Summer 8-14-2020

Reducing Adverse Outcomes in Hepatocellular Carcinoma Patients Undergoing Hepatectomies

Yongyue Qi
University of Nebraska Medical Center

REDUCING ADVERSE OUTCOMES IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING HEPATECTOMIES

by

Yongyue Qi

A DISSERTATION

Presented to the Faculty of

the University of Nebraska Graduate College

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

Epidemiology Graduate Program

Under the Supervision of Professor Paraskevi A. Farazi, PhD

University of Nebraska Medical Center

Omaha, Nebraska

July 2020

Supervisory Committee:

Tricia D. LeVan, PhD

Gleb Haynatzki, PhD, DSc

Chandrakanth Are, MD, MBA, FRCS, FACS

ACKNOWLEDGMENTS

First, I would like to express my sincere gratitude to my committee chair Dr. Paraskevi Farazi for her excellent mentoring, invaluable guidance, and continuous support. I would also like to thank the other members of my supervisory committee Dr. Tricia LeVan, Dr. Gleb Haynatzki and Dr. Chandrakanth Are for their guidance, insight and feedback. I am grateful to many people including Dr. Deborah Levy, Dr. Shinobu Watanabe-Galloway, Dr. Lorena Baccaglini, Dr. KM. Monirul Islam, and Dr. Veenu Minhas who have supported me throughout this journey. This dissertation would not have been possible without the expertise and the willingness to help of all these fabulous faculty.

Next, I would like to thank my family, especially my wife Chao, for her extreme patience and tremendous support. I also want to thank my son Jiahao and my daughter Angela for their encouragement and help in any way possible.

Lastly, I would like to thank my two supervisors in Creighton University Dr. Brenda Coppard and Dr. Keli Mu for their understanding and constant support.

ABSTRACT

REDUCING ADVERSE OUTCOMES IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING HEPATECTOMIES

Yongyue Qi, M.S.

University of Nebraska, 2020

Supervisor: Paraskevi A. Farazi, PhD

The incidence and mortality of liver cancers are increasing in the United States. In addition to the classic risk factors of hepatic viral infection and high alcohol consumption, non-alcoholic Fatty Liver Disease (NAFLD), has emerged as a risk factor for hepatocellular carcinoma (HCC). The most effective curative treatment for HCC is liver resection (hepatectomy), however, hepatectomy is a major operation with potential risks of mortality, hospital readmission and other adverse outcomes such as postoperative complications and longer hospital stay. The reported 90-day mortality and 30-day readmission rates following a hepatectomy vary widely across studies, most of which have limitations due to small sample size, localized study sites and lack of use of national representative samples. Furthermore, very few studies have focused on the impact of NAFLD on postoperative outcomes in HCC patients undergoing hepatectomies. The long-term goal of this proposal was to improve 90-day mortality, unplanned 30-day readmission and other adverse outcomes among HCC patients undergoing hepatectomies. The specific aims of this work were to: (1) develop and test the discriminatory ability of a risk score model to group patients into low, medium, high and excessive risks groups for 90-day mortality following hepatectomy based on the weighting of identified demographic and hospital related risk factors; (2) investigate risk factors associated with 30-day unplanned readmission and address its impact on conditional 90-day mortality; (3) describe 10-year (2005-2014) national trends and patterns of NAFLD prevalence among all hospitalized HCC patients

and compare the impact of NAFLD on adverse outcomes (increased occurrence of postoperative complications, in-hospital mortality and longer hospital stay) in HCC patients who underwent hepatectomy. To address the first aim, a retrospective, cross-sectional study was conducted using one of the largest clinical cancer database in the world – the National Cancer Database (NCDB) to investigate the rate of 90-day mortality and associated risk factors and to build a risk score model based on the weighting of identified risk factors to predict 90-day mortality. For the second aim, a cross-sectional study design was used to identify risk factors associated with 30-day unplanned readmission and assess how a history of 30-day unplanned readmission would affect patients' conditional 90-day mortality using NCDB. For aim 3, another national representative database - Nationwide Inpatient Sample (NIS) was used for a retrospective study to describe the national trend and pattern of NAFLD prevalence among hospitalized HCC patients from 2005 to 2014 and to address the impact of NAFLD on adverse outcomes including postoperative complications, in-hospital mortality and hospital length of stay (LOS) in HCC patients undergoing hepatectomies. Our results indicated that an integer-valued risk score can be developed based on 10 identified risk factors to predict 90-day mortality. The discriminatory ability of this risk score, measured by AUC of 0.69, was comparable with other risk models of prior studies. Our study also showed that patients with a history of 30-day unplanned readmission carried higher risk of conditional 90-day mortality. Interestingly, NAFLD did not seem to increase the risk of postoperative adverse outcomes. Future studies are needed to further improve the risk model by linking NCDB to Midwest CoC accredited hospital databases to add detailed information on comorbidity and complications, by addressing the roles of family care and medication compliance between discharge and readmission, and by repeating study 3 in multi-institutional setting with more accurate and complete diagnosis of NAFLD cases.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AARP American Association of Retired Persons

ACS American Cancer Society

ACoS American College of Surgeons

AFP Alpha Fetoprotein

AHRQ Agency for Healthcare Research and Quality

AJCC American Joint Committee on Cancer

AUC Area Under the Curve

BCLC Barcelona Clinic Liver Cancer

CoC Commission on Cancer

CI Confidence Interval

CLIP Cancer of the Liver Italian Program

DRGs Diagnosis Related Groups

EHR Electronic Health Record

FIPS Federal Information Processing Standard

HBV Hepatitis B Virus

HCC Hepatocellular Carcinoma

HCV Hepatitis C Virus

HPFS Health Professionals Follow-up Study

HRRP Hospital Readmissions Reduction Program

IARC International Agency for Research on Cancer

ICD-O-3 International Classification of Disease for Oncology Third Edition

ICD-9-CM The International Classification of Diseases, Ninth Revision, Clinical Modification

JIS Japan Integrated Staging

LOS Length of Stay

MELD Model for End-Stage Disease

MS Metabolic Syndrome

NAFLD Nonalcoholic Fatty Liver Disease

NASH Nonalcoholic Steatohepatitis

NCDB National Cancer Database

NHS Nurses' Health Study

NIH National Institute of Health

NSQIP National Surgical Quality Improvement Program

OR Odds Ratio

P-POSSUM Portsmouth-Physiological and Operative Severity for the enumeration of Mortality and Morbidity

PR Prevalence Ratio

ROC Receiver Operating Characteristic

SEER Surveillance Epidemiology and End Results

UICC Union for International Cancer Control

US The United States

USDA United States Department of Agriculture

WHO World Health Organization

CHAPTER 1

INTRODUCTION

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is a primary liver cancer arising from liver cells (hepatocytes). It is the most common histological type of liver cancers accounting for approximately 80-90% of all liver malignancies (Chacko & Samanta, 2016). Some of the risk factors for HCC include infection with hepatitis B or C viruses, heavy alcohol consumption, aflatoxin B1 exposure, and non-alcoholic fatty liver disease (NAFLD). Approximately 80% of HCC develop in the background of liver cirrhosis, which is an independent cause of death (Couto, Dvorchik, & Carr, 2007). HCC is often diagnosed late due to the absence of symptoms and lack of effective surveillance strategies for high risk patients (Simmons et al., 2019; Kansagara et al., 2014).

Epidemiology of HCC

HCC is the fifth most common cancer and the second leading cause of cancer deaths worldwide (Akinyemiju et al., 2017). Asian countries including China, Mongolia, Southeast Asia, and Sub-Saharan Western and Eastern African have the highest incidence rates in the world (WHO, 2012). The age-adjusted incidence rates of liver cancer ranked seventh highest among all cancers in the world with approximately 15.1 (male) and 5.6 (female) cases per million people diagnosed for the year of 2017. There were around 819,000 liver cancer-related deaths accounting for 8.6% of all cancer deaths in 2017 globally (Global Burden of Disease Cancer Collaboration, 2019). The incidence and mortality of liver cancers have been increasing for more than three decades from 1975 to

2009 in the United States (Siegel, Naishadham, & Jemal, 2013). However, a recent study using the US Cancer Statistics Registry showed that the incidence of HCC increased 4.5% annually between 2000 and 2009 while it decreased slightly by 0.7% annually from 2010 through 2012 indicating the increase in the incidence of HCC might have slowed or plateaued (White et al., 2017). Most recent cancer statistics projected that 42,030 new cases would occur, and 31,780 patients would die from liver cancer in 2019 (Siegel at al., 2019).

HCC largely affects men with incidence two to four times than the incidence in women (Bosch et al., 2004). However, hazard ratios of risk factors such as viral hepatitis and cirrhosis are similar in male and female stratum (Yi et al., 2018) and this protective effects against the development of HCC in women may come from the role of estrogen, which is strongly evidenced in young women (Davis et al., 2010). Racial disparities in the incidence of HCC are also evident in the US. One research conducted by Yang and colleagues reported that the incidence of HCC was highest among Asian and Pacific Islanders followed by Hispanics and black, with the lowest rates among whites (Yang et al., 2018). The study also discovered that Hispanics and blacks were less likely to be diagnosed with early stage HCC compared with whites. Regardless of whether they were diagnosed at an early stage, Hispanics were less likely to receive curative treatment for HCC than their white counterparts. Blacks demonstrated significantly worse survival than whites before and after adjusting for other important factors including insurance coverage, Child-Pugh class, BCLC tumor stage, and receipt of HCC treatment. These disparities may reflect behavioral differences with regards to other HCC risk factors such as alcohol consumption and unhealthy diet.

Risk Factors of HCC

There are a number of well-established HCC risk factors including cirrhosis, infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV), alcoholic liver diseases, non-alcoholic fatty liver disease (NAFLD), and aflatoxins. Tobacco smoking, androgenic steroids, and diabetes mellitus are suspected risk factors (Ledda et al., 2017). HCC occurs overwhelmingly in the presence of cirrhosis or advanced fibrosis, though among a small portion of patients, HCC is developed without a background of cirrhosis (Adams & Lindor, 2007).

Hepatitis infections

Chronic infections with HBV and HCV are the most commonly recognized risk factors of HCC worldwide (Stuver et al., 2008; Boffetta et al., 2014). It is estimated that 54% of all liver cancers in the world can be attributed to HBV infection (Parkin, 2002). In the United States, approximately 45% to 55% of new HCC cases are contributed to HCV, 10% to 15% to HBV, and 5% are co-infected with HBV and HCV, and 30% to 35% show no association with either HBV or HCV (Mittal & El-Serag, 2013). Individuals with chronic HBV infection have 15- to 20-fold higher odds of developing HCC and the odds are doubled in the case of HBV and HCV co-infection (Mittal & El-Serag, 2013; Shi, Zhu, Liu, & Xie, 2005). HCV infection alone is believed to be associated with approximately 17-fold increased odds of developing HCC (Shi, Zhu, Liu, & Xie, 2005). It is postulated that chronic liver inflammation due to HCV infection leads to the injury of liver parenchyma with subsequent development of fibrosis (Lok et al., 2011). The progression from cirrhosis to HCC in actively HCV-infected patients occurs at an annual rate of 1% to 4% (El-Serag, 2012).

Other etiologic factors that coexist with HBV-infected individuals may further increase the risk of developing HCC. For example, male patients, HBV infection at younger age, Asian and Pacific Islanders, and individuals with heavy alcohol consumption and/or tobacco use have been shown to have increased risk of HCC (El-Serag, 2012). In

addition to these risk factors, HCV genotype also modifies individual's risk of HCC. A meta-analysis has reported that genotype 1b was associated with 78% increased risk of HCC compared to all other genotypes (Kanwal et al., 2014; Kattakuzhy et al., 2016) and genotype 3 is associated with highest risk of cirrhosis (Raimondi et al., 2009).

Alcohol drinking

Approximately 13% to 23% of HCC cases are attributable to alcohol drinking and the effect varies based on patients' race and sex (Makarova-Rusher et al., 2016; Welzel et al., 2013). Most case-control studies have indicated that heavy alcohol drinking is associated with increased risk of primary liver cancer (Bagnardi et al., 2001; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010). A case-control study in Italy enrolled 464 cases with primary diagnosis of HCC and 824 controls. Researchers found the odds of HCC were 7 times higher in individuals with alcohol intake of > 60 g/day compared to those with an intake of ≤60 g/day (Donato et al., 2002). In the National Institutes of Health (NIH) – AARP Diet and Health Study, drinkers with three levels of alcohol consumption were compared. It was found that drinkers of > 3 drinks per day had nearly 2-fold increased odds of developing HCC compared to drinkers of <1 drink per day (Persson et al., 2013). It is believed that alcohol may play a crucial role in initiating cancers through enhancing certain oncogene expression or the impairment of cell's ability to mend their DNA resulting in the increase of oncogenic mutation (Testino, Leone, & Borro, 2014).

Non-Alcoholic Fatty Liver Disease (NAFLD)

Over the last decade, there has been an increase in the proportion of NAFLD-associated cirrhosis and HCC (White, Kanwal, & El–Serag, 2012). Research has reported that between 4% and 22% of HCC cases in Western countries are attributed to NAFLD (Yang et al., 2012; Hucke et al., 2011; Ertle et al., 2011). From 2002 to 2012, the number

of patients with NASH-HCC undergoing a liver transplant increased by 4-fold, almost twice as many as those with HCV-HCC (Wong, Cheung, & Ahmed, 2014). The association between NAFLD and increased risk of HCC was confirmed in a large prospective cohort study involving 130 facilities in the Veteran Health Administration from January 1, 2004 to December 31, 2008. During 2,382,289 person-year of follow-up, NAFLD patients demonstrated a 7.6-fold increased risk of developing HCC than non-NAFLD patients. In addition, approximately 20% of NAFLD patients with HCC had no evidence of cirrhosis (Kanwal et al., 2018). Fatty liver may also increase the risk of HCC in other types of liver disease. Two studies have indicated that in patients with chronic hepatitis C infection, the risk of HCC will increase by 2-3-fold if patients also have a coexisting steatosis compared to those without steatosis (Pekow et al., 2007; Tanaka et al., 2007).

Type 2 diabetes and obesity

Type 2 diabetes is associated with HCC. Literature began to describe the existence of an association between Type 2 diabetes and HCC more than 30 years ago where a case-control study matched 105 HCC patients with 105 patients with either colorectal cancer or femoral bone fracture by age and gender. The study found a 4-fold risk of prevalent type 2 diabetes among patients with HCC compared to those with colorectal cancer or femoral bone fracture (Lawson et al., 1986). In a meta-analysis that included 32 cohort studies and 17 case-control studies, researchers found a 2.3-fold increased risk of HCC prevalence in individuals with type 2 diabetes. In addition, an increased risk of HCC mortality was also noted in diabetic individuals (Wang et al., 2012). A recent cohort study prospectively followed up two cohorts of U.S. men and women. The Nurses' Health Study (NHS) enrolled 120, 826 women in 1980 and followed them through 2012. The Health Professionals Follow-up Study (HPFS) enrolled 50,284 men in 1986 and followed them

through 2012. The study found type 2 diabetes was associated with 4.6-fold increase in the risk of HCC (Simon et al., 2018).

Aflatoxin B1

Aflatoxin B1 (AFB1) is a mycotoxin produced by fungus *Aspergillus flavus* and *Aspergillus parasiticus* which are common and widely distributed in nature (Kew, 2013). Foodstuffs including corn, rice oil seeds, dried fruits and peanuts can be contaminated with AFB1 if they are improperly stored in environment with high temperature and humidity (Baydar et al., 2005). Farm produce such as milk, meat and eggs would also be contaminated if farm animals were fed with aflatoxin-contaminated food (Bennett, 2003; Fink-Gremmels, 1999). AFB1 has been classified as 'group A' carcinogen by World Health Organization (WHO) because evidence showed that exposure to AFB1 significantly increased the risks for HCC (Lopez et al., 2002). Several studies proposed that AFB1 affects liver and increase the risk of HCC via p53 gene mutation (Egal et al., 2005; Bressac, Kew, Wands, & Ozturk, 1991). Aflatoxins are the most common non-infectious food-borne risk factor that threats 4.5 to 5.5 billion people worldwide (Williams et al., 2004; Strosnider et al., 2006). It has reported that the risk of liver cancer in individuals exposed to both HBV and ALB1 is 30 times higher than the risk in those exposed to aflatoxin alone (Groopman, Kensler, & Wild, 2008; Liu & Wu, 2010).

