hepatic failure
   - Defined by total bilirubin of >5 mg/dL on post-operative day 7 or post-operative death without other cause

9) Post-operative ascites
   - One of following criteria:
     - Daily ascites drainage >500 mL, at least one day post operation
     - The total volume of drainage >1,500 mL in 7 days post operation
     - The free peritoneal fluid >500 mL confirmed by ultrasound, CT or MRI.
   - Patients were excluded if drainage contained obvious bile, blood, digestive juice, pancreatic juice or chyle

10) Large volume ascites
   - Post-operative daily ascitic fluid drainage from the thoracic and abdominal drains exceeding 10 mL/kg of preoperative body weight

11) Post-operative liver dysfunction
   - Patients who required post-operative aspiration because of massive ascites or pleural effusion (20 patients) and/or who had hyperbilirubinemia (serum total bilirubin levels >6 mg/dl for more than 5 days) with a disturbance of consciousness higher than hepatic coma grade II postoperatively

12) Intractable ascites (diuretics not effective for more than 1 month) and those with prolonged jaundice (serum bilirubin level more than 3 g/dl continuing for more than 1 month) after operation and those with hospital death were assigned a score of 100

13) Irreversible liver failure after hepatectomy
   - Defined as growing impairment of liver function after resection that led to patient death or required transplantation

14) Post-operative liver failure
   - A serum bilirubin level of >10 mg/dl together with an NH3 level of GE 100 mg/dl or a prothrombin time of <40%
   - A requirement for continuous hemodiafiltration or plasma exchange, as described previously

15) Modification of ISGLS and 50-50 criteria
   - Presence of prolonged and aggravated hyperbilirubinemia on or after post-operative day 5 and the requirement for administration of FFP for a decreased prothrombin time (< 50%) until post-operative day 5

Appendix C. Patient identification from administrative health data

1) Identifying patients with a diagnosis of cirrhosis:

This diagnosis is based on a previously validated algorithm using ICES data (15)

1+ physician visit for cirrhosis
- OHIP dxcode = 571

OR

1+ hospital diagnosis for cirrhosis or non-bleeding esophageal varices
- DAD dxcode (ICD-9) = 456.1, 571.2, 571.5
- DAD dx10code (ICD-10) = I85.9, I98.2, K70.3, K71.7, K74.6, K74.5

This is a pre-existing dataset at ICES with TRIM 2015 0800 166 000.

2) From (1), identifying patients with a diagnosis of hepatocellular carcinoma (HCC):

This diagnosis is based on a previously validated algorithm using ICES data (15)

1+ hospital diagnosis for HCC
- DAD dxcode (ICD-9) = 155.0
- DAD dx10code (ICD-10) = C22.0, C22.9, 81703, 81803

OR

1+ death code for HCC
- ICD-9 = 1550
- ICD-10 = 81703, 81803

OR

2+ physician visits for HCC
- OHIP dxcode = 155

OR

1+ physician visit for cirrhosis AND 1+ procedure
- OHIP dxcode = 571
- OHIP feecode = J069
- DAD procedure code (CCI) = 1.OA.59^^

OR

Ontario Cancer Registry diagnosis of HCC
- Morphology codes: 81703, 81723, 81733, 81743, 81753, 81803
- Topography codes: C220

3) Identifying liver resection/partial hepatectomy

Identified by procedure codes:
- OHIP feecode = S267, S269, S270, S271, S275
- DAD procedure code (CCI) = 1.OA.87.^^

We preferred to use OHIP codes to identify patients. If there was discordance between same-date procedures performed in OHIP and DAD, then identify the procedure as a liver resection if there is no corresponding liver transplant procedure in CORR and if the procedure was performed at an institution with a liver transplant status (i.e. Toronto General Hospital or London Health Sciences).

Type of resection = minor vs. major.

- Minor refers to < 3 anatomical segments of the liver and is captured by OHIP feecode = S269, S270, S275
- Major refers to > 3 anatomical segments of the liver and is captured by OHIP feecode = S267, S271
- Unknown = if only identified by CCI code.

4) Identifying post-operative liver decompensation events:

This diagnosis is based on a previously validated algorithm using ICES data (15):

1+ hospital diagnosis OR death OR procedure for decompensated cirrhosis (portal hypertension, hepatorenal syndrome, jaundice, hepatic coma, hepatic failure, bleeding esophageal varices, gastric varices, and ascites)

- DAD dxcode (ICD-9) = 456.0, 456.2, 572.2, 572.3, 572.4, 782.4, 789.5
- DAD dxcode (ICD-10) = I85, I86.4, I98.2, I98.3, K72.1, K72.9, K76.6, K76.7, R17, R18

- DAD procedure code (CCI) = 1.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD, 1.KQ.76GP-NR, 1.OT.52.HA
- DAD procedure code (CCP) = 10.06, 66.91
- OHIP feecode = J057, Z591

- DAD deathcode (ICD-9) = 456.0, 571.2, 571.5, 572.2, 572.3, 572.4, 572.8
- DAD deathcode (ICD-10) = I85X, I86.4, I98.2X, I98.3, K70.3, K70.4, K71.7, K72.1, K72.9, K74, K74.6, K76.6, K76.7

Type of postoperative liver decompensation event

Ascites

- OHIP feecode = Z591 (paracentesis)
- ICD-9 = 789.5, ICD-10 = R18
- CCI = 1.OT.52.HA

Jaundice

- ICD-10 = R17

Bleeding gastroesophageal varices

- ICD-9 = 456.0, 456.2, ICD-10 = I85, I86.4, I98.2, I98.3
- CCI =.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD

Portal hypertension

- OHIP feecode = J057 – transjugular intrahepatic portosystemic shunt (TIPS)
- ICD-9 = 572.3, ICD-10 = K76.6
- CCI = 1.KQ.76GP-NR

Hepatorenal syndrome

- ICD-9 = 572.4, ICD-10 = K76.7

Hepatic coma/encephalopathy/failure

- ICD-10 = K70.4 (alcoholic failure), K71.7 (toxic liver disease with fibrosis/cirrhosis), K72.1, K72.9
- ICD-9 = 572.2, 572.8

5) Identifying any post-operative (salvage) liver transplantation:

Identified by presence of record in CORR

- Unique identifier in CORR TRANSPLANTED_LIVER dataset

Yes/no Identified by procedure codes:

- OHIP feecode = S294, S266
- DAD procedure code (CCI) = 1.OA.85.^^

Appendix D. Assessment of Cox proportional hazards model

Table S1. Multivariable Cox regression of candidate predictors of POLDE-free survival with sensitivity analysis classifying unknown resections as major (n=611 resected patients).