Staging of HCC

Multiple staging systems are used to direct clinical treatment modalities and to determine prognosis. The Barcelona Clinic Liver Cancer (BCLC) model (Figure 1.1) is a widely endorsed staging system assisting treatment decisions. BCLC classifies patients into 5 stages (0, A, B, C, and D) incorporating patients' tumor characteristics and underlying liver functions (measured as Child-Pugh stage). Other commonly used staging

systems include the Cancer of the Liver Italian Program (CLIP), and two main pathology-based staging systems: the American Joint Committee on Cancer (AJCC)/ Union for

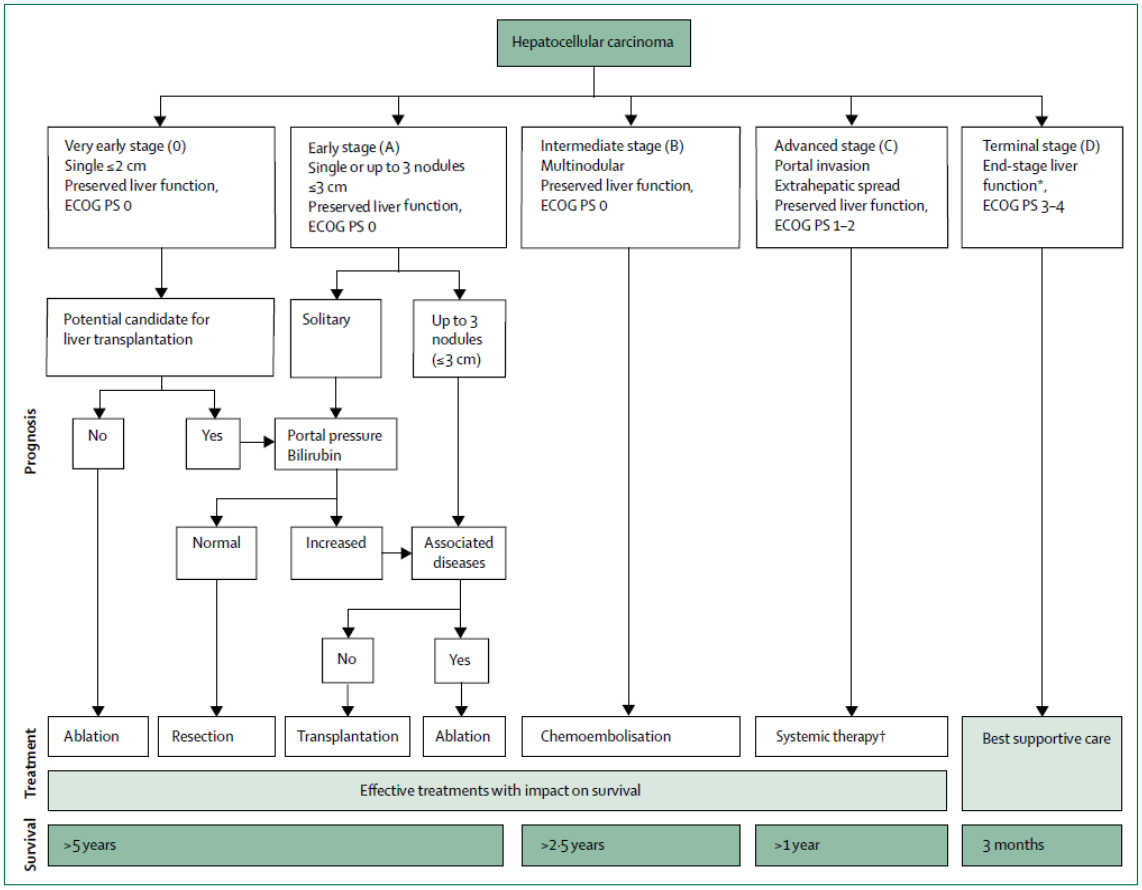

Figure 1. 1: **Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy**
The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Note that liver function should be evaluated beyond the conventional Child-Pugh classification or the Model of End-stage Liver Disease (MELD) score. None of them serves to properly gauge the liver function status, and this evaluation should take into account biochemistry parameters as well as the compensated or decompensated status of the patient. Preserved liver function includes a group of patients with different degrees of liver function reserve that has to be carefully evaluated. For most treatment options, compensated liver disease (Child-Pugh stage A without ascites) is required to obtain optimal outcomes. The sole option that could be applied irrespective of liver function is liver transplantation. ECOG PS=Eastern Cooperative Oncology Group Performance Status. *Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation. In these patients, hepatocellular carcinoma might become a contraindication if it exceeds enlistment criteria. †Currently, sorafenib followed by regorafenib has been shown to be effective. Lenvatinib has been shown to be non-inferior to sorafenib, but no second-line option after lenvatinib has been explored. (Adapted from Forner, Reig, & Bruix. 2018)

International Cancer Control (UICC) staging system and the Japan Integrated Staging (JIS) score (Edge & Compton, 2010; Nanashima et al., 2006). CLIP score takes Child-Pugh grade, tumor morphology, alpha-fetoprotein (AFP) and portal vein thrombosis into account and generates a score ranging from 0 to 6. Rather than make a treatment recommendation, the CLIP system determines prognosis in terms of the number of months that patients will

survive (Cancer of the Liver Italian Program (CLIP) Investigators, 1998). For HCC patients who will undergo either a liver resection or liver transplant, a staging system that includes pathologic assessment of the tumor is recommended. AJCC/UICC and JIS are used for this purpose and both include TNM staging, which assesses tumor size, regional lymph node involvement and metastasis (Edge & Compton, 2010). These staging systems along with other considerations of personal factors such as race/ethnicity are very helpful in directing therapies.

Treatment of HCC

Surgical resection, transplantation, ablation, transarterial chemoembolization and the tyrosine-kinase inhibitors sorafenib, lenvatinib, and regorafenib are treatments with proven survival benefit (Llovet & Bruix, 2003; Llovet et al., 2008; Kudo et al., 2008; Bruix et al., 2017). Other treatment modalities including arterial embolization without chemotherapy, external radiotherapy, and radioembolization have not been definitively shown to have survival benefit (Llovet et al., 2002; Kalogeridi et al., 2015; Sangro et al., 2011).

Surgical resection

A liver resection refers to the surgical removal of all or a portion of the liver. Resection is the most effective, curative treatment, and generally performed in patients without cirrhosis. However, HCC without cirrhosis is rare in Western countries whereas only 5% of HCC developed in a non-cirrhotic liver (Schwartz, Roayaie, & Konstadoulakis, 2007). The evaluation of hepatic reserve is important when a liver resection is considered. Partial hepatectomy may be performed on patients with a localized single tumor without cirrhosis or Child class A cirrhosis with adequate liver parenchyma (Delis & Dervenis, 2008). The overall long-term survivals after liver resection are favorable. Greater than 70% of 5-year

survivals after liver resection were reported in patients with tumor<5cm, no vascular invasion and a negative surgical margin of at least 1 cm (Shi et al., 2007).

In patients with cirrhosis, possible pre-existing liver damage and tumor multifocality may complicate treatment and a preoperative risk evaluation is necessary to achieve long-term survival. A minimum of 40% well-perfused liver volume must remain in situ after liver resection (Vauthey et al., 2000). Studies have shown that resection can be performed in cirrhotic patients without (Eguchi et al., 2011) and even with portal hypertension presenting acceptable mortality rates and oncological benefits (Ishizawa et al., 2008; Verloh et al., 2013). Good 5-year survival of 57% and 38% were achieved among patients whose liver was resected on the basis of BCLC stages of B and C respectively in centers specialized in complex liver surgery (Torzilli et al., 2013).

Liver transplantation

Liver transplantation is the most effective treatment option to prevent intrahepatic recurrence. Milan criteria has been accepted in the US and Europe as the selection standard for eligible patients (Sapisochin & Bruix, 2017). Milan criteria restrict transplantation in patients with HCC as follows: 1) single tumor less than 5 cm in diameter; 2) up to three modules less or equal to 3 cm in diameter; 3) no angioinvasion and 4) no extrahepatic involvement (Mazzaferro et al., 1996). For patients who had liver surgery within Milan criteria, 5-year survival of 50% to 70% can be achieved so the benchmark for liver transplantation is set at 70% overall survival at 5 years (Poon et al., 2002; Giuliante et al., 2012; Clavien et al., 2012). The expanded criteria were proposed in 2001 by Yao and colleagues because they considered Milan criteria were too restrictive. The expanded criteria made transplantation possible for patients with single tumor <6.5 cm or <3 nodules with the largest lesion <4.5 cm and total tumor diameter <8 cm (Yao et al., 2001). Patients with tumors within the expanded criteria had 1-year survival rate of 90%, significantly

higher than the 50% among patients with tumors exceeding these limits (Yao et al., 2001). Liver transplantation can treat HCC and pre-existing cirrhosis or other chronic liver disease simultaneously, however, donor availability is a challenge and patients may wait for a long time during which tumor may progress and impede transplantation.

Surgical Outcomes of HCC

Several adverse outcomes related to liver resection in patients with HCC include perioperative mortality, readmission, postoperative complications and prolonged hospital length of stay.

Perioperative mortality

Prior studies have reported that perioperative mortalities associated with liver resection have improved from 10%-20% to less than 5% (Nagasue & Yukaya, 1989; Thompson, Tompkins & Longmire, 1983; Fan et al., 1995). A meta-analysis that included a large number of studies evaluated the postoperative mortality rates for the sample that comprised more than 35,000 patients with primary and metastatic tumors and found that 3.15% patients died after the hepatectomy (Ramacciato et al., 2012). The mortality rate of 4.01% in HCC patients was significantly higher than the rate of 2.34% in non-HCC cases. In another population-based study, Mayo et al. (2011) used the SEER database to define postoperative mortality. The study included 2,597 patients who underwent hepatic resection during 1991-2006 and found that the 30, 60 and 90-day postoperative mortalities were 5.7%, 8.3% and 10.1% respectively (Mayo et al., 2011). The study also discovered that HCC patients had a higher mortality rate than those with colorectal liver metastasis (15.0% versus 8.4% respectively for 90-day mortality). Dimick et al. (2003) identified 2097 patients (16% with HCC, 52% with secondary metastases) who underwent liver resection between 1996 and 1997 and reported an overall postoperative mortality rate of 5.8%. The

study also found that low hospital volume, older than 65 years, hepatic lobectomy (vs. wedge resection), primary liver tumors (vs. metastases) and liver disease severity were risk factors associated with higher risk of 90-day mortality (Dimick et al., 2003). In a population-based study from Taiwan, researchers reported that the 90-day mortality after hepatectomy was 3.9% and preexisting renal and cirrhosis-related complications were found to be the strongest risk factors of mortality (Chang et al., 2014). Another hospital-based study investigated 774 early stage HCC patients who underwent liver resection and found a lower postoperative mortality of 1.3% (Margonis et al., 2017). An analysis of 1803 consecutive patients who underwent hepatic resection at Memorial Sloan-Kettering Cancer Center from 1991 to 2001 reported an overall mortality after hepatectomy of 3.1% (Jarnagin et al., 2002). Risk factors associated with mortality were the number of hepatic segments resected and the blood loss during the operation. A study with more representative samples from five hepatobiliary centers located in France, China, and USA was performed aiming to examine long-term survival trend for HCC patients experiencing major hepatectomy. The study found the overall 90-day postoperative mortality rate was 4% and there were no differences in patients underwent right hepatectomy and those who received extended hepatectomy (Andreou et al., 2013). In summary, hepatectomy related mortality decreased dramatically from as high as 20% to less than 5% during last 30 years. The postoperative mortality rates are higher in patients with HCC than those with metastasis liver tumors. Risk factors associated with early mortality after hepatectomy include demographic factors (gender and age), clinical factors (surgical procedures, complications, blood loss during operation, postoperative liver function and comorbidities), hospital related factors (hospital type and annual volume), and biochemical factors (bilirubin and serum phosphorus level).

Early readmission after liver resection

In addition to perioperative mortality, early readmission after liver resection is another adverse outcome related to the surgery and associated with substantial burdens in health care spending. Several studies examined the 30- or 90-day readmissions after hepatectomy. An analysis of early readmission and its characteristics, patterns and risk factors reviewed 1,281 patients who underwent hepatic resection from 1996 to 2009 at Duke University Medical Center. The study indicated that 90-day readmission rate was 14.4%. Contributing factors included major hepatectomy, major postoperative complications and index hospitalization>7 days (Barbas et al., 2013). However, indications from this study were contradicted with a research led by Kulaylat that concluded neither index hospitalization>7 days nor postoperative hepatobiliary complications played a significant role for the readmission (Brudvik et al., 2015). Another study conducted at Johns Hopkins Hospital identified 338 patients undergoing hepatectomy from 2008 to 2012. The overall 30-day readmission was 14.2% and, like previous study, postoperative complication was found to be the strongest risk factor for the readmission (Spolverato et al., 2014). Two publications reported higher 90-day readmission rates. In a study that reviewed a prospectively maintained hepatobiliary database for 245 HCC patients undergoing hepatectomy from 2000 to 2012, Kimbrough and colleagues found that the 90-day readmission rate was 18.7% (Kimbrough et al., 2014). A slightly lower 90-day readmission rate of 17.3% was reported in another study that analyzed 1,184 patients who underwent major hepatectomy from three institutions (Emory University, the University of Louisville and the University of Wisconsin) from 2000 through 2012 (Egger et al., 2014). Insurance status is often used as a demographic variable in many studies. A retrospective medical record review for examining risk factors of unplanned hospital readmission compared demographics, severity of illness, family support, symptoms and comorbidities of 78 readmitted cancer patients with those (78 patients) without a readmission. The study found that patients with financial and insurance concerns were more likely to be readmitted

to hospital (Weaver et al., 2006). A more recent study explored risk factors for 30-day unplanned readmissions in patients with parotid cancer who underwent surgery from 2003 to 2012 recorded in NCDB. The study indicated that the odds of readmission were 2.3 times higher for uninsured patients when compared with those privately insured (Zhan et al., 2016). As two of the postoperative outcomes, perioperative mortality and early readmission after surgery are believed to be associated with each other. Studies have found that early readmission is associated with increased postoperative mortality. A cross-sectional study investigated the relationship between time to readmission and mortality in Medicare patients undergoing high-risk surgery from 2005 to 2009. The study found that the odds of postoperative mortality were 4.9, 4.2 and 3.8 times higher for patients readmitted between 1-5 days, 6-10 day and 11-15 days respectively than those not readmitted (Gonzalez et al., 2015). In another population-based study, Hu and colleagues evaluated the impact of 30-day readmission on 90-day postoperative mortality for patients who underwent lung cancer resection. The study used SEER-Medicare linked database and identified 11,432 patients from 2006 to 2011. Researchers reported that the overall 30-day readmission rate was 12.8% and 30-day readmission was associated with 6-fold increased odds of 90-day mortality (Hu et al., 2014). The study also indicated that patient age, preoperative morbidities, and type of operation were associated with 30-day readmission.

Postoperative outcomes in patients with NAFLD-HCC

Though early postoperative mortality and readmission are the two main adverse outcomes following a hepatectomy, there are other outcomes such as postoperative complications and longer hospital stay as well. As mentioned earlier, NAFLD has emerged as playing increasing roles in the development of HCC and affecting its prognosis. Several studies have investigated surgical outcomes for NAFLD-HCC versus HCC with other

etiologies such as HBV or HCV infection. In a study that used consecutive patient data from a multicenter database between 2003 and 2012, researchers noted the similar perioperative outcomes perioperative mortality and morbidity, and comparable overall survival and recurrence-free survival (Yang et al., 2020). To examine the impact of steatosis on the outcomes following hepatic resection in cancer patients, Kooby and colleagues quantified steatosis for 325 patients with fatty liver. Patients with steatosis <30% were classified as having mild steatosis while the rest were classified as having marked steatosis. The study did not observe the differences in complications requiring major medical intervention, hospitalization, or admission to the intensive care unit between mild and marked steatosis groups in univariate analysis. However, in multivariable analysis, steatosis was found to be an independent predictor of complications but did not impact on 60-day mortality (Kooby et al., 2003). NAFDL is believed to be closed related to metabolic syndrome (MS) which include clinicopathological manifestations of hypertension, dyslipidemia, obesity, and diabetes (Starley, Calcano, & Harrison, 2010; El-Serag, Tran, & Everhart, 2004). In a study that compared the outcomes following liver resection between patients with MS-HCC and HCV-HCC, patients with MS-HCC were matched one-to-one with patients with HCV-HCC without metabolic syndrome. The study indicated that patients with MS-HCC had similar lower mortality and higher morbidity rates to patients with HCV-HCC and MS-HCC was associated with much better long-term outcomes (Viganò et al., 2015). Another retrospective, hospital-based study enrolled 147 HCV-HCC patients, 61 HBV-HCC patients and 17 NAFLD-HCC patients aimed to investigate the surgical outcomes of NAFLD-HCC patients. Univariate analyses of the study indicated that postoperative morbidity and 30-day mortality rates were significantly higher in NAFLD-HCC patients. However, these patients showed better disease-free survival on both univariate and multivariable analyses (Wakai et al., 2011). Similar long-term survival outcomes in NAFLD-HCC patients were also reported in another hospital-based study

with a larger sample size. After comparing outcomes of curative treatment between NAFLD-HCC and non-NAFLD-HCC patients, the study concluded that NAFLD-HCC was associated with a higher surgical mortality and postoperative liver failure but a favorable 5-year overall survival. Prospect research revealed that NAFLD-HCC is more often found at a later tumor stage than HCV-HCC resulting in overall worse prognosis. However, if NAFLD-HCC patients are matched with HCV-HCC patients for tumor stage, prognosis for both NAFLD-HCC and HCV-HCC patients are statistically same, which may indicate the natural history is unrelated to the background etiology of liver disease (Piscaglia et al., 2016).

KNOWLEDGE GAPS

Hepatectomy is a major operation with potential risks of mortality and hospital readmission (Kim et al., 2015). Typically, 90-day mortality and 30-day readmission are important quality measures of perioperative care and associated risks. The reported 90-day mortality rates following a hepatectomy vary widely across studies from 2.0% to 10.1% (Hyder et al., 2013; Etra et al., 2014; Bachellier et al., 2011; Margonis et al., 2017; Al-Alem et al., 2016; Chang et al., 2014) and factors such as complications, amount of blood loss, surgical procedures, and liver function were found to affect 90-day mortality (Al-Alem et al., 2016; Jarnagin et al., 2002; Andreou et al., 2012). A handful of studies had proposed some risk score models predicting 90-day mortality after hepatectomies, which generated 3 to 4 risk groups with corresponding 90-day mortality from 0.25% to 35.9%. However, these studies have limited generalizability given the small sample size and localized study sites. None of these studies have examined if these risk scores could be developed and applied to a broader HCC population in the US.

Of the few studies that examined 30-day readmission, most were either US hospital-based or non-US population-based or are outdated. Among these studies, 30-day readmission rates ranged from 10%-20% and postoperative complications were identified as the main risk factors of 30-day readmission. These studies often include HCC and other primary or secondary liver malignancies as well as benign tumors and cannot measures HCC-specific readmission rates and associated risk factors. In addition, no prior studies have investigated the impact of unplanned 30-day readmission on subsequent conditional 90-day mortality in a nationally representative sample that captures 70% of all newly diagnosed cancer cases.

Though early postoperative mortality and readmission are the two main adverse outcomes following a hepatectomy, there are other outcomes such as postoperative complications and longer hospital stay as well. As obesity became pandemic, the prevalence of NAFLD has increased significantly and emerged as playing increasing roles in the development of HCC and affecting the prognosis. However, reports on the prevalence and temporal trend of NAFLD in hospitalized patients with HCC are limited. Furthermore, the impact of NAFLD on surgical outcomes including postoperative complications, in-hospital mortality, and hospital length of stay in HCC patients with NAFLD who underwent liver resection is not well addressed.

SPECIFIC AIMS AND HYPOTHESIS

Aim 1: To develop and test discriminatory ability of a risk score model to group patients with low, medium, high, and excessive risks of 90-day mortality following a hepatectomy based on the weighting of identified demographic and hospital related risk factors.

Hypothesis: As indicated by previous literature, factors such as age, gender, comorbidities, hospital type and volume may affect 90-day mortality and these factors could be weighted and used to develop a risk score model.

Aim 2: To investigate risk factors associated with 30-day unplanned readmission and address its impact on conditional 90-day mortality after hepatectomy.

Hypothesis: Patients' age, gender, insurance program, comorbidity scores, tumor size and surgical procedures may affect unplanned 30-day readmission as suggested by previous literature. Furthermore, patients with a history of 30-DR would have a higher risk of conditional 90-day mortality.

Aim 3: To describe the 10-year (2005-2014) national trends and patterns of NAFLD prevalence among all hospitalized HCC patients and compare the impact of NAFLD on adverse outcomes post-hepatectomy (occurrence of postoperative complications, in-hospital morbidity and longer hospital stay) in HCC patients with and without NAFLD.

Hypothesis: NAFLD may be an independent factor affecting in-hospital outcomes among HCC patients undergoing liver resection.

DATA SOURCES

National Cancer Database (NCDB)

Aim 1 and aim 2 used existing data from the largest cancer database in the United States. NCDB, a clinical oncology database, is jointly sponsored by the American College of Surgeons and the American Cancer Society. More than 1,500 Commission on Cancer (CoC) accredited hospitals contribute to the cancer registry data, which represents 70% of newly diagnosed cancer cases nationwide. The NCDB contains approximately 34 million records and includes variables associated with patients' sociodemographic characteristics, overall health, treatment, and survival (Boffa et al., 2016).

Nationwide Inpatient Sample (NIS)

Aim 3 used another national representative sample of NIS, which is the largest, publicly accessible all-payer inpatient database created and operated by the Agency for Health Research and Quality (AHRQ). The database comprises of discharge data that represent approximately 20% of the United States hospitals. NIS database contains clinical variables on source and type of admissions, diagnosis related groups (DRGs), 25 diagnosis codes from the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), 15 ICD-9CM procedure codes, procedure days from admission, length of stay (LOS) and discharge status. Demographic characteristics (gender, age, race/ethnicity) and nonclinical variables including median household income in the patients' zip code area and rural/urban residence and expected payment source are also included. NIS is widely considered the most valid and reliable source of epidemiological data on inpatient care and outcomes in the United States.

CHAPTER 2

DEVELOPMENT OF AN INTEGER-BASED RISK SCORE TO PREDICT 90-DAY MORTALITY AFTER HEPATECTOMY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

ABSTRACT

Background: The incidence of liver cancer has more than tripled since 1980. Hepatectomy represents the major curative treatment for liver cancer. The risk factors associated with 90-day mortality after hepatectomy are not well understood and there are currently no good prediction models for this outcome. The objectives of the current study were to identify risk factors of 90-day mortality after hepatectomy in patients with hepatocellular carcinoma (HCC) and to develop an integer-based risk score using the National Cancer Database (NCDB).

Methods: Hepatectomies recorded in the NCDB during 2004-2012 were reviewed for 90-day mortality. Risk factors were identified by multivariate logistic regression models. An integer-based risk score was developed using the β coefficients derived from the logistic regression model and tested for discriminatory ability. According to the total risk score, patients were grouped into four risk groups.

Results: The overall 90-day mortality was 10.2%. Ten risk factors were identified, which included sex, age, race/ethnicity, insurance status, education, annual hospital volume, stage, tumor grade, Charlson-Deyo score and surgical procedure. The risk of 90-day mortality was stratified into four groups. The calculated 90-day mortality rates were 2.47%, 5.88%, 12.58% and 24.67% for low, medium, high and excessive risk groups, respectively. An area under curve (AUC) of 0.69 was obtained for model discrimination.

Conclusions: The integer-based risk score we developed could easily quantify each patient's risk level and predict 90-day mortality after hepatectomy. The stratified risk score could be a useful addition to the perioperative risk management and a tool to improve 90-day mortality after hepatectomy.

Key Words: hepatocellular carcinoma, hepatectomy, 90-day mortality, risk factors

Introduction

The incidence and mortality of liver cancer is increasing in the United States (Davila et al., 2012; Siegel, Miller, & Jemal, 2019). The high mortality associated with liver cancer renders it a significant public health problem worldwide. In 2018, the mortality of liver cancer was over three quarters of a million (781,631) accounting for 8.2% of all cancer-related deaths globally (Bray et al., 2018). Hepatocellular carcinoma (HCC) accounts for approximately 80-90% of all primary liver cancers (Chacko & Samanta, 2016). Despite the advances in other modalities of treatments of HCC, hepatectomy (or liver resection), the only potentially curative treatment option (Schiergens et al., 2015), remains the gold standard for patients with resectable HCC (Maluccio & Covey, 2015) and is currently performed more often than in the previous decades (Dimick et al., 2004).

Traditionally, death within 30 days after surgery was reported as operative mortality (Virani et al., 2007; Kamiyama et al., 2010). However, researchers argued that 30-day mortality after hepatectomy may underestimate the mortality associated with liver resection, suggesting 90-day mortality should be reported for better mortality estimation (Schiergens et al., 2015; Mayo et al., 2011).

Ninety-day mortality rates after hepatectomy reported from previous studies have demonstrated a consistent trend but varied from 2.0% to 10.1% depending on the type of study, study population, disease severity and surgical procedures (Hyder et al., 2013; Etra et al., 2014; Bachellier et al., 2011; Margonis et al., 2017; Al-Alem et al., 2016; Chang et

al., 2014). Several predictive models have been developed to help with risk stratification for determining the ideal treatment approach for patients undergoing liver resection (Hyder et al., 2013; Chang et al., 2014; Lee et al., 2016; Balzan et al., 2005; Simons et al., 2009; Simons et al., 2010). Balzan et al. (2005) recommended the "50-50 criteria" on postoperative day 5 as a simple, early and accurate predictor of mortality after hepatectomy (Balzan et al., 2005). Simons and colleagues (2009) developed an integer-based risk score model that included age, sex, Charlson comorbidity scores, procedure type, hospital type and type of neoplasm to predict in-hospital mortality after liver resection. The mortality rates for five risk groups ranged from 0.9% to 35.9% (Simons et al., 2009). In a population-based study conducted in Taiwan, Chang et al. (2014) proposed an integer-based, weighted point system to stratify 90-day mortality risk and divided the 13,159 patients undergoing liver resection into four risk groups. The lowest risk group had a 90-day mortality rate of 1.1%, while the rate for the highest risk group was 15% (Chang et al., 2014).

Even though these previous studies have provided important risk stratification methods for patients undergoing hepatectomy by developing integer-based risk score systems, they are constrained by limited sample size. Most studies were based on single center or multi-hospital data or from population-based data outside of the U.S. No previous research has examined if these risk scores could be developed and applied to broader HCC population in the U.S. Evaluation of the risk for each individual patient undergoing liver resection is valuable for perioperative evaluation and management and patient counseling. To address the aforementioned gaps, the objectives of this study were to 1) estimate the 90-day mortality rate for patients with HCC after hepatectomy using the NCDB, 2) investigate risk factors associated with 90-day mortality after hepatectomy, and 3) develop and test discriminatory ability of an integer-based risk score derived from the

logistic regression model to group patients into four risk groups according to their total risk scores and calculate mortality rates for each of the risk groups.

Methods

Study Design

This is a retrospective, cross-sectional study utilizing existing data from the largest clinical cancer registry in the world (Boffa et al., 2017), NCDB.

NCDB contains approximately 34 million records from cancer registries of more than 1,500 Commission on Cancer (CoC) accredited hospitals across the U.S. It covers approximately 70% of all newly diagnosed cancer cases at the institutional level and includes variables associated with patients' sociodemographic characteristics, overall health, treatment, and survival (Boffa et al., 2017).

Study Population

The study population included patients 18 years and older who were diagnosed with HCC between January 1st, 2004 and December 31st, 2012 and underwent liver resection in the U.S. Patients were identified based on the International Classification of Disease for Oncology, third edition (ICD-O-3) code C220 and histology codes 8170 through 8175. Patients were excluded if they did not have surgery, had a total hepatectomy and transplant, or received only loco-regional treatment. Patients who underwent extrahepatic bile duct resection, had missing information on surgery type, or had unknown 90-day mortality status were also excluded.

Outcome Measure

The primary outcome was 90-day mortality after hepatectomy. This was identified by the database variable named 'PUF_90_DAY_MORT_CD', which recorded mortality within 90 days after the most definitive primary site surgery. This was determined by the documented date of the most definitive (most extensive) surgical procedure of the primary site that was performed as part of the first course of treatment, if known, otherwise, this was based on the earliest date on which any first-course surgical procedure was performed.

Predictor Variables

Predictor variables included age, sex, race/ethnicity, insurance status, annual household income, education, urban or rural residence, Charlson/Deyo comorbidity score, American Joint Committee on Cancer (AJCC) analytic stage group, tumor grade, tumor size, surgical procedure, facility type, and annual hospital volume.

Age was grouped as 18-49, 50-64, 65-74 and 75+ years. Race/ethnicity was classified as White, non-Hispanic; Black, non-Hispanic; Hispanic, and Other, non-Hispanic. Insurance status at the time of initial diagnosis and/or treatment was categorized as not insured, privately insured, insured with Medicaid, insured with Medicare and other government insurance program, and unknown status. Income was estimated by the median household income derived from 2000 U.S. Census data by matching patients' documented zip code of residence. Income was grouped into four categories: less than $30,000, $30,000-$34,999, $35,000- $45,999, and $46,000 and more. The percentage of adults who had not graduated from high school in patients' documented zip code of residence was used as a proxy measure of education; this was categorized as less than 14%, 14-19.9%, 20-28.9%, 29% or more, and information not available. Federal Information Processing Standard (FIPS) code recorded at time of diagnosis for patients' state and county was matched to United States Department of Agriculture (USDA)

Economic Research Service data (2003) to determine patients' metro/urban/rural status of residence.

The Charlson/Deyo value is a weighted score derived from the sum of the scores for all comorbid conditions (American College of Surgeons, 2017). Each of the following reported ICD-9-CM secondary diagnoses was assigned a score of 1: a) myocardial infarction, b) congestive heart failure, c) peripheral vascular disease, d) cerebrovascular disease, e) dementia, f) chronic pulmonary disease, g) rheumatologic disease, h) peptic ulcer disease, i) mild liver disease and j) diabetes. Patients with diabetes and chronic complications, hemiplegia or paraplegia, or renal disease were given a score of 2. Patients diagnosed with AIDS were given a score of 6. Charlson/Deyo score was reported for patients diagnosed in 2003 and later and categorized as 0, 1 and 2 or more. Tumor grade was coded as 1 if well differentiated, 2 if moderately differentiated, 3 if poorly differentiated and 4 if undifferentiated, the latter representing the most aggressive grade.[29] Tumor size, the largest dimension of the diameter of the primary tumor in millimeter (mm), was categorized as ≤30mm, > 30mm and ≤50mm, and >50mm. Surgical procedures were grouped as wedge or segmental resection, lobectomy, extended lobectomy, and unknown type.

Facility type was categorized as 1) Community Cancer Program, 2) Comprehensive Community Cancer Program, 3) Academic Comprehensive Cancer Program and NCI-Designated Network Cancer Program, 4) Integrated Network Cancer Program, and 5) other or unknown type of cancer program (American College of Surgeons, 2016). Each individual facility was assigned a unique random identifier, regardless of cancer site. This unique identifier was used to calculate the total number of hepatectomies performed annually in each facility (annual hospital volume) which were then grouped into low (< 4/year), medium (4-15/year), and high (>15/year) hospital volume.

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina) and SPSS version 25.0 software (IBM Corp., Armonk, N.Y.). For descriptive statistics, numerical variables were summarized as mean with standard deviation, while categorical variables, count with percentage. Patient's characteristics were summarized and compared between those who died within 90 days after liver resection and those who survived beyond 90 days using Pearson Chi-Square/Fisher's exact test or independent t test. Predictor variables with a p value 0.1 or less were included in a multivariate logistic regression model to predict the 90-day mortality. The final model was determined by the stepwise model selection method. The β coefficients derived from the logistic regression model were used to develop an integer-based score model to stratify the risk for 90-day mortality. Risk factors were assigned risk scores at each level of the factor. First, the reference group for each of the factors was assigned a score of 0. Second, among all the β coefficients, the smallest (here the number was 0.00853 from Black, non-Hispanic) was assigned a risk score of 1. Third, all other β coefficients were divided by 0.00853 and the quotients were rounded to the nearest integers. These integers would be the risk score for each level of the risk factors. Finally, a total risk score for each patient was calculated by summing all the risk scores from each of the factors. Patients were then stratified into four risk groups based on their total risk scores. Patients with total risk scores <105, 105-199, 200-305, and >305 were considered having low, medium, high and excessive risk of 90-day mortality respectively. The cutoffs of risk scores were set to reflect the corresponding mortality rates that were approximately 24%, 58%, 123%, and 242% of the overall 90-day mortality rates. The predictability of the risk score was tested using the area under the receiver operating characteristic (ROC) curve. All p-values less than 0.05 for all statistical two-sided tests were considered statistically significant.

RESULTS

Patient characteristics

The NCDB database for liver diseases included 135,800 patients diagnosed between January 1st, 2004 and December 31st, 2012. After applying exclusion criteria, 8,598 patients who underwent hepatectomy and met inclusion criteria were identified.

Patient characteristics are summarized in Table 1. Patient mean age was 61.9±12.9 years old, with 42.7% aged 55 to 64 years. The majority of patients were male and White, non-Hispanic (69.6% and 57.8%) respectively. Most patients lived in metro areas (85.0%) and had private insurance (41.1%) or were insured by Medicare and other government sponsored insurance programs (42.2%). More than two-thirds of patients (67.8%) were diagnosed or treated in academic or research-type facilities.

Over half of patients (54.7%) had a Charlson-Deyo score of 0 indicating no major comorbidities before hepatectomy. Approximately two-thirds of patients (65.3%) were either stage I or stage II and most (54.6%) had a tumor size greater than 50mm. Approximately one-third of patients (33.2%) underwent hepatectomies in facilities where more than 15 liver resections were performed annually.

Association between demographic and clinical factors with 90-day mortality

Table 2.1 (Table 2.1a and 2.1b) shows the univariate analysis results of the association between demographic as well as clinical variables and 90-day mortality after hepatectomy. The overall 90-day mortality rate after hepatectomy was 10.2%. Potential demographic risk factors for 90-day mortality included age group, sex, race/ethnicity, insurance status, annual household income, education, distance to facility, rurality, facility type, and hospital volume. Clinical factors included Charlson/Deyo score, AJCC stage, tumor grade, tumor size, and surgical procedures. The results indicated that older age,

male sex, Hispanic race, lack of private insurance, living in communities with lower education and less annual household income, treatment at facility types other than academic or research, and lower annual hospital volume were significantly associated with higher 90-day mortality after hepatectomy. For clinical predictors, higher Charlson-Deyo score, advanced NCDB analytic stage group, tumor grade III, larger tumor in size, and surgical procedures other than wedge or segmental resection were also significantly associated with increased 90-day mortality. Distance to treating facility and place of residence (urban or rural) were found not to be significantly associated with 90-day mortality.