		HR	95% C.I.	p-value
Age (per year)		1.01	1.00–1.02	0.1
Sex				
	Female	Reference		
	Male	1.20	0.89–1.61	0.23
Diabetes				
	No	Reference		
	Yes	1.33	1.03–1.73	0.03
Cirrhosis etiology				0.02[a]
	Hepatitis C	Reference		
	Hepatitis B	0.73	0.49–1.07	0.10
	Alcohol-related	1.18	0.77–1.80	0.45
	NAFLD or Cryptogenic	0.95	0.66–1.36	0.76
	Other	1.65	0.99–2.75	0.05
Extent of liver resection				
	Minor	Reference		
	Major*	1.40	1.08–1.82	0.01
History of previous non-malignant decompensation				
	No	Reference		
	Yes	2.07	1.45–2.97	<0.0001

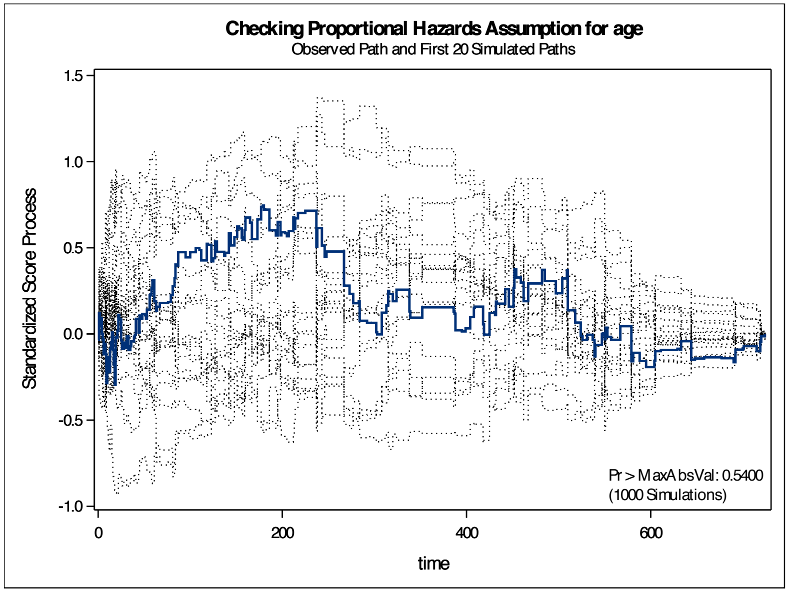
HR: hazard ratio, C.I.: confidence interval, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as major for analyses.
[a]: indicates p-value for type 3 test.

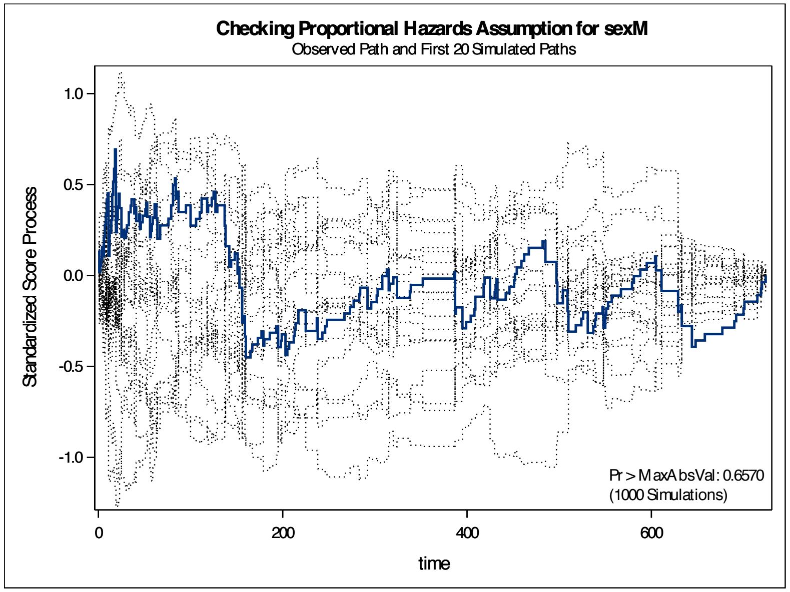
Table S2. Kolmogorov-type supremum test for proportional hazards assumption.

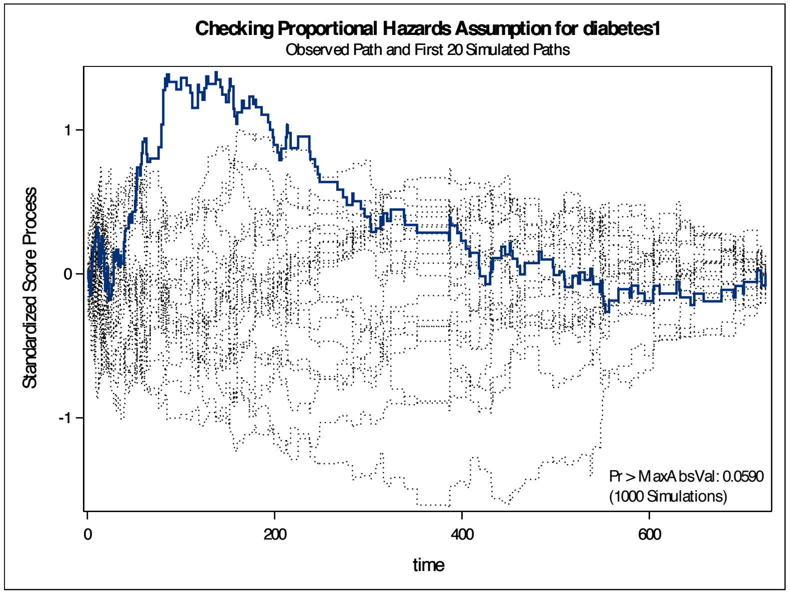
		Maximum absolute value	Replications	Seed	p-value
Age		0.74	1000	1236653545	0.54
Sex					
	Female	Reference			
	Male	0.69	1000	1236653545	0.66
Diabetes					
	No	Reference			
	Yes	1.40	1000	1236653545	0.06
Cirrhosis etiology					
	Hepatitis C	Reference			
	Hepatitis B	1.31	1000	1236653545	0.24
	Other	0.92	1000	1236653545	0.45
	Alcohol-related	0.56	1000	1236653545	0.97
	NAFLD or Cryptogenic	1.32	1000	1236653545	0.30
Extent of liver resection					
	Minor*	Reference			
	Major	1.06	1000	1236653545	0.22
History of previous non-malignant decompensation					
	No	Reference			
	Yes	0.64	1000	1236653545	0.75

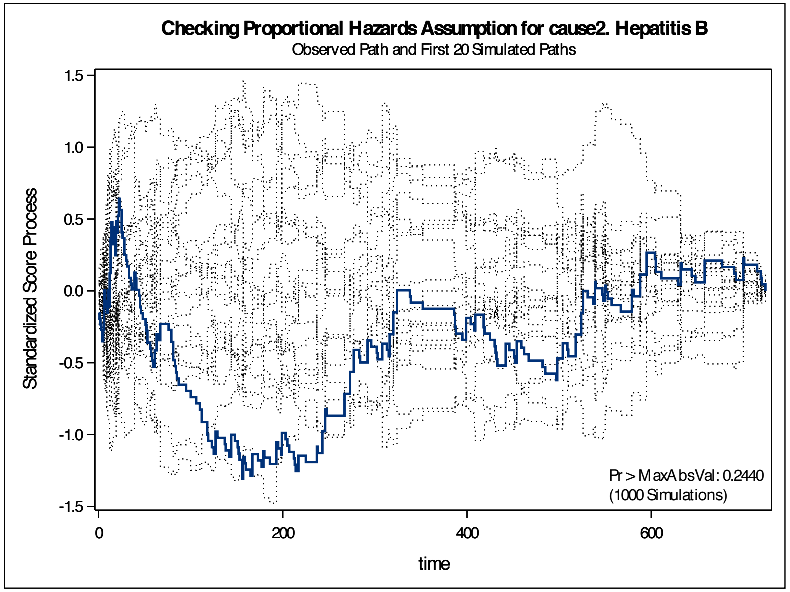
NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.