The final model using multivariable logistic regression identified 10 risk factors of 90-day mortality. Odds ratios and 95% confidence intervals are shown in Table 2.2. Patients of male gender, older age, Hispanic origin, with insurance other than private or without insurance, residing in communities with higher percentage of residents not graduated from high school, higher Charlson-Deyo score, higher NCDB analytic stage group, advanced tumor grade, lower hospital volume, and undergoing lobectomy and extended lobectomy were associated with increased odds of 90-day mortality after hepatectomy.

Development of a risk score model for prediction of 90-day mortality post hepatectomy

This multivariate logistic regression model was then used to develop an integer-based risk model as detailed in the methods section. The β coefficients and calculated risk scores for each of the factors are shown in Table 2.3. Patients were grouped into four risk groups based on their total risk scores. The 90-day mortality rate for the first two groups of patients were 2.47% and 5.88%, respectively, which were lower than the overall mortality rate of 10.2%. The 90-day mortality rate for the last two risk groups of patients were 12.58% and 24.67%, respectively, which were higher than the overall mortality rate.

Integer-based risk groups and their levels of mortality are illustrated in Figure2.1. The area under the curve of the risk score model was calculated as 0.69 (Figure 2.2).

DISCUSSION

This study identified 8,598 hepatectomies between 2004 and 2012 from NCDB and is, so far, the first and largest analysis of 90-day mortality in patients with HCC after hepatectomy within the U.S. With this U.S.-based NCDB data, we developed an integer-based risk score to predict 90-day mortality after hepatectomy for patients with HCC. We defined four risk groups and found approximately 10-fold difference between the lowest risk and highest risk groups. The overall 90-day mortality rate was 10.2%, whereas the mortality rates based on our defined risk groups ranged from 2.47% to 24.67%. Factors that were most significantly associated with higher risk of 90-day mortality after hepatectomy included patients with stage III or IV disease, being uninsured or insured by Medicaid, and having a Charlson-Deyo score of 2.

The 90-day mortality rate in our study was 10.2%, which was higher than the 3.15% in a meta-analysis that included 35,000 hepatic resections (Ramacciato et al., 2012). In our study, we only selected patients diagnosed with primary HCC, and the rate calculation excluded patients with unknown 90-day mortality status, who were followed up for less than 90 days or who had missing information on date of surgery/last contact. The above meta-analysis included tumors that did not originate from the liver but had spread to the liver from other organs of the body, in which the resection was found to have relatively lower post-operative mortality. The 90-day mortality rates reported from several studies ranged from as low as 2.0% to as high as 10.1% (Mayo et al., 2011; Margonis et al., 2017; Al-Alem et al., 2016; Chang et al., 2014; Simons et al., 2009; Resende et al., 2011; Mullen et al., 2007). This variation may be partially due to the factor differences in each individual study in terms of age, gender, extent of hepatectomy and presence of cirrhosis. Moreover,

population-based studies tend to reveal higher mortality following hepatectomy compared to single hospital-based studies. More specifically, Mayo et al (2011) demonstrated that mortality rate was 1.5 times higher in a study using the National Inpatient Sample than mortality rate calculated from single hospital-based studies. This difference may be partially due to reporting bias, in which institution-specific data tend to report favorable outcomes (Asiyanbola et al., 2008). Despite these variations in mortality rates across studies, the perioperative mortality associated with liver resection have greatly improved from 10 - 20% (Nagasue et al., 1993; Thompson et al., 1983, Fan et al., 1995) to 5 - 7% (Ramacciato et al., 2012; Dhir et al., 2016).

Many studies have been performed to examine the factors associated with early mortality after hepatectomy. Some researchers noted that specific, early, postoperative laboratory tests were indicative of post-hepatectomy mortality while others found factors of patient demographics and clinical parameters had significant impact on post-hepatectomy mortality. The “50-50 criteria” proposed by Balzan and colleagues (2005) suggested that the combination of prothrombin time <50% and serum bilirubin >50 μmol/L on postoperative day 5 was a strong predictor of mortality after hepatectomy .[18] However, this rule was criticized for lacking reliability (Mullen et al., 2007). In another study based on a single institution database for patients undergoing major hepatectomy, Etra et al. (2014) found that the total bilirubin ≥3 mg/dl at postoperative day 3 was associated with increased risk of 90-day mortality. To increase the predictability of models from previous studies, Hyder et al. (2013) proposed a composite weighted score model that included variables of Clavien-Dindo complication classification, laboratory values of creatinine, and bilirubin and international normalized ratio (INR) at postoperative day 3. This additive model was weighted by the coefficients derived from multivariate logistic regression model (Hyder et al., 2013). The model discriminated well and achieved higher area under the

ROC curve of 0.89. These studies used variables such as laboratory tests, which are not available for over 60% of the cases in NCDB.

A handful of previous studies have attempted to develop integer-based risk models to better predict early mortality after liver resection. Those studies were either based on administrative data (Asiyanbola et al., 2008; Nagasue et al., 1993), individual hospital data (Hyder et al., 2013), or population-based data from outside of the U.S. (Chang et al., 2014; Lee et al., 2016). In an effort to develop and validate a risk score model based on available preoperative parameters to predict 90-day mortality after hepatectomy, Chang et al. (2014) established a weighted composite score using the parameters available before surgery. Four risk groups were stratified by the composite score, and the 90-day mortality rates ranged from 1.1% to 15.0% (Chang et al., 2014). This study was population-based, focusing more on preexisting comorbidity information (such as heart failure and renal disease) using Taiwan's National Health Insurance Research Database. Our study used a similar score development strategy to generate the composite risk scores. Compared to our study in which the c-statistic was 0.69, the aforementioned research had a slightly better predictability with a c-statistic of 0.75. However, this study was conducted in a single race population with liver tumors that included HCC, cholangiocarcinoma, metastatic malignancy as well as benign tumors. This risk score would not be representative of HCC patients within the ethnically diverse US population . There is evidence in the literature that the discriminatory ability of commonly used risk scores is not consistent in different cohorts of patients undergoing hepatectomy. For example, the AUC for Model of End-Stage Liver Disease (MELD) score in predicting postoperative mortality was 0.71 (Fromer et al., 2016) in a study using retrospective administrative database while the AUC dropped to 0.69 (Ghamarnejad et al., 2020) in another prospective study based on consecutive patient data. Portsmouth-Physiological and Operative Severity for the enumeration of Mortality and Morbidity (P-POSSUM) is currently widely used as a predictive scoring

system for perioperative care. When this score was applied to a sample of 529 patients undergoing liver resection in University Hospital Heidelberg (Knoblich et al., 2020), it showed similar discriminatory ability (AUC=0.68) with our model (AUC=0.69).

Since detailed preexisting comorbidity information was not available in the NCDB, the variables that were used in our study were those available before or immediately after the hepatectomy. Compared to studies that rely on laboratory test values for creating risk scores, our study selected 10 readily available variables comprised of four clinical parameters (stage, tumor grade, Charlson-Deyo score, and surgical procedure) and six non-clinical characteristics (gender, age, race/ethnicity, insurance status, education, and annual hospital volume). Among these 10 variables, eight are available before the surgery and two (stage, tumor grade) are available either before the surgery if a biopsy has been conducted or immediately after the surgery.

The incidence of HCC has been increasing and is expected to continue increasing in the future. Despite improved surgical techniques, patient selection for treatment, and perioperative care (Kamiyama et al., 2010), hepatectomy is still associated with perioperative mortality and high morbidity (Balzan et al., 2005; Mullen et al., 2006; Asiyanbola et al., 2008). This study developed an integer-based risk model on a national level to assess the risks of 90-day mortality after hepatectomy for patients with HCC only. Even though the NCDB is not population based, it does cover approximately 70% of all newly diagnosed cancer cases at the institutional level, which could be considered nationally representative. Therefore, compared to studies that were hospital-based and conducted in single or multiple institutions, our risk model may have improved generalizability. Furthermore, our model did not use any information of laboratory tests and therefore may be applied to databases where laboratory test results are not available.

The current study has some limitations as well. First, the NCDB does not provide information on causes of death, making further investigation of cause of death impossible.

Second, other than the Charlson-Deyo score, no detailed preoperative comorbidity and postoperative complication information is available, therefore we were unable to relate 90-day mortality to postoperative complications. Lastly, the widely used measures of Child-Pugh and the MELD scores for the assessment of liver cirrhosis are not available in NCDB. These indicators are important in predicting post-operative prognosis. However, in clinical practice, Child-Pugh class A (which represents the least severe liver disease) is dominant in patients with HCC who are eligible for liver resection (Zou et al., 2017), and MELD score is used in determining the priority of liver transplant candidates (Peng, Qi, & Guo, 2016). Therefore, we do not expect that lack of availability of Child-Pugh score had a significant impact on our results.

Despite these limitations, the developed risk model can generate risk scores for each patient in three easy steps, which included assigning 0 to reference groups, rounding the quotient of factor β coefficients and the smallest β to the nearest integer, and summing up risk scores of all significant factors. By completing the three steps, the risk level and probability of 90-day mortality at that level can be quantified. Since the study used the largest clinical cancer registry of NCDB, this score may well be representative and could be generalized to all patients with HCC who undergo hepatectomy. The model could also be applied to HCC-related research where secondary databases are used and detailed laboratory tests are not available. The model may provide additional risk assessment of 90-day mortality in patients with HCC undergoing hepatectomy and assist informative conversation between patients and clinicians regarding perioperative management of potential adverse outcomes after hepatectomy.

Conclusion

In this study, we demonstrated a simple, integer-based risk score that could be used to predict risk of 90-day mortality after hepatectomy in patients with HCC even without

information on detailed postoperative complications and laboratory test values. We believe that this risk score may be a useful tool in improving 90-day mortality after hepatectomy.

Table 2. 1a. Univariate analysis of the demographics for patients undergoing hepatectomy, 2004-2012

Variable	Total n (%)	Alive* n (%)	Dead* n (%)	p-value
Total	8598	7721 (89.8)	877 (10.2)	
Age at diagnosis				<0.001
18-49	1174 (13.7)	1092 (14.1)	82 (9.4)	
50-64	3673 (42.7)	3327 (43.1)	346 (39.5)	
65-74	2307 (26.8)	2069 (26.8)	238 (27.1)	
>74	1444 (16.8)	1233 (16.0)	211 (24.1)	
Gender				<0.001
Male	5986 (69.6)	5325 (69.0)	661 (75.4)	
Female	2612 (30.4)	2396 (31.0)	216 (24.6)	
Race/Ethnicity				<0.001
White, non-Hispanic	4973 (57.8)	4470 (57.9)	503 (57.4)	
Black, non-Hispanic	1158 (13.5)	1040 (13.5)	118 (13.5)	
Hispanic	1112 (12.9)	964 (12.5)	148 (16.9)	
Others, non-Hispanic	1355 (15.8)	1247 (16.2)	108 (12.3)	
Insurance Status				<0.001
Not insured	292 (3.4)	249 (3.2)	43 (4.9)	
Private insurance	3537 (41.1)	3275 (42.4)	262 (29.9)	
Medicaid	813 (9.5)	710 (9.2)	103 (11.7)	
Medicare or other	3618 (42.1)	3183 (41.2)	435 (49.6)	
Unknown	338 (3.9)	304 (3.9)	34 (3.9)	
Distance to facility				0.657
Less than 12.5 miles	3834 (45.6)	3435 (45.4)	399 (47.1)	
12.5 to 49.9 miles	2598 (30.9)	2341 (31.0)	257 (30.3)	
50 miles or more	1976 (23.5)	1784 (23.6)	192 (22.6)	
Missing	190			
Percentage of resident not graduated from high school				<0.001
29% or more	1748 (21.2)	1566 (21.2)	182 (21.8)	
20%-28.9%	1947 (23.7)	1710 (23.1)	237 (28.4)	
14%-19.9%	1823 (22.2)	1634 (22.1)	189 (22.7)	
Less than 14%	2712 (33.3)	2486 (33.6)	226 (27.1)	
Missing	368			
Annual median household income				<0.001
Less than $30,000	1326 (16.1)	1158 (15.7)	168 (20.1)	
$30,000-$34,999	1442 (17.5)	1277 (17.3)	165 (19.8)	
$35,000-$45,999	2253 (27.4)	2036 (27.5)	217 (26.0)	
$46,000 or more	3211 (39.0)	2927 (39.6)	284 (34.1)	
Missing	366			
Urban or rural residence				0.051
Metro	7010 (85.0)	6322 (85.3)	688 (82.3)	
Urban	1111 (13.5)	981 (13.2)	130 (15.6)	
Rural	128 (1.6)	110 (1.5)	18 (2.2)	
Missing	349			
Facility type				<0.001
Community	282 (3.5)	239 (3.3)	43 (5.0)	
Comprehensive	1857 (22.8)	1616 (22.2)	241 (28.1)	
Academic/research	5515 (67.8)	5000 (68.7)	515 (60.0)	
Other	478 (5.9)	419 (5.8)	59 (6.9)	
Missing	466			
Annual hospital hepatectomy volume				<0.001
<4/year	3132 (36.4)	2714 (35.2)	418 (47.7)	
4-15/year	2613 (30.4)	2362 (30.6)	251 (28.6)	
>15/year	2853 (33.2)	2645 (34.3)	208 (27.7)	

*at 90 days post hepatectomy

Table 2. 1b. Univariate analysis of clinical characteristics for patients undergoing hepatectomy, 2004-2012

Variable	Total n (%)	Alive* n (%)	Dead* n (%)	p-value
Total	8598	7721	877	
Charlson-Deyo score				<0.001
0	4702 (54.7)	4292 (55.6)	410 (46.8)	
1	2449 (28.5)	2195 (28.4)	254 (29.0)	
2	1447 (16.8)	1234 (16.0)	213 (24.3)	
NCDB analytic stage group				<0.001
I	3560 (41.4)	3320 (43.0)	240 (27.4)	
II	2054 (23.9)	1874 (24.3)	180 (20.5)	
III	1788 (20.8)	1518 (19.7)	270 (30.8)	
IV	334 (3.9)	269 (3.5)	65 (7.4)	
Unknown	862 (10.0)	740 (9.6)	122 (13.9)	
Tumor grade				<0.001
I	1715 (19.9)	1583 (20.5)	132 (15.1)	
II	3759 (43.7)	3397 (44.0)	362 (41.3)	
III	1595 (18.6)	1372 (17.8)	223 (25.4)	
IV	265 (3.1)	240 (3.1)	25 (2.9)	
Not determined	1264 (14.7)	1129 (14.6)	135 (15.4)	
Tumor size				<0.001
≤30 mm	1566 (18.2)	1450 (18.8)	116 (13.2)	
>30mm and ≤50 mm	1990 (23.1)	1819 (23.6)	171 (19.5)	
>50 mm	4694 (54.6)	4189 (54.3)	505 (57.6)	
Unknown	348 (4.0)	263 (3.4)	85 (9.7)	
Surgical procedure				<0.001
Wedge or segmental resection	4533 (52.7)	4129 (53.5)	404 (46.1)	
Lobectomy	2741 (31.9)	2423 (31.4)	318 (36.3)	
Extended lobectomy	608 (7.1)	539 (7.0)	69 (7.9)	
Unknown type	716 (8.3)	630 (8.2)	86 (9.8)	

*at 90 days post hepatectomy

Table 2. 2. Multivariate logistic regression analysis of the risk factors of 90-day mortality after hepatectomy