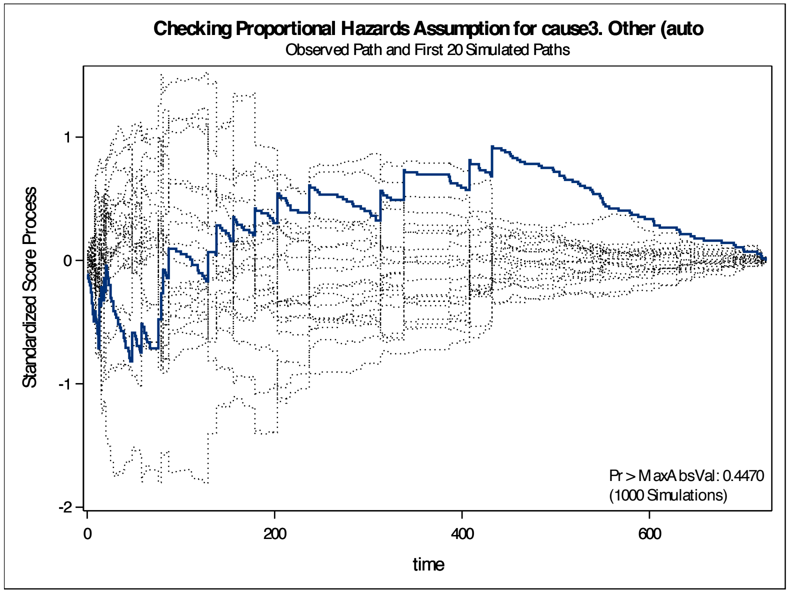
A non-significant p-value for this test means that the deviation of cumulative Martingale residuals (maximum absolute value above) is not large enough to violate the proportional hazards assumption.

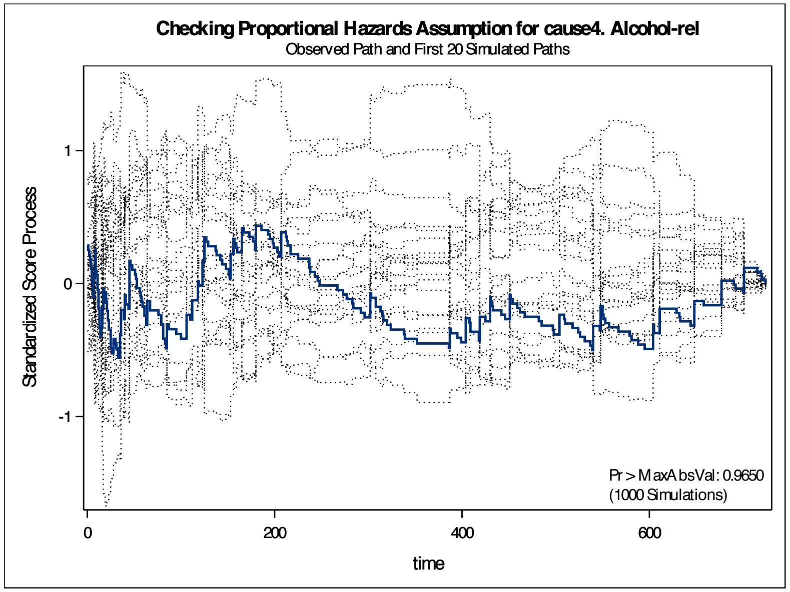

Checking Proportional Hazards Assumption for age
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.5400
(1000 Simulations)

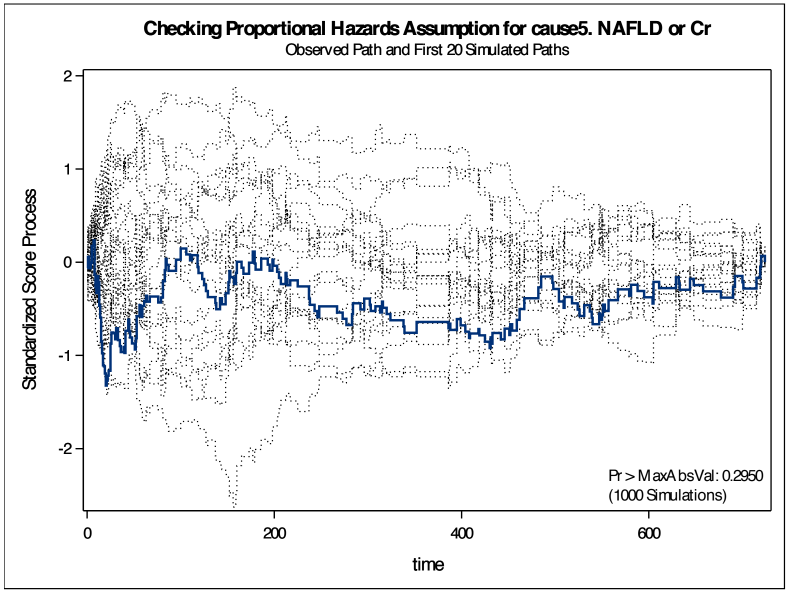

Checking Proportional Hazards Assumption for sexM
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.6570
(1000 Simulations)

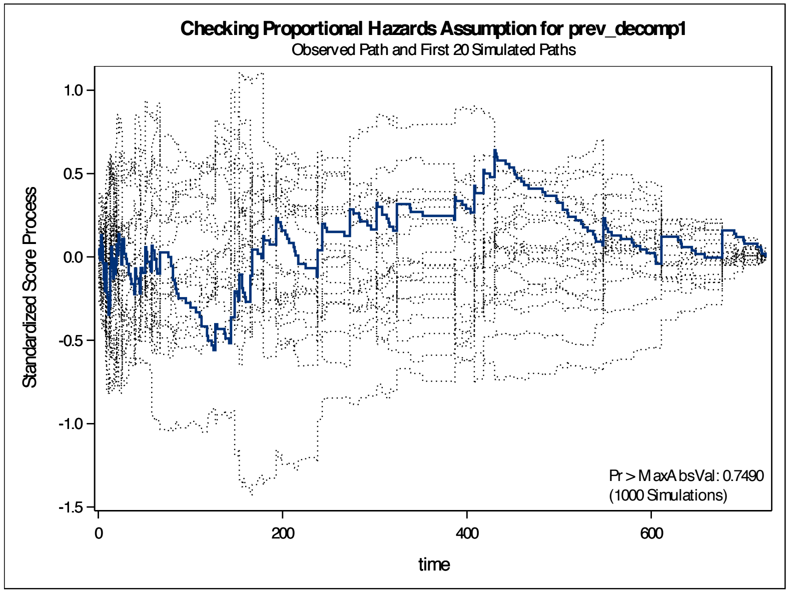

Checking Proportional Hazards Assumption for diabetes1
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.0590
(1000 Simulations)

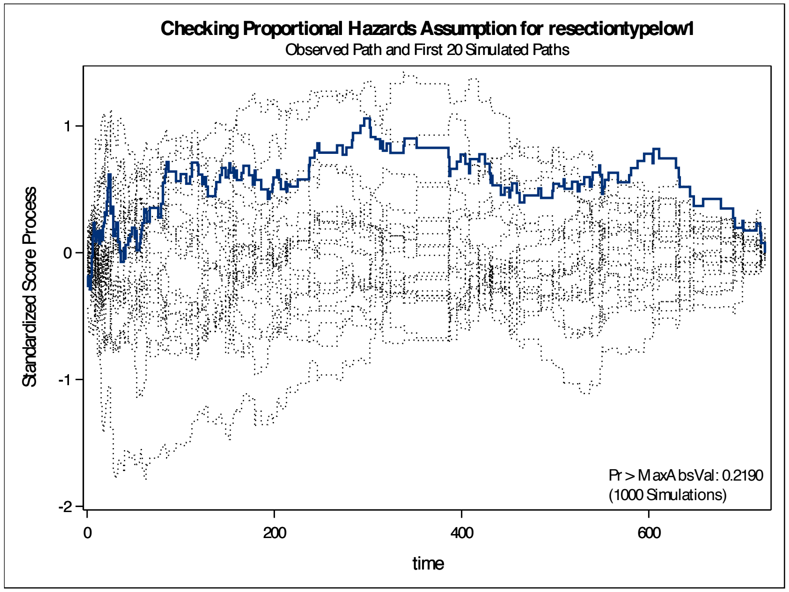

Checking Proportional Hazards Assumption for cause2. Hepatitis B
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.2440
(1000 Simulations)


Checking Proportional Hazards Assumption for cause3. Other (auto
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.4470
(1000 Simulations)


Checking Proportional Hazards Assumption for cause4. Alcohol-rel
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.9650
(1000 Simulations)


Checking Proportional Hazards Assumption for cause5. NAFLD or Cr
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.2950
(1000 Simulations)


Checking Proportional Hazards Assumption for prev_decomp1
Observed Path and First 20 Simulated Paths
Standardized Score Process
time
Pr > MaxAbsVal: 0.7490
(1000 Simulations)



These plots depict the standardized score residuals of each covariate against follow-up time, with 1000 simulations. Large deviations from 0 represent a violation of the proportional hazards assumption.

Appendix E. Stratified multivariable regression by institution transplant status

Table S3. Multivariable Cox regression of candidate predictors of POLDE-free survival, stratified by institution transplant status (n=611 resected patients).

		Non-transplant centre (n=251)			Liver transplant centre (n=360)		
		HR	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**
Age (per year)		1.01	0.99–1.03	0.47	1.01	1.00–1.03	0.14
Sex							
	Female	Reference			Reference		
	Male	1.20	0.78–1.85	0.41	1.24	0.82–1.88	0.30
Diabetes							
	No	Reference			Reference		
	Yes	1.36	0.91–2.04	0.13	1.44	1.01–2.04	0.04
Cirrhosis etiology							
	Hepatitis C	Reference			Reference		
	Hepatitis B	0.72	0.34–1.53	0.40	0.74	0.47–1.17	0.19
	Alcohol-related	1.58	0.83–3.00	0.16	0.79	0.43–1.47	0.46
	NAFLD or Cryptogenic	1.03	0.58–1.86	0.91	0.82	0.51–1.32	0.42
	Other	1.77	0.84–3.73	0.14	1.30	0.61–2.78	0.50
Extent of liver resection							
	Minor*	Reference			Reference		
	Major	1.46	1.00–2.14	0.05	1.51	1.06–2.16	0.02
History of previous non-malignant decompensation							
	No	Reference			Reference		
	Yes	1.92	1.09–3.39	0.02	2.44	1.51–3.94	0.0003

HR: hazard ratio, C.I.: confidence interval, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.
[a]: indicates p-value for type 3 test.

Table S4. Comparison of resected patients by the institution's liver transplant status (n=611 resected patients).

	Resected (n=611) Value (%)	Non-transplant centre (n=251) Value (%)	Liver transplant centre (n=360) Value (%)	p-value
Age				
Mean / SD	62.8 / 11.4	63.8 / 10.7	62.0 / 11.8	0.05
Median / IQR	63.0 / 15.0	65.0 / 14.0	62.0 / 16.0	
Sex				
M	451 (73.8)	177 (70.5)	274 (76.1)	0.12
F	160 (26.2)	74 (29.5)	86 (23.9)	
Specific comorbidities				
Asthma	79 (12.9)	32 (12.7)	47 (13.1)	0.91
CHF	29 (4.7)	14 (5.6)	15 (4.2)	0.42
COPD	103 (16.9)	44 (17.5)	59 (16.4)	0.71
Diabetes	224 (36.7)	91 (36.2)	133 (36.9)	0.86
Hypertension	350 (57.3)	149 (59.4)	201 (55.8)	0.39
Cirrhosis etiology				
Hepatitis B	164 (26.8)	35 (13.9)	129 (35.8)	<0.0001
Hepatitis C	121 (19.8)	42 (16.7)	79 (21.9)	
Alcohol	75 (12.3)	42 (16.7)	33 (9.2)	
NAFLD/Cryptogenic	216 (35.4)	112 (44.6)	104 (28.9)	
Other	35 (5.7)	20 (8.0)	15 (4.2)	
History of non-malignant decompensation				
Yes	61 (10.0)	24 (9.6)	37 (10.3)	0.77
No	550 (90.0)	227 (90.4)	323 (89.7)	
Time from HCC diagnosis to liver resection (days)				
Mean / SD	59.3 / 48.0	52.1 / 46.0	64.4 (48.8)	0.002
Median / IQR	50.0 / 72.0	42.0 / 66.0	60.0 / 75.0	
Extent of liver resection				
Major	335 (54.8)	121 (48.2)	214 (59.4)	0.01
Minor	255 (41.7)	123 (49.0)	132 (36.7)	
Unknown	21 (3.4)	7 (2.8)	14 (3.9)	
Length of stay (days)				
Mean / SD	10.9 / 12.7	11.4 / 14.4	10.6 / 11.4	0.18
Median / IQR	7.0 / 6.0	6.0 / 9.0	7.0 / 6.0	
Missing / Unknown	8 (1.3)	6 (2.4)	2 (0.6)	
Readmission to hospital				
30-day	69 (11.3)	35 (13.9)	34 (9.4)	0.08
90-day	118 (19.3)	57 (22.7)	61 (16.9)	0.08
Number of ED visits after discharge				
Mean / SD	2.2 / 3.2	2.3 / 3.0	2.1 / 3.3	0.16
Median / IQR	1.0 / 3.0	1.0 / 3.0	1.0 / 3.0	
Number of hospitalizations after discharge				
Mean / SD	1.3 / 1.7	1.4 / 2.0	1.1 / 1.5	0.15
Median / IQR	1.0 / 2.0	1.0 / 2.0	1.0 / 2.0	
POLDEs				
Yes	160 (26.2)	81 (32.3)	79 (21.9)	0.004
No	451 (73.8)	170 (67.7)	281 (78.1)	
Post-operative liver transplant				
Yes	17 (2.8)	8 (3.2)	9 (2.5)	0.63
No	594 (97.2)	243 (96.8)	351 (97.5)	

Post-operative mortality				
30-day	26 (4.3)	15 (6.0)	11 (3.1)	0.08
90-day	55 (9.0)	30 (12.0)	25 (6.9)	0.03
2-year	189 (30.9)	85 (33.9)	104 (28.9)	0.19

SD: standard deviation, IQR: interquartile range, POLDEs: post-operative liver decompensation event, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, NAFLD: non-alcoholic fatty liver disease, HCC: hepatocellular carcinoma, ED: emergency department.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson’s disease, autoimmune hepatitis.

Table S5. Multivariable cause-specific hazards of candidate predictors of POLDE and death, stratified by institution transplant status (n=611 resected patients).

	Non-transplant centre (n=251)						Liver transplant centre (n=360)					
	POLDE (n=81)			Death (n=40)			POLDE (n=78)			Death (n=66)		
	HR	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**	**HR**	**95% C.I.**	**p-value**
Age (per year)	1.00	0.97–1.02	0.78	1.02	0.99–1.05	0.22	1.00	0.98–1.02	0.94	1.02	0.98–1.01	0.06
Sex												
Female	Reference			Reference			Reference			Reference		
Male	0.94	0.56–1.59	0.82	1.46	0.68–3.15	0.33	1.47	0.81–2.65	0.20	1.09	0.61–1.95	0.76
Diabetes												
No	Reference			Reference			Reference			Reference		
Yes	1.84	1.12–3.02	0.02	0.82	0.40–1.68	0.59	1.51	0.93–2.43	0.09	1.12	0.67–1.88	0.66
Cirrhosis etiology			0.001[a]			0.36[a]			0.13[a]			0.93[a]
Hepatitis C	Reference			Reference			Reference			Reference		
Hepatitis B	0.24	0.08–0.76	0.02	2.57	0.67–9.88	0.17	0.48	0.27–0.87	0.02	1.32	0.61–2.88	0.49
Alcohol-related	1.75	0.86–3.55	0.12	1.29	0.26–6.47	0.76	0.54	0.24–1.24	0.15	1.52	0.47–4.05	0.41
NAFLD or Cryptogenic	0.65	0.33–1.28	0.21	2.46	0.71–8.55	0.16	0.56	0.30–1.05	0.07	1.34	0.60–2.99	0.48
Other	1.07	0.44–2.59	0.88	3.92	0.90–17.1	0.07	0.88	0.32–2.40	0.8	1.46	0.43–4.98	0.55
Extent of liver resection												
Minor*	Reference			Reference			Reference			Reference		
Major	1.62	1.02–2.59	0.04	1.11	0.58–2.14	0.75	1.11	0.69–1.79	0.68	1.84	1.04–3.23	0.04
History of previous non-malignant decompensation												
No	Reference			Reference			Reference			Reference		
Yes	1.57	0.77–3.22	0.22	1.88	0.74–4.80	0.19	2.00	1.08–3.72	0.03	2.13	0.99–4.57	0.05

HR: hazard ratio, C.I.: confidence interval, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.
[a]: indicates p-value for type 3 test.