Predictor variables	Total	Mortality n (%)	Adjusted OR (95% CI)	p-value
Age group				
18-49	1174	82 (7.0)	Reference	
50-64	3673	346 (9.4)	1.062 (0.777-1.479)	0.714
65-74	2307	238 (10.3)	1.122 (0.790-1.618)	0.528
>74	1444	211 (14.6)	1.577 (1.093-2.305)	0.017
Sex				
Female	2612	216 (8.3)	Reference	
Male	5986	661 (11.0)	1.284 (1.073-1.542)	0.007
Race/Ethnicity				
White, non-Hispanic	4973	503 (10.1)	Reference	
Black, non-Hispanic	1158	118 (10.2)	0.992 (0.769-1.268)	0.947
Hispanic	1112	148 (13.3)	1.332 (1.060-1.663)	0.013
Others, non-Hispanic	1355	108 (8.0)	0.814 (0.630-1.040)	0.107
Insurance status				
Private	3537	262 (7.4)	Reference	
Not insured	292	43 (14.7)	1.967 (1.279-2.941)	0.001
Medicaid	813	103 (12.7)	1.927 (1.458-2.529)	<0.001
Medicare or other	3618	435 (12.0)	1.360 (1.089-1.703)	0.007
Unknown	338	34 (10.1)	1.200 (0.694-1.983)	0.495
Percentage of resident not graduated from high school				
Less than 14%	2712	226 (8.3)	Reference	
29% or more	1748	182 (10.4)	1.185 (0.939-1.494)	0.152
20%-28.9%	1947	237 (12.2)	1.370 (1.104-1.701)	0.004
14%-19.9%	1823	189 (10.4)	1.262 (1.011-1.574)	0.039
Charlson-Deyo score				
0	4702	410 (8.7)	Reference	
1	2449	254 (10.4)	1.111 (0.921-1.338)	0.269
2	1447	213 (14.7)	1.691 (1.380-2.068)	<0.001
NCDB analytic stage group				
I	3560	240 (6.7)	Reference	
II	2054	180 (8.8)	1.348 (1.084-1.674)	0.007
III	1788	270 (15.1)	2.251 (1.829-2.770)	<0.001
IV	334	65 (19.5)	3.086 (2.078-4.494)	<0.001
Unknown	862	122 (14.2)	1.861 (1.409-2.438)	<0.001
Tumor grade				
I	1715	132 (7.7)	Reference	
II	3759	362 (9.6)	1.170 (0.931-1.480)	0.183
III	1595	223 (14.0)	1.525 (1.180-1.979)	0.001
IV	265	25 (9.4)	1.199 (0.656-2.098)	0.539
Not determined	1264	135 (10.7)	1.225 (0.912-1.642)	0.177
Annual hospital hepatectomy volume				
>15/year	2853	208 (7.3)	Reference	
<4/year	3132	418 (13.3)	1.636 (1.343-1.997)	<0.001
4-15/year	2613	251 (9.6)	1.187 (0.958-1.473)	0.118
Surgical procedure				
Wedge or segmental resection	4533	404 (8.9)	Reference	
Lobectomy	2741	318 (11.6)	1.437 (1.204-1.714)	<0.001
Extended lobectomy	608	69 (11.3)	1.370 (1.007-1.838)	0.040
Unknown type	716	86 (12.0)	1.230 (0.901-1.654)	0.181

OR = odds ratio, CI = confidence interval

Table 2. 3. Predictor score development based on multivariate logistic regression model

Predictor variables	β Coefficient	Score Assigned
Age group		
18-49	Reference	0
50-64	0.0601	7
65-74	0.1152	14
>74	0.4553	54
Sex		
Female	Reference	0
Male	0.2497	29
Race/Ethnicity		
White, non-Hispanic	Reference	0
Black, non-Hispanic	-0.00853	-1
Hispanic	0.2863	34
Others, non-Hispanic	-0.2062	-24
Insurance status		
Private	Reference	0
Not insured	0.6766	80
Medicaid	0.6557	77
Medicare or other	0.3078	36
Unknown	0.1819	21
Percentage of resident not graduated from high school		
Less than 14%	Reference	0
29% or more	0.1696	20
20%-28.9%	0.3152	37
14%-19.9%	0.2327	27
Charlson-Deyo score		
0	Reference	0
1	0.1053	12
2	0.5256	62
NCDB analytic stage group		
I	Reference	0
II	0.2984	35
III	0.8112	95
IV	1.1268	133
Unknown	0.6211	73
Grade		
I	Reference	0
II	0.1571	18
III	0.4222	50
IV	0.1813	21
Unknown	0.2027	24
Annual hospital volume		
>15/year	Reference	0
<4/year	0.4920	58
4-15/year	0.1714	20
Surgical procedure		
Wedge or segmental resection	Reference	0
Lobectomy	0.3624	43
Extended lobectomy	0.3145	37
Unknown type	0.2070	24

Table 2. 4. Stratified risk score group and corresponding mortality rate observed

Risk group	Risk score range	Observed Mortality Rate (%)
Low risk group	<105	2.47
Medium risk group	105-199	5.88
High risk group	200-305	12.58
Excessive risk group	306+	24.67

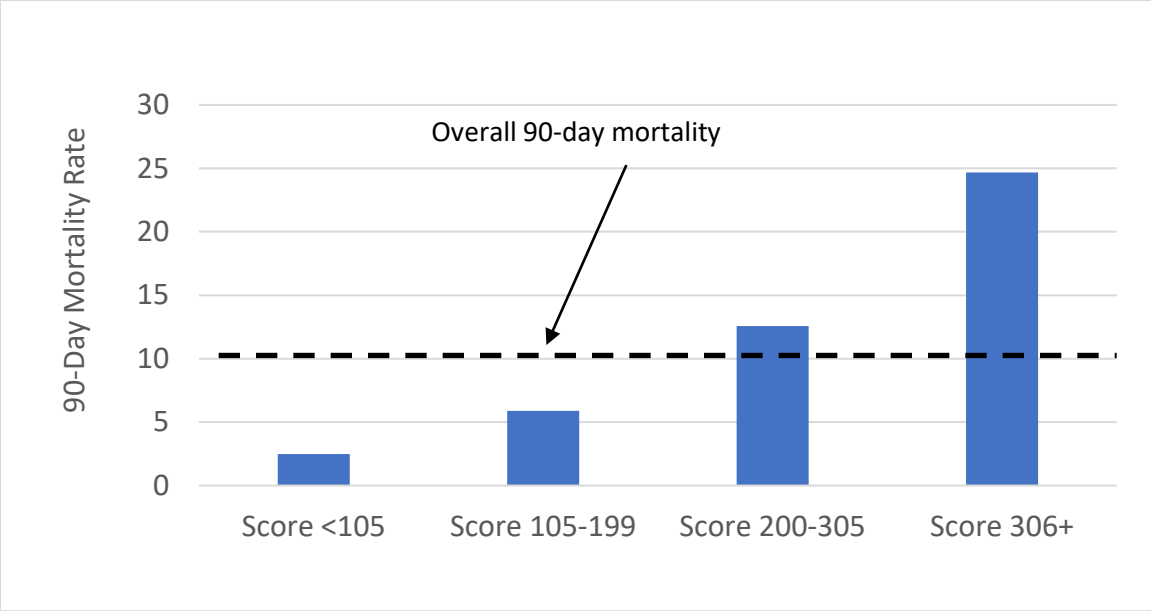

Figure 2. 1. Observed 90-day mortality rates (%) after hepatectomy based on stratified risk score groups

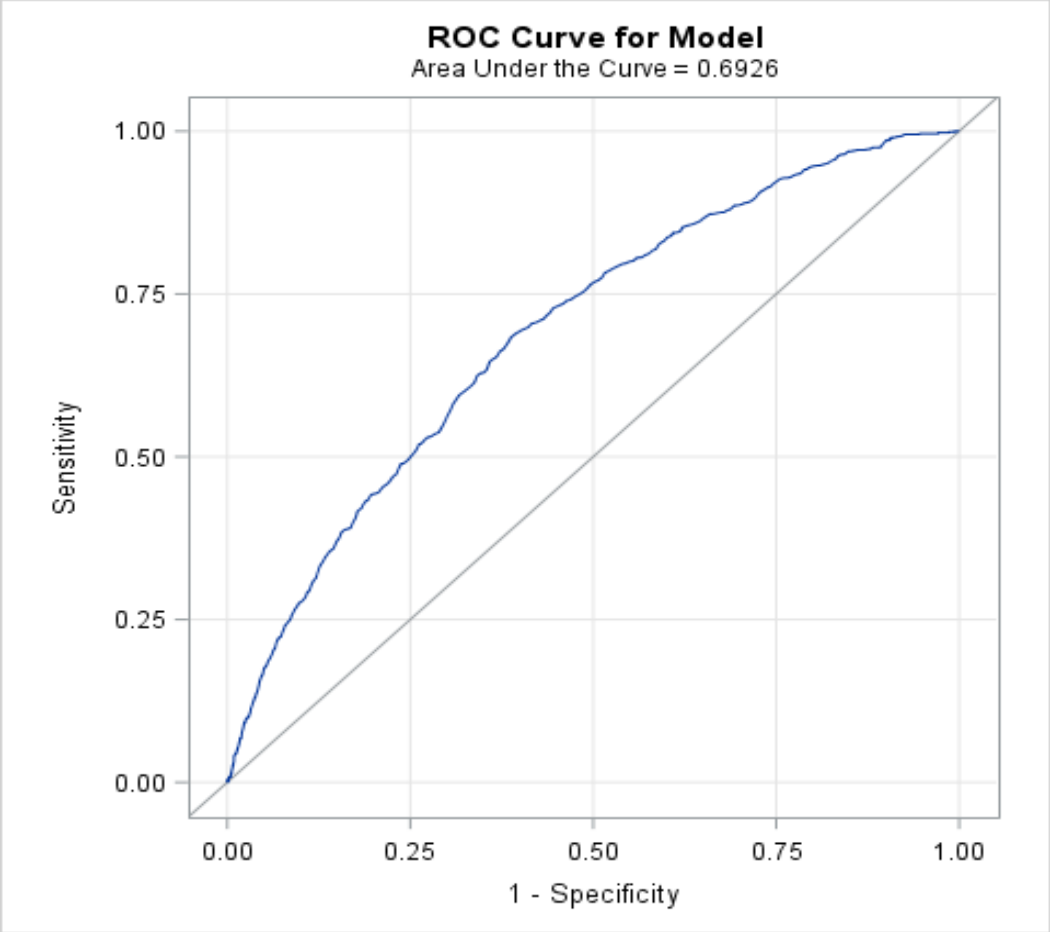

Figure 2. 2. Area under the curve based on risk scores

CHAPTER 3

THIRTY-DAY UNPLANNED READMISSION AND ITS EFFECT ON 90-DAY MORTALITY IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING PARTIAL HEPATECTOMY

ABSTRACT

Background: Despite advances of surgical techniques, hepatectomy continues to be potentially dangerous and is associated with postoperative mortality, morbidity and readmission. The objective of this study was to determine the effect of 30-day unplanned readmission on 'conditional' 90-day mortality among hepatocellular carcinoma (HCC) patients who underwent partial hepatectomy.

Methods: National Cancer Database (NCDB) was queried from 2004 to 2012 for patients with hepatocellular carcinoma (HCC) who underwent partial hepatectomy. Thirty-day unplanned readmission rate, and associated risk factors, was determined for 7,696 patients. The association between 30-day unplanned readmission and conditional 90-day mortality was further addressed.

Results: The 30-day unplanned readmission rate for patients with HCC that underwent partial hepatectomy was 5.2%. Risk factors associated with 30-day unplanned readmission were sex, race/ethnicity, Charlson-Deyo score, and annual hospital hepatectomy volume. An overall adjusted odds ratio of having conditional 90-day mortality was 2.325 times higher (95% CI 1.643 – 3.219) among patients with a history of 30-day unplanned readmission than those without. This association was dependent on age, sex, race/ethnicity, insurance status, alpha-fetoprotein (AFP), liver fibrosis, Charlson-Deyo comorbidity score and annual hospital hepatectomy volume.

Conclusion: Efforts in patient care should be taken to reduce 30-day unplanned readmission after partial hepatectomy for patients with HCC to reduce conditional 90-day mortality.

INTRODUCTION

The reported cost of unplanned hospital readmissions is approximately $44 billion of healthcare spending annually (Ostrovsky et al., 2016), yet a substantial proportion of these readmissions could be avoidable. The Medicare Payment Advisory Commission estimated that reducing potentially preventable readmissions could save up to $12 billion every year (Montero et al., 2016). In 2019, the Hospital Readmissions Reduction Program (HRRP) evaluated 3,129 general hospitals and penalized 83% of these hospitals for excess 30-day readmissions with estimated fines of $563 million (Rau, 2019). Among patients with private insurance, the average cost for readmission after hepatectomy was approximately $34,100/person (Narula et al., 2018), much higher than the average hospital readmission cost of $14,400 for 18 main diagnosis categories (Becker's Healthcare, 2019).

Despite advances of surgical techniques, hepatectomy continues to be potentially dangerous and is associated with postoperative mortality, morbidity and readmission. Readmission rates after hepatectomy vary depending on the study population. Three hospital-based studies reported 90-day readmission rates after hepatectomy for any etiology ranging from 14.4% to 18.7% (Barbas et al., 2013; Egger et al., 2015; Kimbrough et al., 2014), which were higher than the 30-day readmission rates of 13.0% and 14.2% from two other hospital-based studies (Tamandl et al., 2015; Spolverato et al., 2014). A relatively lower 30-day readmission rate of 10.5% was noted in a study using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database (Kim et al.,2015).

Contributing factors affecting readmission after hepatectomies include major hepatectomies (≥4 segments resected), major postoperative complications and index hospitalization of >7 days (Barbas et al., 2013). However, another study found that neither index hospitalization nor postoperative hepatobiliary complications played a significant role in 45-day readmission (Brudvik et al., 2015). Other risk factors include extensive blood loss, postoperative pulmonary embolism, red blood cell transfusion, surgical infection, and peak postoperative total bilirubin (Egger et al., 2014). Among these, postoperative complications were identified as the strongest and dominant risk factor affecting readmission (Spolverato et al., 2014; Kimbrough et al., 2014).

Significant correlations between 30-day readmission and subsequent 90-day mortality have been reported, but results are inconsistent. Evidence suggests that a history of readmission increases the risk of postoperative mortality (Berman et al., 2011). Though not studied in patients with HCC, a 6-fold increase in 90-day mortality was found among lung cancer patients with a history of 30-day readmission compared to those without a 30-day readmission (Hu et al., 2014).

Most previous studies were based on single or 2-3 centers with limited sample size where the readmission rate could easily be influenced by small changes in hospital readmission. Furthermore, research on readmission after hepatectomy often include HCC and other primary and secondary liver malignancies as well as benign tumors to increase sample size. These studies cannot measure HCC-specific readmission rate and associated risk factors. Moreover, no studies have evaluated the impact of 30-day unplanned readmission on conditional 90-day mortality in a nationally representative sample in patients with HCC who underwent hepatectomies.

The objective of this study was to determine the effect of 30-day unplanned readmission on conditional 90-day mortality among hepatocellular carcinoma (HCC) patients that underwent partial hepatectomy.

METHODS

Data source

We used the National Cancer Database (NCDB) for all analyses. NCDB, a clinical oncology database, is jointly sponsored by the American College of Surgeons and the American Cancer Society. More than 1,500 Commission on Cancer (CoC) accredited hospitals contribute to the cancer registry data, which represents 70% of newly diagnosed cancer cases nationwide at the institutional level.

Study Population

NCDB was queried for all patients with HCC using International Classification of Disease for Oncology, third edition (ICD-O-3) code C220 with histology codes 8170, 8171, 8172, 8173, 8174 and 8175. Only patients who were 18 years or older, diagnosed from 2004 to 2012 and underwent partial hepatectomy were included in the study. Patients were excluded if they developed more than two cancers following HCC diagnosis or had total hepatectomy and transplant. Patients who survived less than 30 days after hepatectomy or had missing information on surgery procedures, 30-day readmission status, and 90-day mortality status were also excluded.

Dependent measure

The first outcome measure was 30-day unplanned readmission. In NCDB, this variable became available from 2003 onward. It describes patients' readmission status and is coded as: 0, 1, 2, 3 and 9. A value of 0 indicates that no surgical procedure of the primary site was performed or the patient was not readmitted to the same hospital within 30 days of discharge; value of 1 means a 30-day unplanned readmission to the same

hospital after a surgical procedure; value of 2 represents a 30-day planned readmission to the same hospital; value of 3 denotes a patient having both 30-day planned and unplanned readmission after a surgical procedure to the same hospital. For this study, we only used the data for patients with known 30-day unplanned readmission status (status=1). The second outcome measure was conditional 90 days after a hepatectomy.

Independent measures

Independent variables included age, sex, race/ethnicity, insurance status, annual household income, education, urban or rural residence, distance to treatment facility, annual hospital volume, facility type, alpha fetoprotein tumor marker (AFP), liver fibrosis, Charlson/Deyo score, NCDB pathologic/clinical stage, tumor grade, tumor size, and surgical procedure.

Age was grouped as 18-49, 50-64, 65-74 and 75+ years. A new variable "race/ethnicity" was generated based on NCDB variables race and Hispanic origin and classified as 1) White non-Hispanic, 2) Black non-Hispanic, 3) Hispanic, and 4) other non-Hispanic. Insurance status refers to the patient's primary insurance carrier at the time of initial diagnosis and/or treatment and was categorized as not insured, privately insured, Medicaid, Medicare and other government insurance plans, and unknown status. Income is the estimation of median household income derived from 2000 US Census data by matching patients' zip code of residence. It was grouped into four levels: less than $30,000, $30,000-$34,999, $35,000- $45,999 and $46,000 and above. The percentage of adults not graduated from high school in patients' zip code of residence was used as a measure of education and was categorized as 29% or more, 20%-28.9%, 14%-19.9%, less than 14%. In NCDB, patient state and county of Federal Information Processing Standard (FIPS) code recorded at diagnosis is matched against 2003 files published by the USDA Economic Research Service to determine patient metro/urban/rural status of

residence. NCDB defines metro counties as counties in metro areas with a population ranging from fewer than 250,000 to 1 million or more. Urban counties refer to areas with a population ranging from 2,500 to 20,000 or more either adjacent or not adjacent to a metro area. Rural counties include completely rural or less than 2,500 urban population either adjacent or not adjacent to a metro area.