Appendix F. Fine-Gray sub-distribution hazards

Table S6. Multivariable sub-distribution hazards regression of candidate predictors of POLDE (n=611 resected patients).

		HR	95% C.I.	p-value
Age (per year)		1.00	0.98–1.01	0.79
Sex				
	Female	Reference		
	Male	1.18	0.81–1.73	0.39
Diabetes				
	No	Reference		
	Yes	1.47	1.05–2.07	0.03
Cirrhosis etiology				0.001[a]
	Hepatitis C	Reference		
	Hepatitis B	0.41	0.24–0.70	0.001
	Alcohol-related	1.18	0.71–1.95	0.52
	NAFLD or Cryptogenic	0.66	0.42–1.04	0.07
	Other	1.12	0.58–2.15	0.74
Extent of liver resection				
	Minor*	Reference		
	Major	1.25	0.89–1.75	0.20
History of previous non-malignant decompensation				
	No	Reference		
	Yes	1.64	1.02–2.64	0.04

HR: hazard ratio, C.I.: confidence interval, NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.
*Unknown resection types (n=21) were classified as minor for analyses.
[a]: indicates p-value for type 3 test.

Appendix G. Additional results

Table S7. Pre- and post-operative bloodwork among resected patients.

	Resected (n=611)	POLDE – (n=451)	POLDE + (n=160)
Pre-operative bloodwork	Mean / SD	Mean / SD	Mean / SD
Albumin (n=361)	37.2 / 7.3	37.6 / 7.2	36.3 / 7.5
AST (n=381)	137.4 / 180.1	137.5 / 190.9	137.5 / 141.7
ALT (n=412)	116.9 / 141.0	117.3 / 141.3	115.6 / 140.9
Total bilirubin (n=402)	17.3 / 21.5	16.3 / 14.6	20.6 / 35.8
Creatinine (n=447)	81.9 / 29.0	80.8 / 28.4	85.4 / 30.6
INR (n=419)	1.2 / 0.3	1.2 / 0.3	1.3 / 0.3
MELD score (n=370)	10.1 / 3.5	9.9 / 3.2	10.9 / 4.4
Platelets (n=404)	191.0 / 81.7	193.9 / 70.9	182.3 / 108.1
Sodium (n=431)	138.9 / 2.8	138.9 / 2.7	138.8 / 3.0
Post-operative bloodwork			
Total bilirubin (n=324)	33.5 / 36.2	32.3 / 30.7	37.5 / 49.8
INR (n=293)	1.3 / 0.4	1.3 / 0.4	1.3 / 0.3

SD: standard deviation, IQR: interquartile range, POLDEs: post-operative liver decompensation event, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio.
The number (n) of patients with available bloodwork is indicated for each test.

Table S8. Adjustment for multiple comparisons for the log-rank test. (Supplement to figure 2)

Cirrhosis etiology strata comparison		Chi-Square	p-values raw	p-values Sidak
Hepatitis C	Hepatitis B	2.92	0.09	0.60
Hepatitis C	Other	2.64	0.10	0.67
Hepatitis C	Alcohol-related	2.18	0.14	0.78
Hepatitis C	NAFLD or Cryptogenic	0.006	0.94	1.00
Hepatitis B	Other	13.42	0.0002	0.003
Hepatitis B	Alcohol-related	10.48	0.001	0.012
Hepatitis B	NAFLD or Cryptogenic	1.91	0.17	0.84

Table S8. Adjustment for multiple comparisons for the log-rank test. (Supplement to figure 2)

Cirrhosis etiology strata comparison		Chi-Square	p-values	
			raw	Sidak
Other	Alcohol-related	0.02	0.89	1.00
Other	NAFLD or Cryptogenic	2.13	0.15	0.79
Alcohol-related	NAFLD or Cryptogenic	1.80	0.18	0.86

NAFLD: non-alcoholic fatty liver disease.
Other cirrhosis etiology includes: hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis.

Appendix H. Ethics approval

Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB)

HSREB Initial Ethics Clearance

January 22, 2020

Dr. Zuhaib Mir
Department of Surgery
Queen's University

TRAQ #: 6028657
Department Code: SURG-496-20
Study Title: "SURG-496-20 Postoperative liver decompensation events following partial hepatectomy for hepatocellular carcinoma among patients with cirrhosis"
Supervisor: Dr. Patricia A Groome
Review Type: Delegated
Date Ethics Clearance Issued: January 22, 2020
Ethics Clearance Expiry Date: January 22, 2021

Dear Dr. Mir:

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

Document Name	Comments	Version Date
Protocol	Study proposal and methods	2020/01/18

Documents Acknowledged:
- Ethics training certificates
- CV – Dr. Mir
- Thesis committee approval

Amendments: No deviation from, or changes to the protocol, informed consent form and conduct of study should be initiated without prior written clearance or an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the study.

Renewals: An annual renewal event form or a study closure event form must be submitted annually as per the TCPS 2 Article 6.14. As a courtesy, the Office of Research Ethics may send reminders 30 days in advance of the ethics clearance expiry date. All lapses in ethics clearance will be documented on the annual renewal clearance letter. Suspension letters may be issued for lapses in ethics clearances one day or greater, with subsequent termination and closure of the ethics file for lapses greater than 10 business days. Terminations should be reported to applicable regulatory authorities (e.g., Health Canada, FDA).

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the submission of a study closure event in TRAQ.

Reporting of Serious Adverse Events: Any unexpected serious adverse events occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint.

Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Investigators please note that if your study is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Regards,

Albert F. Clark

Albert F. Clark, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the international Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Product Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#: 00004184, IRB#: 00001173. HSREB members involved in the research project do not participate in the review, discussion or decision.

Appendix I. ICES dataset creation plan

<table>
<tr><th colspan="3">Project Initiation
This Section must be Completed Prior to Project Dataset(s) Creation</th></tr>
<tr><td>Project Title:</td><td colspan="2">Postoperative liver decompensation events following partial hepatectomy for hepatocellular carcinoma among patients with cirrhosis.</td></tr>
<tr><td>Project TRIM number:</td><td colspan="2">2020 0800 283 000</td></tr>
<tr><td>Research Program:</td><td colspan="2">Cancer</td></tr>
<tr><td>Site:</td><td colspan="2">ICES Queens</td></tr>
<tr><td rowspan="2">Project Objectives:</td><td colspan="2">Insert Project Objectives as listed in the approved ICES Project PIA</td></tr>
<tr><td colspan="2">1) To describe postoperative liver decompensation events in patients with cirrhosis undergoing partial hepatectomy for hepatocellular carcinoma.
2) To identify independent predictors of postoperative liver decompensation events occurring within 2 years of resection for hepatocellular carcinoma.</td></tr>
<tr><td rowspan="2">ICES Project PIA Initial Approval Date:</td><td colspan="2">The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)</td></tr>
<tr><td colspan="2">2020-Feb-06</td></tr>
<tr><td>Principal Investigator (PI):</td><td colspan="2">Zuhaib M. Mir</td></tr>
<tr><td>Check the applicable box if the PI is an ICES Student/Trainee</td><td colspan="2">☒ ICES Student ☐ ICES Fellow ☐ ICES Post-Doctoral Trainee ☐ Visiting Scholar</td></tr>
<tr><td rowspan="2">Responsible ICES Scientist:</td><td colspan="2">Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist</td></tr>
<tr><td colspan="2">Patti Groome</td></tr>
<tr><td rowspan="3">Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):</td><td colspan="2">All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) <u>and the date they joined the project</u> must be recorded</td></tr>
<tr><td>Maya Djerboua</td><td>2020-Feb-01</td></tr>
<tr><td>Zuhaib M. Mir</td><td>2020-Feb-01</td></tr>
<tr><td rowspan="2">Other ICES Project Team Members and date joined (list all):</td><td colspan="2">All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) <u>and the date they joined the project</u> must be recorded</td></tr>
<tr><td>Jennifer Flemming
Sulaiman Nanji</td><td>yyyy-mon-dd</td></tr>
<tr><td rowspan="3">Confirmation that DCP is consistent with Project Objectives:</td><td colspan="2">The following individuals must confirm that the ICES Data provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA <u>prior to initial Project Dataset creation</u>: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research and Analysis Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.</td></tr>
<tr><td>Principal Investigator</td><td>☐ yyyy-mon-dd</td></tr>
<tr><td>Responsible ICES Scientist or Second ICES Scientist/Lead</td><td>☐ yyyy-mon-dd</td></tr>
</table>

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation			
	ICES Research and Analysis Staff Creating the DCP	☐	yyyy-mon-dd
	ICES Analytic Staff	☐	yyyy-mon-dd
Designated ICES Research and Analysis Staff accountable for Project Documentation:	*The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion*		

DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*
	Date	***Name***
	2020-Apr-09	Zuhaib Mir

ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	
The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA *Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment*	*Mandatory for all datasets that are available by individual year*
General Use Datasets – Health Services	***Years (where applicable)***
CIHI DAD	1991-2019
CIHI SDS	1991-2019
CONTACT	1991-2017
ERCLAIM	1991-2016
NACRS	2000-2018
ODB	1991-2018
OHIP	1991-2019
General Use Datasets – Care Providers	
IPDB	1991-2015
CPDB	1991-2019
General Use Datasets – Population	
RPDB	1991-2019
POP	1991-2016
General Use Datasets – Coding/Geography	
DIN	1991-2019
REF	1991-2017
General Use Datasets - Facilities	

ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	
INST	1991-2017
General Use Datasets - Other	
CHF	
COPD	
CORR	
HYPER	
ODD	
ONMARG	
Controlled Use Datasets	
ALR	2005-2018
OCR	1991-2017
ORGD	1991-2018
Other Datasets	
OLIS	2007-2017
Project Specific Data (TRIM 2015 0800 166 000)	
TGLN	2016-2018

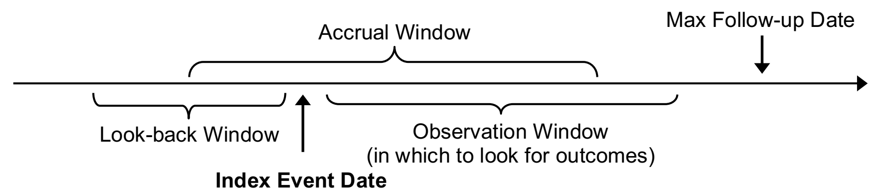
Project Amendments and Reconciliation			
ICES Project PIA Amendment History (add additional rows as needed):	*Privacy approval date*	*Person who submitted amendment*	*Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	Pending	Zuhaib Mir	Added CORR, ASTHMA, and Project Specific Data (TRIM 2015 0800 166 000)
DCP Amendment History (add additional rows as needed):	*Date DCP amended*	*Person who made the DCP amendment*	*Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	2020-Apr-18	Zuhaib Mir	1) Removed myocardial infarction, mental health, renal failure, and stroke variables. 2) Clarified CCI lookback window. 3) Clarified duration variables for conversion to level 4 data. 4) Clarified HCC diagnosis to surgery timeframe. 5) Added potential competing risks regression in addition to cox regression. 6) Clarified OHIP eligibility.
	2020-May-05	Maya Djerboua	1) Extended time window for capturing pre-operative lab values from 1 month prior to liver resection to any time between 1 month prior to HCC diagnosis and liver resection date. 2) Included "Non-malignant decompensation event prior to liver resection" as additional variable
	2020-May-08	Maya Djerboua	1) Modified criteria for identifying liver transplant procedures as an outcome and exclusion procedure: liver transplants will be identified through CORR. 2) Changed exclusion criteria 3 to exclude patients who underwent liver transplant prior to and on liver resection procedure date. 3) Additional information and clarification around identifying liver resection procedures: If there is discordance between same-date procedures performed in OHIP and DAD, then identify the procedure as a liver resection if there is no corresponding liver transplant procedure in CORR and if the procedure was performed at an institution with a liver transplant status

Project Amendments and Reconciliation			
			(i.e. Toronto General Hospital or London Health Sciences) 4) Additional exclusion criteria removing patients who received liver resection as a liver transplant donor.
	2020-Jun-09	Zuhaib Mir	5) Add 4 new variables to DCP (Elixhauser co-morbidity index, number of emergency department visits after liver resection, number of hospital admissions after liver resection, follow-up days among non-decompensated patients.
Date Programs/DCP reconciled	*The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed* yyyy-mon-dd		

Project Cohort	
Study Design	☒ Cohort study ☐ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Inclusion Criteria	**6) Patients with a diagnosis of cirrhosis** This diagnosis is based on a previously-validated algorithm using ICES data: 1+ physician visit for cirrhosis - OHIP dxcode = 571 OR 1+ hospital diagnosis for cirrhosis or non-bleeding esophageal varices - DAD dxcode (ICD-9) = 456.1, 571.2, 571.5 - DAD dx10code (ICD-10) = I85.9, I98.2, K70.3, K71.7, K74.6, K74.5 *This is a pre-existing dataset with TRIM 2015 0800 166 000.* **7) From (1), patients with a diagnosis of hepatocellular carcinoma (HCC)** This diagnosis is based on a previously-validated algorithm using ICES data: 1+ hospital diagnosis for HCC - DAD dxcode (ICD-9) = 155.0 - DAD dx10code (ICD-10) = C22.0, C22.9, 81703, 81803 OR 1+ death code for HCC - ICD-9 = 1550 - ICD-10 = 81703, 81803

Project Cohort	
	OR 2+ physician visits for HCC - OHIP dxcode = 155 OR 1+ physician visit for cirrhosis AND 1+ procedure - OHIP dxcode = 571 - OHIP feecode = J069 - DAD procedure code (CCI) = 1.OA.59^^ OR Ontario Cancer Registry diagnosis of HCC - Morphology codes: 81703, 81723, 81733, 81743, 81753, 81803 - Topography codes: C220 **Year of HCC diagnosis (2007-2017)** *At present, this project is set-up to identify incident diagnoses of HCC among patients with prevalent cirrhosis. Maya, for patients only identified using OCR, would you please also create the following binary variable: date of cirrhosis diagnosis = date of HCC diagnosis (Yes/No)
Estimated Size of Cohort (if known)	~8800
Exclusions (in order)	*Step* Description
	1 Invalid IKN.
	2 Age < 18 years.
	3 Underwent liver transplant prior (date) to liver resection date or HCC index date for non-resected patients. Identified by record in CORR: - Unique identifier in TRANSPLANTED_LIVER dataset Identified by procedure codes: - OHIP feecode = S294, S295, S266 - DAD procedure code (CCI) = 1.OA.85.^^
	4 Liver resection was for a liver donor. Identified by procedure codes: - OHIP feecode = S265, S274
	4 HCC diagnosis > 1 year prior to cirrhosis diagnosis.
	5 OHIP eligibility minimum 2 years prior to HCC diagnosis date.