AFP was grouped into two levels of negative/normal and positive/elevated while liver fibrosis was categorized as none to moderate and severe to cirrhosis based on Ishak score of 0-4 and 5-6, respectively (Ishak et al., 1995). The Charlson/Deyo value is a weighted score derived from the sum of scores for all comorbid conditions. Each of the ten reported ICD-9-CM secondary diagnoses below has a score of 1 for each condition: 1) myocardial infarction, 2) congestive heart failure, 3) peripheral vascular disease, 4) cerebrovascular disease, 5) dementia, 6) chronic pulmonary disease, 7) rheumatologic disease, 8) peptic ulcer disease, 9) mild liver disease and 10) diabetes. In addition, a patient is given a score of 2 if the patient has diabetes with chronic complications, hemiplegia or paraplegia, or renal disease. A score of 6 is given to patients with AIDS. Charlson/Deyo score is reported in the NCDB for patients diagnosed in 2003 and later and categorized as 0, 1 and 2 or more. Tumor grade describes the resemblance of tumor cells to the normal cells and is grouped as well differentiated, moderately differentiated, poorly differentiated and undifferentiated which represents the most aggressive grade that grows and spreads faster than tumors with lower grades. NCDB analytic stage group was categorized as I, II, III, IV and unknown. Its value reflects reported pathologic stage group, or clinical stage group if the former is not available. Tumor size describes the largest diameter of the primary tumor in millimeter (mm). The variable tumor size was categorized as ≤ 30mm, >30 and ≤50, >50. Surgical procedures were grouped as wedge or segmental resection, lobectomy, extended lobectomy and unknown type.

Facility type was categorized as 1) Community Cancer Program, 2) Comprehensive Community Cancer Program, 3) Academic Comprehensive Cancer Program and NCI-Designated Network Cancer Program, 4) Integrated Network Cancer Program, and 5) other or unknown type of cancer program. In the NCDB, the name of the facility is replaced with a unique random identifier, which can be used to calculate the total number of hepatectomies performed annually in each facility (annual hospital volume). Annual hospital volume was then grouped into low (< 4/year), medium (4-15/year), and high (>15/year) categories.

Statistical analysis

We first calculated overall 30-day unplanned readmission rate among patients with HCC and underwent hepatectomies and then compared patients' demographic, clinical and facility characteristics between patients with and without 30-day unplanned readmission using Pearson Chi-Square test for categorical variables. Independent t-test was used to compare mean difference between the two groups. A multivariate logistic regression model was performed, which included all variables with a p value less than or equal to 0.1 in the univariate analysis. Adjusted odds ratios, 95% confidence intervals and p values were reported. To evaluate the effect of 30-day unplanned readmission on conditional 90-day mortality, we fit univariate and multivariate logistic regression models using 30-day unplanned readmission as an independent variable and conditional 90-day mortality as the dependent variable. Selected subgroup analysis was conducted to further investigate how the association between 30-day unplanned readmission and conditional 90-day mortality varied between subgroups.

RESULTS

A total of 18,751 patients who were 18 years or older, diagnosed with HCC between 2004 to 2012, had no more than one other cancer diagnosis during this time period, and underwent partial hepatectomy were identified in the database. We excluded 8,696 patients who underwent total hepatectomy and transplant, leaving 10,055 patients for calculating overall unplanned readmission rate. Of the 10,055 patients, 522 patients experienced 30-day unplanned readmission, 152 patients experienced 30-day planned readmission, 8 patients experienced both planned and unplanned readmission, and 322 patients whose readmission status was unknown. The overall 30-day unplanned readmission rate was 5.2%. After further excluding patients who had planned readmission, had both planned and unplanned readmission, survived fewer than 30 days, had missing 90-day mortality status, and had missing surgery date, we identified 7,696 patients to be included in the study (Figure3.1). The average age of patients was 61.7±12.9 and 5,329 were male (69.2%). Approximately 42.7% of patients were aged 50-64, 58.1% were white, non-Hispanic, 83.6% had private insurance, Medicare or other, 39.2% had median annual household income of $46,000 or more, and 68.6% were treated in academic or research type facilities (Table3.1a). Additionally, over half (55.0%) of patients had a Charlson-Deyo score of 0, 42.5% belonged to stage I, and 43.9% were diagnosed with grade II tumor (Table3.1b). The major surgery procedures these patients underwent were wedge or segmental resection, which accounted for 53.3%.

Comparison of patients experiencing 30-day unplanned readmission vs. those without readmission

Univariate analysis demonstrated differences of patient demographics, hospital and clinical characteristics between patients with 30-day unplanned readmission and patients without readmission (Tables3.1a and 3.1b). Patients with 30-day unplanned readmission were slightly younger compared to those without a readmission (60.2 years vs. 61.8 years,

p=0.01), more likely to be male (74.4% vs. 68.9%, p=0.02), Hispanic (17.9% vs. 12.3%, p<0.01), and to have private insurance (45.7% vs. 41.6%, p<0.01). In addition, patients with 30-day unplanned readmission were more likely to have a Charlson -Deyo score of ≥ 1 (53.6% vs. 44.4%, p<0.01), and to be diagnosed with grade II tumor vs. all other grade tumor (48.6% vs. 43.6%, p=0.028). Although a higher proportion of readmitted patients had severe fibrosis/cirrhosis (12.2% vs. 9.0%, p=0.011), over three quarters (76.5%) of patients did not have fibrosis scores available. Annual household income, education, distance to treating facility, urban or rural residence, AFP tumor marker, NCDB analytic stage group, tumor size and surgical procedures did not differ by 30-day unplanned readmission status (Tables 3.1a and 3.1b).

Risk factors of 30-day unplanned readmission

Table 3.2 shows the odds ratios and 95% confidence intervals from multivariate logistic regression investigating risk factors associated with 30-day unplanned readmission. After adjusting for age, sex, race/ethnicity, insurance status, annual median household income, facility type, hospital hepatectomy volume, Charlson-Deyo score, and tumor grade, males had 29% increased odds of experiencing a 30-day unplanned readmission than females. Hispanics had 39% increased odds of 30-day unplanned readmission compared to non-Hispanic white. Patients with Charlson-Deyo scores of 1 and 2 had 31% and 55% increased odds experiencing 30-day unplanned readmission compared to patients with Charlson-Deyo score of 0, respectively. In addition, patients treated in hospitals where annual hospital hepatectomy volume was 4-15/year had 38% lower odds experiencing 30-day unplanned readmission compared to those treated in hospitals performing more than 15 hepatectomies annually.

Effect of 30-day unplanned readmission on conditional 90-day mortality

The conditional 90-day mortality refers to those patients who died between 31 and 90 days after partial hepatectomy. The conditional 90-day mortality rate for patients with an unplanned readmission was 10.0% while the rate for those not readmitted was only 4.5%. The crude odds of conditional 90-day mortality was 2.342 (95% CI: 1.663 - 3.225, p<0.001) times higher in patients with a 30-day unplanned readmission than in patients without a readmission (Table 3.3). After adjusting for sex, age group, race/ethnicity, insurance status, Charlson -Deyo score and annual hospital hepatectomy volume, the odds of conditional 90-day mortality was similar to the crude odds, 2.325 (95% CI: 1.643 - 3.219, p<0.001) (Table 3.3).

Association between 30-day unplanned readmission and conditional 90-day mortality in select subgroups (Table 3.4)

Age and sex

Patients 75 years and older that experienced 30-day unplanned readmission had the highest odds of conditional 90-day mortality (OR 3.081, 95% CI 1.453-6.044, p=0.002) followed by age 50-64 (OR 2.846, 95% CI 1.626-4.728, p<0.001). Female patients who had 30-day unplanned readmission, had twice the odds of 90-day mortality (OR 3.809, 95% CI 1.909-7.114, p<0.001) compared to male patients (OR 1.985 95% CI 1.314-2.903, p<0.001).

Race/Ethnicity and insurance type

The association between 30-day unplanned readmission and conditional 90-day mortality was only significant among white, non-Hispanic patients (OR 3.287, 95% CI 2.164-4.862, p<0.001). Thirty-day unplanned readmission was also associated with a 11-fold (OR 11.247, 95% CI 1.666-77.316, p=0.01) increased odds of conditional 90-day

mortality among uninsured patients, 2.4 fold (OR 2.391, 95% CI 1.347-4.012, p<0.01) increased odds in privately insured patients and twice the odds (OR 2.140, 95% CI 1.252-3.472, p<0.01) in patients enrolled in Medicare or other government insurance programs.

AFP tumor marker and cirrhosis score

AFP tumor marker was reported for 5,229 (out of 7,696) patients, of whom, more than one-third (n=1,914, 36.6%) had negative/normal AFP values and the rest (n=3,315, 63.4%) had positive/elevated values. Among patients with an elevated AFP, the adjusted odds of conditional 90-day mortality after partial hepatectomy were 2.1 times higher for those with a 30-day unplanned readmission than those without. No significant association between 30-day unplanned readmission and conditional 90-day mortality was noted in patients with a normal AFP. In addition to AFP, NCDB also provides liver fibrosis information based on Ishak score (Ishak et al., 1995) starting in 2004. For our dataset, only 1,805 (out of 7,696) patients had complete fibrosis information where 1,099 patients were reported as having none-moderate fibrosis and 706 having severe fibrosis to cirrhosis. Significant impact of 30-day unplanned readmission on conditional 90-day mortality was identified only in patients with Ishak score of 5-6 (adjusted OR 3.768, 95% CI 1.478-8.815, p=0.003).

A significant impact of 30-day unplanned readmission on conditional 90-day mortality was observed across all subgroups of Charlson-Deyo Score and showed a linear trend with increasing score. Specifically, 30-day unplanned readmission was associated with 2.0 (OR 2.002, 95% CI 1.139-3.312, p=0.01), 2.4 (OR 2.435, 95% CI 1.257-4.383, p<0.01) and 2.7 (OR 2.741, 95% CI 1.410-5.029, p<0.01) fold increased odds of having 90-day mortality in patients with Charlson-Deyo scores of 0, 1 and 2, respectively. In patients treated in facilities that performed more than 15 hepatectomies annually, 30-day

unplanned readmission increased the odds of 90-day mortality by approximately 4 fold (OR 3.969, 95% CI 2.312-6.561, p<0.01).

DISCUSSION

In this study, we used one of the largest cancer databases in the world to investigate the rate and associated risk factors of 30-day unplanned readmission after partial hepatectomy and evaluated how this readmission impacted conditional 90-day mortality in patients with HCC. The study found that the overall 30-day unplanned readmission rate following partial hepatectomy was 5.2%, which was much lower than previously reported rates of 10.2% for partial hepatectomy from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) dataset (Kim et al., 2015), 14.2% from a hospital-based study (Spolverato et al., 2014) and 15.5% from a population-based study using Surveillance, Epidemiology, and End Results (SEER) database (Schneider et al., 2012). Studies on readmission after partial hepatectomy have been very limited and the definition of readmission varied largely across studies. Readmission at 30-day, 90-day and 1 year after discharge following a surgical procedure has been reported (Lucas et al., 2014; Kimbrough et al., 2014; Egger et al., 2015; Tamandl et al., 2015; Brudvik et al., 2015). To our knowledge, this study was the first to describe the 30-day unplanned readmission rates after partial hepatectomy in patients with HCC using a national database that captures 70% of newly diagnosed cancer cases. The NCDB collects information only on 30-day readmission, which includes unplanned readmission, planned readmission and both planned and unplanned readmission; therefore, we were unable to compare 90-day or 1-year readmission with other studies. The lower rate of 30-day unplanned readmission for the current study may partially reflect the fact that NCDB only captures patients readmitted to the same treating facility. In another words, if a patient was discharged from hospital A, but readmitted to hospital B due to postoperative

complications, then the patient was not considered having an unplanned readmission in NCDB. In our study, patients with an unplanned 30-day readmission resided in zip code areas that were significantly closer to their treating facility than those without readmission (37.6 miles vs 56.1 miles, $p<0.001$). Saunders and colleagues also found that patients living far away from treating hospitals would go to a closer hospital for readmission either because of convenience or patients being too sick to return to the original hospital (Saunders et al., 2014). In a study that used States Inpatient Database of 5 states, researchers reported that almost 1 of 4 readmissions were to a different hospital than the original facility (Tapper, Halbert, & Mellinger, 2016).

Risk factors independently associated with 30-day unplanned readmission were sex, race/ethnicity, Charlson-Deyo score, and annual hospital hepatectomy volume. Consistent with other studies (Spolverato et al., 2014; Brudvik et al., 2015), our results did not indicate a significant association between age and 30-day unplanned readmission. However, we found that male gender was associated with a 29% increased odds of 30-day unplanned readmission. One explanation may be the negative role of liver fibrosis/cirrhosis in readmission (Chirapongsathorn et al., 2020). Our study showed that 41.9% of males had severe fibrosis or cirrhosis compared to 32.6% of females who had the same condition ($p<0.001$). The other explanation is the lack of social support which is not directly measured in NCDB. Previous studies have reported that men are less likely to seek help and more likely to be socially isolated than women, which contributes to worse health outcomes (Woz et al., 2012; Tang & Maselli, 2014). Our study also indicated a racial disparity on 30-day unplanned readmission. Hispanics had a 39% increased odds of 30-day unplanned readmission than Caucasians. The risk of 30-day readmission after partial hepatectomy in Hispanics had not been reported and the comparison was often made between white and non-white races in past studies, especially hospital-based studies. Even though individual comorbidity cannot be identified in NCDB, research has

reported higher prevalence of obesity, diabetes, hypertension and metabolic syndrome among Hispanic patients (Guzman, 2012). These chronic conditions along with language barriers and lower overall health literacy (Mochari-Greenberger et al., 2015), have adversely impacted Hispanics' health behavior and clinical outcomes including readmission.

The current study found that the Charlson-Deyo score was significantly associated with 30-day unplanned readmission. Males and Hispanics had higher proportion of index score>0. The overall odds of 30-day unplanned readmission were 1.3 and 1.6 times higher in patients with an index score of 1 and ≥2, respectively when compared to the index score of 0. This finding was consistent with a study that reported 30-day unplanned readmission among general medicine patients at six academic medical centers (Hasan et al., 2010). They used self-reported Charlson comorbidity index of 0-9 and found the odds of readmission increased 9% with each one-unit increase in the index. A second study that used the NCDB for parotid cancer research discovered 57% and 108% increased odds of readmission for the index scores of 1 and >1, respectively (Zhan et al., 2016). For major abdominal procedures, an index score ≥3 was associated with a 77% increase in the odds of 90-day readmission among patients recorded in the Truven Health MarketScan Commercial Claims and Encounters Database (Kim et al., 2016). We believe a higher Charlson-Deyo index has a negative impact on 30-day unplanned readmission. The impaired physiological system and depleted physiological reserve at discharge puts patients in a vulnerable situation (Krumholz, 2013) where comorbidities might be exacerbated and lead to new acute conditions that increase the risk of readmission (Donzé et al., 2013).

The major goal of this study was to evaluate the impact of 30-day unplanned readmission on conditional 90-day mortality. Patients who died between 30 and 90 days were considered as having conditional 90-day mortality. The conditional 90-day mortality

rate was 10.0% in patients who experienced a 30-day unplanned readmission and was 4.5% among those without readmission. This translated to an unadjusted 86% higher rate of conditional 90-day mortality in patients with a 30-day unplanned readmission than those without. After adjusting for covariates, a higher odds of 2.3 for conditional 90-day mortality was noted among patients readmitted within 30 days. This is the first time that the effect of 30-day unplanned readmission in future conditional 90-day mortality following a partial hepatectomy among patients with HCC is reported using a national cancer database. This association is likely reflective of the impact of comorbidities and perioperative complications on mortality. We have shown that Charlson-Deyo score was a strong, independent predictor of 30-day unplanned readmission. Comorbidity has been reported as an independent risk factor of postoperative complications (Inokuchi et al., 2014), and postoperative complication was also significantly associated with 90-day mortality (Tzeng et al., 2014). This finding is in concordance with outcomes derived from 2006-2010 SEER-Medicare database showing a 6-fold increase in odds of 90-day mortality among lung cancer patients with a 30-day readmission history (Hu et al., 2014). One earlier study using the 1992-2002 SEER-Medicare database found that among patients undergoing colectomy, 1-year postoperative mortality was 16% in those readmitted within 30 days of discharge compared to 7% in those not readmitted (Greenblatt et al., 2010). Awareness of patient 30-day readmission status may assist further monitoring and managing postoperative care that aims to reduce 90-day mortality.

The finding that 30-day unplanned readmission affects 90-day mortality is especially obvious in certain subgroups of patients. More specifically, among patients 75 years and older, 30-day unplanned readmission was associated with a 3.1-fold increase in subsequent conditional 90-day mortality. The significant association between 30-day readmission and 90-day mortality was observed in both sexes, but the odds were higher in female than male patients (OR: 3.809 and 1.985, respectively). This indicated that

despite the overall lower odds of short-term readmission and mortality for females, the odds of 90-day mortality was higher than males once female patients were readmitted within 30 days of discharge. One important finding of this study was that the impact of 30-day readmission on conditional 90-day mortality was only significant among the white, non-Hispanic group. This may be related to the relatively older age of patients in this group compared to other race groups. Patients aged 65 years and above accounted for 20% in the white, non-Hispanic group, while they accounted for only 11.4% in all other groups combined.