Project Time Frame Definitions	



Accrual Start/End Dates	January 01, 2007 – December 31, 2017; index event date = date of liver resection Timeframe to look for liver resection = within 6 months of HCC diagnosis.
Max Follow-up Date	December 31, 2019
When does observation window terminate?	The observation window for each patient terminates 2 years after their liver resection date, OR if/when they either receive a liver transplant or die prior to this.
Lookback Window(s)	April 1991 – lookback window for cirrhosis, not for HCC.

Variable Definitions (add additional rows as needed)	
Main Exposure or Risk Factor	**Liver resection/partial hepatectomy** Identified by procedure codes: - OHIP feecode = S267, S269, S270, S271, S275 - DAD procedure code (CCI) = 1.OA.87.^^ Prefer to use OHIP codes to identify. If there is discordance between same-date procedures performed in OHIP and DAD, then identify the procedure as a liver resection if there is no corresponding liver transplant procedure in CORR and if the procedure was performed at an institution with a liver transplant status (i.e. Toronto General Hospital or London Health Sciences). **Date and type of liver resection/partial hepatectomy** Date of liver resection will be obtained from the date of the OHIP feecode and/or DAD procedure code. Using this, duration (in days) from diagnosis to resection will be calculated. Type of resection = minor vs. major. - Minor refers to < 3 anatomical segments of the liver and is captured by OHIP feecode = S269, S270, S275 - Major refers to $\geq$ 3 anatomical segments of the liver and is captured by OHIP feecode = S267, S271 - Unknown = if only identified by CCI code. **VARIABLE SUMMARY:** - Liver resection (Yes/No) - If yes, date of liver resection - If yes, type of liver resection (major vs. minor; use major if both present)
Primary Outcome Definition	**Postoperative liver decompensation event** (POLDE) (defined by any one of 2 methods) *must occur after liver resection date*

Variable Definitions (add additional rows as needed)	
	1) <u>Previously-validated algorithm using ICES data</u> 1+ hospital diagnosis OR death OR procedure for decompensated cirrhosis (portal hypertension, hepatorenal syndrome, jaundice, hepatic coma, hepatic failure, bleeding esophageal varices, gastric varices, and ascites) - DAD dxcode (ICD-9) = 456.0, 456.2, 572.2, 572.3, 572.4, 782.4, 789.5 - DAD dxcode (ICD-10) = I85, I86.4, I98.2, I98.3, K72.1, K72.9, K76.6, K76.7, R17, R18 - DAD procedure code (CCI) = 1.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD, 1.KQ.76GP-NR, 1.OT.52.HA - DAD procedure code (CCP) = 10.06, 66.91 - OHIP feecode = J057, Z591 - DAD deathcode (ICD-9) = 456.0, 571.2, 571.5, 572.2, 572.3, 572.4, 572.8 - DAD deathcode (ICD-10) = I85X, I86.4, I98.2X, I98.3, K70.3, K70.4, K71.7, K72.1, K72.9, K74, K74.6, K76.6, K76.7 *Lapointe-Shaw L, Georgie F, Carlone D, et al. Identifying cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma in health administrative data: a validation study. PLoS One. 2018;13(8):e0201120.* 2) <u>International Study Group of Liver Surgery (ISGLS) criteria for post-hepatectomy liver failure</u> Definition = A postoperatively-acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio (INR) and concomitant hyperbilirubinemia on or after postoperative day 5. The cut-off values are determined by the normal ranges of the local laboratory. This will be measured as a Yes/No variable. If serum bilirubin (LOINC = 14631-6) and INR (LOINC = 6301-6) are elevated above reference range, then ISGLS = yes. Otherwise, ISGLS = no. This applies from postoperative day 5 to postoperative day 30. *Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery. 2011;149(5): 713-724.* **<u>VARIABLE SUMMARY:</u>** - POLDE? (Yes/No) - If yes, identified by algorithm (Yes/No) - If yes, identified by ISGLS (Yes/No) - If yes, to algorithm, POLDE type (see below)?
Secondary Outcome Definition(s)	**Type of postoperative liver decompensation event** Ascites - OHIP feecode = Z591 (paracentesis) - ICD-9 = 789.5, ICD-10 = R18 - CCI = 1.OT.52.HA Jaundice

Variable Definitions (add additional rows as needed)	
	- ICD-10 = R17 Esophageal/gastric varices - ICD-9 = 456.0, 456.2, ICD-10 = I85, I86.4, I98.2, I98.3 - CCI =.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD Portal hypertension - OHIP feecode = J057 – transjugular intrahepatic portosystemic shunt (TIPS) - ICD-9 = 572.3, ICD-10 = K76.6 - CCI = 1.KQ.76GP-NR Hepatorenal syndrome - ICD-9 = 572.4, ICD-10 = K76.7 Hepatic coma/encephalopathy/failure - ICD-10 = K70.4 (alcoholic failure), K71.7 (toxic liver disease with fibrosis/cirrhosis), K72.1, K72.9 - ICD-9 = 572.2, 572.8 **Date of postoperative liver decompensation event** Duration (in days) from resection to occurrence of first POLDE will be calculated using this date. As per the maximum follow-up window specified above, this duration cannot exceed 2 year (i.e. 730 days) **Mortality** Vital status at end of study (yes/no). For those with yes, date/year of death obtained using RPDB. Cause of death obtained from ORGD. Duration (in days) from surgical resection to death will be calculated. **Post-surgical liver transplant** Yes/no Identified by record in CORR - Unique identifier in CORR TRANSPLANTED_LIVER dataset Yes/no Identified by procedure codes: - OHIP feecode = S294, S266 - DAD procedure code (CCI) = 1.OA.85.^^ Date of transplant (if applicable) will be obtained using the procedure codes specified above. Using this, calculate duration (in days) from date of surgical resection to date of transplant.
Baseline Characteristics	
Age	- Obtained from the RPDB - Patient's age (in years) at the time of HCC diagnosis.
Sex	- Obtained from the RPDB - Patient's sex (Male vs. Female) at the time of HCC diagnosis.
Income quintile	1 – lowest incomes in dissemination area 2 3 4 5 – highest incomes in dissemination area
Charlson-Deyo Comorbidity Index	0 (prior to dx date) 1 2 3+ unknown

Variable Definitions (add additional rows as needed)	
	2 year lookback from the date of HCC diagnosis (includes date of diagnosis) using hospitalization data. Use most recent value. If no hospitalization data available in this timeframe, then classified as unknown. If hospitalization data available but no diagnoses listed, then classify as 0.
Elixhauser Comorbidity Index	Value 2 year lookback from the date of HCC diagnosis (includes date of diagnosis) using hospitalization data. Use most recent value. If no hospitalization data available in this timeframe, then classified as unknown. If hospitalization data available but no diagnoses listed, then classify as 0.
Asthma history	Identified using ICES-validated algorithm: - OHIP/DAD dxcode (ICD9) = 493 - DAD dxcode (ICD-10) = J45 - Yes/No variable
Diabetes history	Identified using ICES-validated algorithm: - OHIP/DAD dxcode (ICD9) = 250 - DAD dxcode (ICD-10) = E08-E13 - Yes/No variable
Hypertension history	Identified using ICES-validated algorithm: - OHIP/DAD dxcode (ICD-9) = 401, 402, 403, 404, 405 - DAD dxcode (ICD-10) = I10, I11, I12, I13, I15 - Yes/No variable
Congestive heart failure (CHF) history	Identified using ICES-validated algorithm: - OHIP/DAD dxcode (ICD-9) = 428 - DAD dxcode (ICD-10) = I500, I501, I509 - Yes/No variable
Chronic obstructive pulmonary disease (COPD) history	Identified using ICES-validated algorithm: - OHIP/DAD dxcode (ICD-9) = 491, 492, 496 - DAD dxcode (ICD-10) = J41, J43, J44 - Yes/No variable
Cirrhosis etiology	Using previously-validated algorithm: - Viral (Hepatitis B or C) - Autoimmune (autoimmune hepatitis, primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC]) - Other/metabolic disorder (hereditary hemochromatosis [HH], alpha-1 antitrypsin deficiency [A1AT], Wilson's disease) - Alcohol-related - NAFLD or cryptogenic Phillip G, Djerboua M, Carlone D, & Flemming JA. Validation of hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data. *PLoS One.* 2020;15(2):e0229218.
Preoperative serum creatinine	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 14682-9
Preoperative serum sodium	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 2951-2