Variations in the risk of 90-day mortality were also found among patients enrolled in different insurance programs. In the subgroup of uninsured patients, the odds of 90-day mortality were 21 times higher for those with a 30-day readmission history compared to those without. On the other hand, among patients with private insurance, the odds was only 1.9 times higher. Previous studies have demonstrated that uninsured patients had poorer survival than privately insured patients and this may be related to poorer overall health with more comorbidities (Kwok et al., 2010) and no or inadequate management of chronic conditions prior to cancer diagnosis (Slatore et al., 2010).

The association between 30-day unplanned readmission and conditional 90-day mortality was significant in patients with an elevated AFP tumor marker and in patients with severe liver fibrosis. However, this significant association was not noted in patients with a negative AFP tumor marker and in patients with none-moderate liver fibrosis. No studies have compared the impact of AFP and cirrhosis on 30-day unplanned readmission and conditional 90-day mortality. However, previous studies have indicated that markedly elevated serum AFP was an indicator of poor prognosis (Peng et al., 2004.). Decreased survival among HCC resection patients was not associated with progressive increase in fibrosis stage until complete cirrhosis is established (Wang et al., 2013). Severe fibrosis/cirrhosis may diminish liver coagulability (Amitrano, Guardascione, Brancaccio, &

Balzano, 2002) and increase susceptibility to infection (Thalheimer et al., 2005), which may then lead to the rise of postoperative complications and the risk of mortality.

Our study has several limitations. Given the retrospective nature of the NCDB, we were able to demonstrate associations and not causative relationships between predictors and outcomes. NCDB only records readmissions to the same hospital, consequently the recorded 30-day unplanned readmission may underestimate the true readmission rate due to not tracking patients readmitted to a different hospital. The causes of 30-day unplanned readmission are not collected in NCDB making the analysis for the most common causes for early readmission unfeasible. Although NCDB included liver fibrosis information, data were not available for more than three quarters of patients; therefore, we were unable to verify the conclusion from one study that claimed neither cirrhosis nor fibrosis is associated with readmission (Kimbrough et al.,2014). Instead, we addressed the association between 30-day unplanned readmission and conditional 90-day mortality by fibrosis score.

Despite these limitations, NCDB provides national level readmission and mortality information with a large sample size for HCC patients undergoing partial hepatectomies, which enables us to explore the relationship between 30-day unplanned readmission and conditional 90-day mortality among subgroups. This is the first study based on NCDB to identify multiple predictors of 30-day unplanned readmission for HCC patients following partial hepatectomies. Most importantly, this was the first time to report that 30-day unplanned readmission was significantly associated with conditional 90-day mortality after partial hepatectomy. The study also detailed how this association varied among different subgroups.

CONCLUSION

In this study, we demonstrated that male sex, Hispanic ethnicity, higher Charlson-Deyo score, and higher annual hospital hepatectomy volume were significant predictors of 30-day unplanned readmission. We further demonstrated that 30-day unplanned readmission had a significant impact on conditional 90-day mortality among patients with HCC who underwent partial hepatectomies. The study documented more than 3-fold increases in the odds of 90-day-mortality in subgroups of patients 75 years and older, female sex, white, non-Hispanic race, uninsured, with severe fibrosis/cirrhosis and treated in hospitals with more than 15 hepatectomies annually.

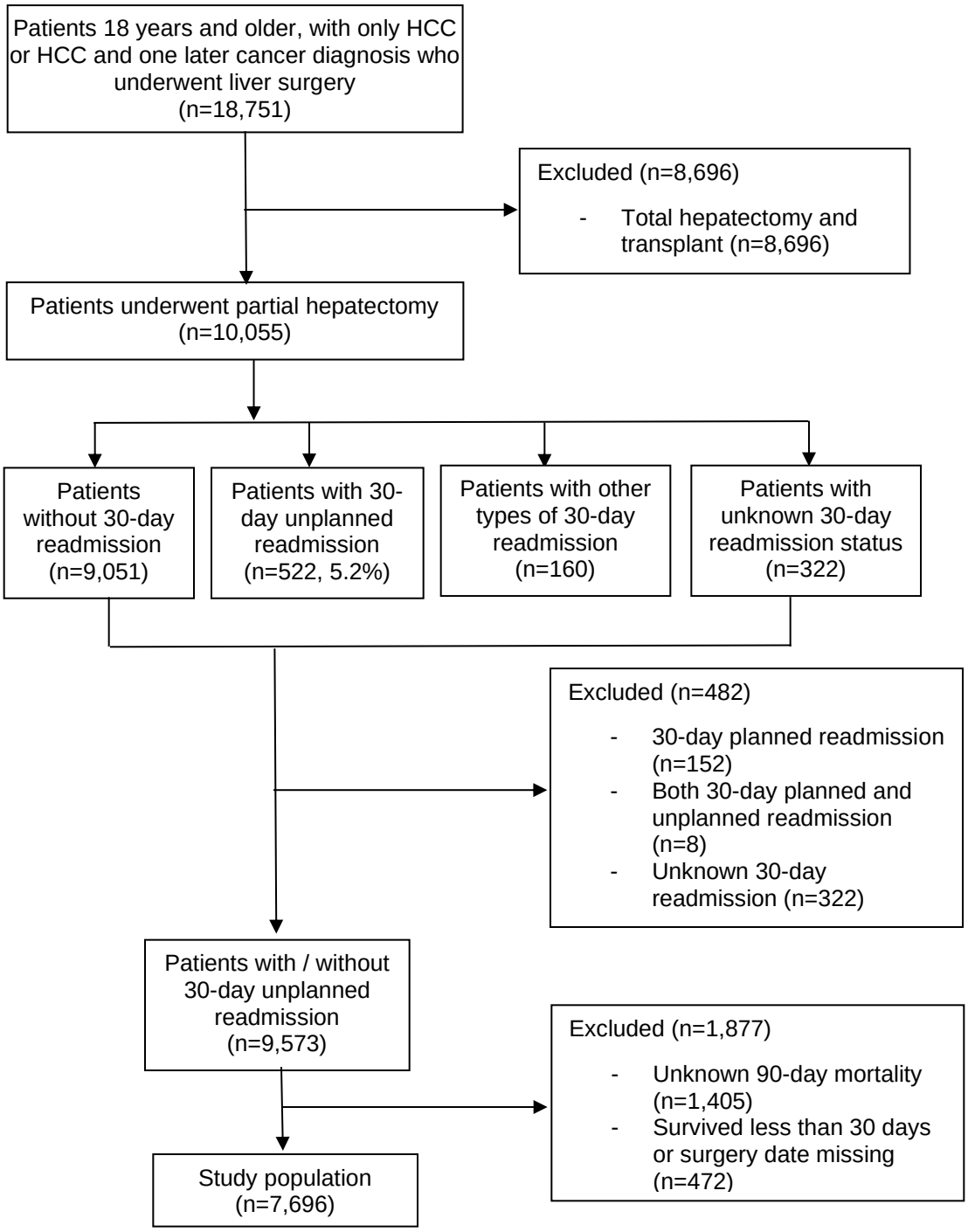

Figure 3. 1. Flow chart of study population

Table 3. 1a. Demographic and facility characteristics of patients undergoing partial hepatectomy (2004-2012), stratified by 30-day unplanned readmission

Variable	All, n (%)	30-Day Unplanned Readmission, n (%)		p-value
		No	Yes	
Total	7696	7254	442	
Age (mean years± SD[a])	61.7 ± 12.9	61.8 ± 12.9	60.2 ± 13.5	0.010
18-49	1074 (14.0)	994 (13.7)	80 (18.1)	0.059
50-64	3283 (42.7)	3096 (42.7)	187 (42.3)	
65-74	2080 (27.0)	1969 (27.1)	111 (25.1)	
>74	1259 (16.4)	1195 (16.5)	64 (14.5)	
Gender				0.015
Male	5329 (69.2)	5000 (68.9)	329 (74.4)	
Female	2367 (30.8)	2254 (31.1)	113 (25.6)	
Race/Ethnicity				0.003
White, non-Hispanic	4468 (58.1)	4218 (58.2)	250 (56.6)	
Black, non-Hispanic	1030 (13.4)	971 (13.4)	59 (13.4)	
Hispanic	974 (12.7)	895 (12.3)	79 (17.9)	
Others, non-Hispanic	1224 (15.9)	1170 (16.1)	54 (12.2)	
Insurance Status				0.003
Not insured	245 (3.2)	227 (3.1)	18 (4.1)	
Private insurance	3216 (41.8)	3014 (41.6)	202 (45.7)	
Medicaid	707 (9.2)	661 (9.1)	46 (10.4)	
Medicare or other	3214 (41.8)	3042 (41.9)	172 (38.9)	
Unknown	314 (4.1)	310 (4.3)	4 (0.9)	
Percentage of residents not graduated from high school				0.917
29% or more	1547 (20.1)	1454 (20.0)	93 (21.0)	
20%-28.9%	1729 (22.5)	1630 (22.5)	99 (22.4)	
14%-19.9%	1620 (21.0)	1526 (21.0)	94 (21.3)	
Less than 14%	2478 (32.2)	2342 (32.3)	136 (30.8)	
Missing	322 (4.2)	302 (4.2)	20 (4.5)	
Annual median household income				0.091
Less than $30,000	1156 (15.0)	1083 (14.9)	73 (16.5)	
$30,000-$34,999	1290 (16.8)	1228 (16.9)	62 (14.0)	
$35,000-$45,999	2039 (26.5)	1905 (26.3)	134 (30.3)	
$46,000 or more	2891 (37.6)	2738 (37.7)	153 (34.6)	
Missing	320 (4.2)	300 (4.1)	20 (4.5)	
Urban or rural residence				0.333
Metro	6283 (81.6)	5920 (81.6)	363 (86.1)	
Urban	991 (12.9)	942 (13.0)	49 (11.1)	
Rural	113 (1.5)	104 (1.4)	9 (2.0)	
Missing	309 (4.0)	288 (4.0)	21 (4.8)	
Distance to facility				0.206
Less than 12.5 miles	3390 (44.0)	3192 (44.0)	198 (44.8)	
12.5 to 49.9 miles	2334 (30.3)	2188 (30.2)	146 (33.0)	
50 miles or more	1810 (23.5)	1720 (23.7)	90 (20.4)	
Missing	162 (2.1)	154 (2.1)	8 (1.8)	
Facility type				0.060
Community	230 (3.0)	223 (3.1)	7 (1.6)	
Comprehensive	1616 (21.0)	1540 (21.2)	76 (17.2)	
Academic/research	4986 (64.8)	4683 (64.6)	303 (68.6)	
Other	436 (5.7)	410 (5.7)	26 (5.9)	
Missing	428 (5.6)	398 (5.5)	30 (6.8)	
Annual hospital hepatectomy volume				0.013
<4/year	2633 (34.2)	2492 (34.4)	141 (31.9)	
4-15/year	2383 (31.0)	2264 (31.2)	119 (26.9)	
>15/year	2680 (34.8)	2498 (34.4)	182 (41.2)	

[a] *SD*, standard deviation

Table 3. 1b. Clinical characteristics of patients undergoing partial hepatectomy (2004-2012), stratified by 30-day unplanned readmission

Variable	All, n (%)	30-Day Unplanned Readmission, n (%)		p-value
		No	Yes	
Total	7696	7254	442	
[a]AFP tumor marker				0.202
Negative/normal	1914 (24.9)	1818 (25.1)	96 (21.7)	
Positive/elevated	3315 (43.1)	3124 (43.1)	191 (43.2)	
Unknown	2467 (32.1)	2312 (31.9)	155 (35.1)	
Fibrosis score				0.011
0-4 (none-moderate fibrosis)	1099 (14.3)	1024 (14.1)	75 (17.0)	
5-6 (severe fibrosis/cirrhosis)	706 (9.2)	652 (9.0)	54 (12.2)	
Unknown	5891 (76.5)	5578 (76.9)	313 (70.8)	
Charlson-Deyo score				<0.001
0	4236 (55.0)	4031 (55.6)	205 (46.4)	
1	2203 (28.6)	2067 (28.5)	136 (30.8)	
2	1257 (16.3)	1156 (15.9)	101 (22.9)	
NCDB analytic stage group				0.115
I	3268 (42.5)	3102 (42.8)	166 (37.6)	
II	1821 (23.7)	1706 (23.5)	115 (26.0)	
III	1576 (20.5)	1469 (20.3)	107 (24.2)	
IV	291 (3.8)	276 (3.8)	15 (3.4)	
Unknown	740 (9.6)	701 (9.7)	39 (8.8)	
Tumor grade				0.028
I	1547 (20.1)	1467 (20.2)	80 (18.1)	
II	3378 (43.9)	3163 (43.6)	215 (48.6)	
III	1408 (18.3)	1323 (18.2)	85 (19.2)	
IV	251 (3.3)	246 (3.4)	5 (1.1)	
Not determined	1112 (14.4)	1055 (14.5)	57 (12.9)	
Tumor size				0.392
≤30 mm	1410 (18.3)	1317 (18.2)	93 (21.0)	
>30mm and ≤50 mm	1816 (23.6)	1712 (23.6)	104 (23.5)	
>50 mm	4202 (54.6)	3969 (54.7)	233 (52.7)	
Unknown	268 (3.5)	256 (3.5)	12 (2.7)	
Surgical procedure				0.965
Wedge or segmental resection	4099 (53.3)	3863 (53.3)	236 (53.4)	
Lobectomy	2434 (31.6)	2298 (31.7)	136 (30.8)	
Extended lobectomy	551 (7.2)	518 (7.1)	33 (7.5)	
Unknown type	612 (8.0)	575 (7.9)	37 (8.4)	

[a]AFP: alpha-fetoprotein

Table 3. 2. Multivariate logistic regression analysis of the risk factors for 30-day unplanned readmission after partial hepatectomy

Variable	Total	Readmission n (%)	Adjusted OR[a] (95% CI[b])	p-value
Total	7696	442 (5.7)		
Age			0.992 (0.980 – 1.004)	0.213
Gender				
Female	2367	113 (4.8)	Reference	
Male	5329	327 (6.1)	1.294 (1.025 – 1.649)	0.033
Race/Ethnicity				
White, non-Hispanic	4468	250 (5.6)	Reference	
Black, non-Hispanic	1030	59 (5.7)	0.953 (0.682 – 1.311)	0.774
Hispanic	974	79 (8.1)	1.394 (1.037 – 1.851)	0.025
Others, non-Hispanic	1224	54 (4.4)	0.746 (0.532 – 1.026)	0.080
Insurance Status				
Private insurance	3216	202 (6.3)	Reference	
Not insured	245	18 (7.3)	0.901 (0.465 – 1.592)	0.738
Medicaid	707	46 (6.5)	0.821 (0.549 – 1.196)	0.320
Medicare or other	3214	172 (5.4)	0.861 (0.663 – 1.119)	0.264
Unknown	314	4 (1.3)	0.216 (0.062 – 0.572)	0.006
Annual median household income				
$46,000 or more	2891	153 (5.3)	Reference	
$35,000-$45,999	2039	134 (6.6)	1.187 (0.923 – 1.525)	0.181
$30,000-$34,999	1290	62 (4.8)	0.770 (0.553 – 1.059)	0.114
Less than $30,000	1156	73 (6.3)	1.152 (0.841 – 1.566)	0.372
Facility type				
Academic/research	4986	303 (6.1)	Reference	
Community	230	7 (3.0)	0.567 (0.234 – 1.172)	0.162
Comprehensive	1616	76 (4.7)	0.831 (0.611 – 1.120)	0.229
Other	436	26 (6.0)	1.035 (0.657 – 1.564)	0.876
Annual hospital hepatectomy volume				
>15/year	2680	182 (6.8)	Reference	
4-15/year	2383	119 (5.0)	0.619 (0.477 – 0.799)	<0.001
<4/year	2633	141 (5.4)	0.765 (0.575 – 1.015)	0.065
Charlson-Deyo score				
0	4236	205 (4.8)	Reference	
1	2203	136 (6.2)	1.309 (1.032 – 1.658)	0.026
2	1257	101 (8.0)	1.550 (1.179 – 2.025)	0.002
Tumor grade				
I	1547	80 (5.2)	Reference	
II	3378	215 (6.4)	1.180 (0.896 – 1.569)	0.248
III	1408	85 (6.0)	1.192 (0.855 – 1.664)	0.299
IV	251	5 (2.0)	0.834 (0.271 – 2.066)	0.722
Not determined	1112	57 (5.1)	0.943 (0.644 – 1.369)	0.760

Table 3. 3. Association between 30-day unplanned readmission and 90-day mortality after partial hepatectomy

Predictor	Unadjusted OR[a] (95% CI[b])	p-value	Adjusted[c] OR[a] (95% CI[b])	p-value
30-day unplanned readmission				
No	Reference		Reference	
Yes	2.342 (1.663-3.225)	<0.001	2.325 (1.643-3.219)	<0.001

[a] *OR*: odds ratios; [b] *CI*: confidence interval
[c] Adjusted for age, sex, race/ethnicity, insurance status, annual hospital volume and Charlson-Deyo score.