Variable Definitions (add additional rows as needed)	
Preoperative platelet count	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 777-3
Preoperative serum albumin	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 1751-7
Preoperative alanine aminotransferase (ALT)	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 1742-6, 1743-4, 1744-2
Preoperative aspartate aminotransferase (AST)	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 1920-8
Preoperative serum total bilirubin	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 14631-6
Preoperative INR	Obtained from OLIS using the latest value within 1 month before HCC diagnosis to the date of liver resection: - LOINC = 6301-6
Preoperative initial model for end stage liver disease (MELD) score	Calculated using creatinine in mg/dL, bilirubin in mg/dL, and INR (unitless): MELD(i) = 0.957 x ln (Cr) + 0.378 x ln (bilirubin) + 1.120 x ln (INR) + 0.643 This score is then rounded to the tenth decimal place and multiplied by 10. The maximum MELD score is 40. Lab values < 1.0 are set to 1.0. Cr is set at 4.0 mg/dL if: - Cr > 4.9 mg/dL - Two or more dialysis treatments within last 7 days - Continuous veno-venous hemodialysis for 24 hours within last 7 days If MELD(i) > 11, then the score is re-calculated: MELD = MELD(i) + 1.32*(137–Na) – [0.033*MELD(i)*(137–Na)] Na values > 137 mmol/L are set at 137 and < 125 mmol/L are set at 125 mmol/L. https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf
History of non-malignant liver decompensation event	Non-malignant decompensation event identified by validated algorithm (Lapointe-Shaw et al., 2018) at any time prior to HCC diagnosis. Previously validated algorithm using ICES data: 1+ hospital diagnosis OR procedure for decompensated cirrhosis (portal hypertension, hepatorenal syndrome, jaundice, hepatic coma, hepatic failure, bleeding esophageal varices, gastric varices, and ascites) - DAD dxcode (ICD-9) = 456.0, 456.2, 572.2, 572.3, 572.4, 782.4, 789.5 - DAD dxcode (ICD-10) = I85, I86.4, I98.2, I98.3, K72.1, K72.9, K76.6, K76.7, R17, R18

Variable Definitions (add additional rows as needed)	
	- DAD procedure code (CCI) = 1.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD, 1.KQ.76GP-NR, 1.OT.52.HA - DAD procedure code (CCP) = 10.06, 66.91 - OHIP feecode = J057, Z591 *Lapointe-Shaw L, Georgie F, Carlone D, et al. Identifying cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma in health administrative data: a validation study. PLoS One. 2018;13(8):e0201120.*
Other Variables	
Preoperative portal venous embolization	Identified by procedure codes: - (CCI) 1.KQ.51 - (OHIP) J048 - Yes/no variable (yes if either code present; no if none present) - Must occur after diagnosis but before liver resection
Preoperative chemotherapy (HCC)	Identified by billing codes: - (OHIP) G381, G281, G345, G359, G075, G390, G339, G382, G388 - Must occur after HCC diagnosis date and before liver resection date - Yes/no variable - Billing physician specialty must be Medical Oncologist/Hematologist
Preoperative chemotherapy (ALL)	Identified by billing codes: - (OHIP) G381, G281, G345, G359, G075, G390, G339, G382, G388 - Must occur before HCC diagnosis date - Yes/no variable - Billing physician specialty must be Medical Oncologist/Hematologist
Institution	- Refers to institution where liver resection took place - Institution number - Institution name
Institution transplant status	Is the institution a liver transplant centre? - Yes (if patient underwent resection at London Health Sciences Centre or Toronto University Hospital Network)
Postoperative length of stay	Measured using DAD. LOS = (discharge date – surgery/admission date) LOS = 1 if the both dates are the same
Postoperative readmission(s)	These are 2 variables, one measured at 30 and the other at 90 days after discharge from surgical visit.
Postoperative day 5 serum total bilirubin	Obtained from OLIS on postoperative day 5 (if not available, then next available value after day 5 but before day 30). - LOINC = 14631-6
Postoperative day 5 INR	Obtained from OLIS on postoperative day 5 (if not available, then next available value after day 5 but before day 30). - LOINC = 6301-6
OCR variables	Among patients identified with HCC via OCR codes: - Primary number for HCC - If value is not 1, then identity of last 3 cancers diagnosed and year of diagnosis for each.
Emergency department visits	Number of emergency department visits following discharge from hospital after liver resection. Timeframe = discharge to end of study.
Hospital admissions	Number of hospital admissions with length of stay > or = 1 day following discharge from hospital after liver resection. Timeframe = discharge to end of study.

Variable Definitions (add additional rows as needed)	
Follow-up days	Days from liver resection to end of study follow-up period. Only required for patients that received liver resection (n=611).

Analysis Plan and Dummy Tables (expand/modify as needed)	
Descriptive Tables (insert or append dummy tables), e.g.: see attached tables.	
Table 1. Baseline characteristics of patients with incident HCC between 2007-2017.	
Table 2. Postoperative outcomes of patients that underwent liver resection/partial hepatectomy.	
Table 3. Variables associated with POLDEs among patients following liver resection/partial hepatectomy.	
Statistical Model(s)	
Type of model	Cox/competing risks regression
Primary independent variable	Liver resection/partial hepatectomy
Dependent variable	POLDE
Covariates	Age, Sex, MELD, Etiology of Cirrhosis, Diabetes, Preoperative Platelets, Preoperative Bilirubin, Preoperative INR, Type of Liver Resection
Sensitivity Analysis #1	Excluding patients that underwent pre-operative portal venous embolization
Type of model	Cox/competing risks regression
Primary independent variable	Liver resection/partial hepatectomy
Dependent variable	POLDE
Covariates	Age, Sex, MELD, Etiology of Cirrhosis, Diabetes, Preoperative Platelets, Preoperative Bilirubin, Preoperative INR, Type of Liver Resection
Sensitivity Analysis #2	Excluding patients with mortality or POLDEs occurring within 30 days after surgery
Type of model	Cox/competing risks regression
Primary independent variable	Liver resection/partial hepatectomy
Dependent variable	POLDE
Covariates	Age, Sex, MELD, Etiology of Cirrhosis, Diabetes, Preoperative Platelets, Preoperative Bilirubin, Preoperative INR, Type of Liver Resection

Quality Assurance Activities	
RAE Directory of SAS Programs	
RAE Directory of Final Dataset(s)	*The final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn't make the final cut. This would permit an analyst to easily re-run the models in the future.*

Quality Assurance Activities		
RAE README file available: ☐Yes ☐No		
Date results of quality assurance tools for final dataset shared with project team (where applicable):		
	%assign	yyyy-mon-dd
	%evolution	yyyy-mon-dd
	%dinexplore	yyyy-mon-dd
	%track / %exclude	yyyy-mon-dd
	%codebook	yyyy-mon-dd
Additional comments:		