Table 3. 4. Impact of 30-day unplanned readmission on conditional 90-day mortality in selected subgroups

	Unadjusted			Adjusted		
Factor	OR[a]	95% CI[b]	p value	OR[a]	95% CI[b]	p value
Age						
18-49	1.442	0.423-3.730	0.499	1.440	0.413-3.871	0.512
50-64	2.736	1.578-4.493	<0.001	2.846	1.626-4.728	<0.001
65-74	1.993	0.983-3.677	0.039	1.947	0.953-3.628	0.049
75 and above	3.190	1.525-6.155	0.001	3.081	1.453-6.044	0.002
Sex						
Male	1.960	1.303-2.854	<0.001	1.985	1.314-2.903	<0.001
Female	3.777	1.946-6.818	<0.001	3.809	1.909-7.114	<0.001
Race/Ethnicity						
White, non-Hispanic	3.334	2.213-4.887	<0.001	3.287	2.164-4.862	<0.001
Black, non-Hispanic	1.369	0.403-3.512	0.559	1.165	0.336-3.080	0.781
Hispanic	1.095	0.373-2.582	0.851	1.186	0.396-2.880	0.731
Others, non-Hispanic	1.033	0.166-3.485	0.964	1.374	0.214-4.945	0.677
Insurance Status						
Private	2.521	1.432-4.187	<0.001	2.391	1.347-4.012	0.002
Not insured	7.367	1.446-31.021	0.008	11.247	1.666-77.316	0.011
Medicaid	1.653	0.478-4.381	0.361	1.692	0.471-4.766	0.362
Medicare or others	2.180	1.281-3.516	0.002	2.140	1.252-3.472	0.003
AFP[c] tumor marker						
Negative/normal	2.264	0.853-5.021	0.066	2.716	0.805-4.952	0.088
Positive/elevated	2.545	1.548-4.005	<0.001	2.149	1.245-3.529	0.004
Fibrosis score						
0-4 (none-moderate)	2.146	0.717-5.212	0.123	2.511	0.820-6.342	0.072
5-6 (severe fibrosis/cirrhosis)	3.606	1.471-7.987	0.003	3.768	1.478-8.815	0.003
Charlson-Deyo score						
0	2.067	1.187-3.379	0.006	2.002	1.139-3.312	0.010
1	2.270	1.182-4.032	0.008	2.435	1.257-4.383	0.005
2	2.658	1.385-4.795	0.002	2.741	1.410-5.029	0.002
Annual Hospital Volume						
<4/year	1.881	1.012-3.244	0.032	1.667	0.888-2.910	0.089
4-15/year	1.682	0.774-3.238	0.149	1.633	0.743-3.191	0.182
>15/year	3.749	2.231-6.095	<0.001	3.969	2.312-6.561	<0.001

[a] *OR*: odds ratios; [b] *CI*: confidence interval; [c] AFP: alpha-fetoprotein

CHAPTER 4

NAFLD DOES NOT INCREASE THE RISK OF POSTOPERATIVE ADVERSE OUTCOMES FOLLOWING HEPATIC RESECTION FOR HEPATOCELLULAR CARCINOMA

ABSTRACT

Background Non-alcoholic fatty liver disease (NAFLD) is increasingly found in patients with hepatocellular carcinoma (HCC). The aim of this study was to analyze the impact of NAFLD on postoperative outcomes following hepatectomy for HCC by using a national database representative of the US population.

Methods Hospitalizations of HCC patients with NAFLD were identified in the National Inpatient Sample (NIS) from 2005 through 2014 using ICD-9-CM codes. The prevalence of NAFLD in patients with HCC and trends over the 10-year period were determined. Univariate and multivariable regression analyses were performed to evaluate the impact of NAFLD and other risk factors on postoperative outcomes including frequencies of complications, in-hospital mortality and length of stay (LOS).

Results Among 31,015 hospitalizations with primary diagnosis of HCC, prevalence of NAFLD and hospital admissions with NAFLD increased 24.5% and 35.2% respectively over the course of the study . From this cohort, 283 NAFLD and 3,081 non-NAFLD patients who underwent either partial hepatectomy or hepatic lobectomy were further identified. In multivariable analyses, factors associated with increased occurrence of postoperative complications included comorbidity index and hepatic lobectomy. Risk factors of in-hospital mortality were morbidity index, hepatic lobectomy, and five postoperative complications. Risk factors associated with increased odds of longer LOS comprised female gender, comorbidity index, and hepatic lobectomy. Postoperative complications associated with increased odds of longer LOS included cardiovascular complications, bleeding, pulmonary complications, infection, digestive system complications, wound

complications, DVT, and acute renal failure. NAFLD was not predictive of increased occurrence of postoperative complications and in-hospital mortality. NAFLD was associated with 9% reduced hospital length of stay.

Conclusion HCC with NAFLD may not carry higher surgical risks of postoperative complications, in-hospital mortality and prolonged hospital LOS when compared to HCC occurring on classical liver diseases.

INTRODUCTION

In the United States, the age-adjusted mortality rate of liver cancer increased by 43% between 2000 and 2016 (Xu, 2018). Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer accounting for 80-90% of all primary liver cancers (Chacko & Samanta, 2016). Surgical resection or transplantation are the only potentially curative treatment options for HCC. (Tsim et al., 2010). Historically, liver resection has been associated with high mortality of 10-20% and morbidity of 20-40% (Martínez-Mier et al., 2016). Due to the substantial improvement of perioperative management and advances in surgical techniques, the mortality and morbidity rates after liver resection have dropped significantly (Yamazaki & Takayama, 2017).

The global rise in the prevalence of obesity has significantly contributed to the increase of non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease since first described approximately 30 years ago (Mikolasevic et al., 2016; Pais et al., 2016). NAFLD is believed to affect 20-30% of the general population in Europe (Armstrong et al., 2012; Bedogni et al., 2005) and 25-46% in the United States (Chalasani et al., 2012; Rinella, 2015; Williams et al., 2011). NAFLD represents a range of conditions characterized by fat accumulation in ≥ 5% of hepatocytes without evidence of significant alcohol consumption (<30g/day for men and <20g/day for women) (Puri & Sanyal, 2012). The histologic spectrum of NAFLD ranges from simple hepatic steatosis and nonalcoholic

steatohepatitis (NASH) to fibrosis and cirrhosis (Alkhouri & McCullough, 2012). It has been reported that 10%-40% of all individuals diagnosed with NAFLD are at risk for advanced liver disease including hepatic fibrosis, cirrhosis with an increased risk of HCC (Younossi et al., 2012), 10%-20% of patients with NAFLD progress to NASH, of which 8.3% develop cirrhosis. Up to 50% of NASH with cirrhosis advance to HCC (Kew, 2015). Previous studies have reported the rise in the prevalence of NAFLD, which were documented by an increased prevalence from 15% in 2005 to 25% in 2010 worldwide (Younossi et al., 2016), a doubled increase of prevalence in the U.S. from 1988 to 2008 (Younossi et al., 2011), and a tripled admission of patients with NAFLD to hospitals in the U.S. from 2007-2014 (Adejumo et al., 2019). However, reports on the prevalence and temporal trend of NAFLD in hospitalized patients with HCC are limited. Furthermore, the impact of NAFLD on surgical outcomes following hepatic resection for HCC is not well delineated. Therefore, the purpose of this study was to describe a 10-year (2005-2014) national trend and pattern of NAFLD prevalence among patients with HCC and investigate the impact of NAFLD on adverse outcomes in patients undergoing liver resection for HCC.

METHODS

Data Source and Data Extraction

For this retrospective analysis of preexisting deidentified data, we used the Nationwide Inpatient Sample (NIS) database, the largest publicly accessible all-payer inpatient database created and operated by the Agency for Health Research and Quality (AHRQ). The database represents approximately 20% of all discharges for over 4500 non-federal community hospitals in the United States. The NIS database contains clinical variables on source and type of admissions, diagnosis-related groups (DRGs), 25-30 diagnosis codes from the International Classification of Disease, 9th Revision, Clinical

Modification (ICD-9-CM), 15 ICD-9-CM procedure codes, procedure days from admission, length of stay (LOS) and discharge status. Demographic characteristics (gender, age, race/ethnicity) and nonclinical variables including median household income in the patients' zip code area and rural/urban residence and expected payment source are also included. NIS is widely considered the most valid and reliable source of epidemiological data on inpatient care and outcomes in the United States. On average, NIS dataset contains about 7 million discharges each year. In this study we extracted data from 2005 – 2014 using standard SAS code provided by HCUP-NIS to ensure the right coding and labeling for all variables.

Study Population and Variables of Interest

We identified all patients 18 years and older with the primary diagnosis of HCC using ICD-9-CM codes of 155.0 (Malignant neoplasm of liver, primary) between 2005 and 2014. This cohort was used as the denominator for the prevalence of NAFLD. NAFLD was identified from any of the 14 secondary diagnoses using ICD-9-CM codes of 571.5 (cirrhosis of the liver without mention of alcohol), 571.8 (other nonalcoholic liver disease), and 571.9 (unspecified chronic liver disease without mention of alcohol), excluding patients with any ICD-9-CM codes that were related to alcoholic use and other etiologies of Hepatitis A, B and C, and patients with comorbidity of alcohol abuse. We expected 85% accuracy of identifying NAFLD by using this algorithm (Allen et al., 2018). We then selected patients who underwent either partial hepatectomy or hepatic lobectomy with ICD-9-CM procedure codes of 50.22 and 50.3 respectively. Patients who underwent a liver resection were divided into two groups based on NAFLD status.

There were three primary outcome variables: increased occurrence of postoperative complications, in-hospital mortality, and hospital length of stay. Postoperative complications included cardiovascular complications, bleeding/transfusion, pulmonary

complications, infection/sepsis, wound complications, deep vein thrombosis/pulmonary embolism, device (Wong & Devereaux, 2019) complications, acute renal failure, acute liver failure, and other complications.

We extracted demographic information on age, gender (male and female), race/ethnicity (White, Black, Hispanic and other), insurance status (Medicare, Medicaid, private, self-pay and no charge), and household income of residence zip-code (1^{st}, 2^{nd}, 3^{rd}, and 4^{th} quartile). We also collected hospital and procedure related information which included hospital region (Northeast, Midwest, South, and West), hospital location/teaching status (rural, urban/nonteaching, and urban teaching), hospital bed size (small, medium, and large), and surgical procedure (partial hepatectomy and hepatic lobectomy). Finally, we extracted 29 comorbidities that covered both physical and psychological types of comorbidities.

Statistical Analysis

To describe the national trend and pattern of NAFLD prevalence in hospitalized HCC patients, we calculated the prevalence for each year by dividing the number of patients with a diagnosis of NAFLD by the total number of patients with HCC. Multivariable log-binomial regression model was used to analyze trends in prevalence of NAFLD over time. The dependent variable in this model was the diagnosis of NAFLD (NAFLD=1; non-NAFLD=0) and the predictor variables were entered for the year, age group, gender, and race/ethnicity. We compared the differences of demographic characteristics, hospital, procedure information, comorbidities, and postoperative outcomes between NAFLD and non-NAFLD cohorts using Chi-square test for categorical variables, independent t-test for age, and Mann-Whitney U test for LOS. To examine the association between NAFLD and in-hospital mortality, we fit univariate and multivariable logistic regression models. We also performed negative binomial regression analysis to address the impact of NAFLD on

increased occurrence of postoperative complications and LOS. Instead of using 29 individual comorbidities for adjustment in multivariable models, we adopted the comorbidity index score as one score for all comorbidities. This score was calculated as a weighted sum of each binary comorbidity variable and has been validated and proved effective in assessing the influence of comorbidity in models evaluating the risk of in-hospital mortality and readmissions using administrative data (Moore et al., 2017). The final multivariable models included predictors with a $p \leq 0.1$ in univariate analysis. We reported odds ratios and 95% confidence intervals (95% CI) for all regression models.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). All statistical tests are two-sided and a p-value less than 0.05 is considered statistically significant.

RESULTS

Trends in NAFLD prevalence

We identified 31,015 patients with a primary diagnosis of HCC between 2005 and 2014, of which 2,995 were also diagnosed with NAFLD. Admissions with NAFLD among hospitalized HCC patients increased approximately 1.4-fold over the 10 years of study (264 in 2005 and 357 in 2014). The prevalence of NAFLD was 9.4% in 2005 and 11.7% in 2014 (Table 4.1), representing an increase of 24.5%. Patients 65 and older had approximately twice the prevalence than those younger than 65 years of age across all study years. Female patients showed consistently higher prevalence rates over the 10-year period. Hispanics had the highest and black had the lowest prevalence rates of NAFLD, whereas the prevalence among whites fell in between. Each advancing calendar year was associated with a 3.6% increased prevalence of NAFLD (PR, 1.036, 95% CI,

1.022-1.049). Prevalence trend over the 10-year period is shown in Figure 4.1. Statistically significant increases in trend were observed for almost all age, gender, and race/ethnicity subgroups except for black race and other races. The greatest increase in annual prevalence of NAFLD was found in females (PR, 1.044, 95% CI, 1.023-1.066, p<0.001), followed by Hispanic patients (PR, 1.043, 95% CI, 1.015-1.072, p<0.001).

Demographics and clinical characteristics

Among 31,015 patients, 3,364 underwent either partial hepatectomy (n=2,105, 62.6%) or hepatic lobectomy (n=1,259, 37.4%). In patients undergoing liver resection, a little over half were younger than 65 years (n=1,761, 52.3%) and male patients accounted for 65.8% (n=2,212). Approximately 51.8% of the study population were white, followed by other races (16.8%), black (9.8%), and Hispanics (9.7%). Nearly half (45.6%) were covered by Medicare insurance and 37.4% had private insurance. In addition, nearly one third (31.9%) of patients were hospitalized in hospitals located in the South and one fourth (25.6%) in Northeast. Patients were mostly (89.9%) admitted to teaching hospitals in urban areas and hospitals with a large bed size (80.2%).

When stratified by NAFLD status, patients with NAFLD were older compared to those without NAFLD (67±11 vs. 62±13, p<0.001) (Table 4.2). Higher proportion of white and Hispanics were in the NAFLD group (59.0% vs 51.2% and 12.4% vs. 8.3%, respectively) while a higher proportion of black and other races was observed in the non-NAFLD group (10.2% vs. 6.0% and 17.3 vs. 10.6%, respectively). More patients with NAFLD were covered by Medicare (60.8% vs. 44.2%, p<0.001) and underwent partial hepatectomy (70.3% vs. 61.9%, p=0.005). Household income, hospital region and bed size had similar distributions between the NAFLD and non-NAFLD groups (Table 4.2).

Comorbidities associated with NAFLD were coagulopathy (18.4% vs. 11.9%, p=0.002), chronic pulmonary disease (13.4% vs. 10.3%, p=0.015), coagulopathy (11.9%

vs. 8.3%, p=0.002),uncomplicated diabetes (37.5% vs. 23.5%, p<0.001), liver disease (100.0% vs. 40.8%, p<0.001), obesity (18.7% vs. 6.3%, p<0.001), peripheral vascular disorders (8.1% vs.3.7%, p<0.001), and renal failure (7.8% vs. 4.9%, p=0.036). On the other hand, patients without NAFLD were more likely to have alcohol abuse (8.9% vs. 0%, p<0.001), drug abuse (2.5% vs. 0.4%, p=0.023), and metastatic cancer (9.3% vs. 4.9%, p=0.014). In addition, NAFLD group had higher proportion of patients with cirrhosis (79.5% vs. 31.4%, p<0.001) (Table 4.3).

Postoperative complications

At least one postoperative complication was reported in approximately 33% of patients with HCC undergoing liver resection. One hundred sixty-five patients (4.9%) died during hospitalization. The most common complication was bleeding/transfusion (15.7%) followed by pulmonary complications (10.8%) and acute renal failure (10.1%). Incidence of other complications is shown in Table 4.4. Univariate analysis indicated that acute renal failure was significantly higher in NAFLD group compared to non-NAFLD group (14.1% vs. 9.7%, p=0.019).

Factors associated with increased occurrence of complications in multivariable negative binomial regression were comorbidity index (OR, 1.049, 95% CI, 1.044-1.055, p<0.001) and hepatic lobectomy (vs. partial hepatectomy) (OR, 1.338, 95% CI, 1.191-1.504, p<0.001) (Table 4.5). NAFLD was not associated with increased occurrence of complications (p=0.952).

Mortality

In the univariate analysis, patients with NAFLD were more likely to die during hospitalization (8.1% vs. 4.6%, p=0.009) (Table 4.4), though these results were not supported after adjustment for covariates (p=0.625).

Factors associated with in-hospital mortality included hepatic lobectomy (vs. partial hepatectomy) (OR, 1.770, 95% CI, 1.164-2.694, p=0.008), comorbidity index (OR, 1.049, 95% CI, 1.030-1.069, p<0.001), and cirrhosis (OR, 1.870, 95% CI, 1.193-2.932, p=0.006) (Table 4.6).

We found that five complications were associated with 2.8 to 8.2-fold higher odds of in-hospital mortality (Table 4.6). They were pulmonary complications/ pneumonia (OR, 5.695, 95% CI, 3.698-8.771, p<0.001), infection/sepsis (OR, 2.805, 95% CI, 1.668-4.718, p<0.001), acute renal failure (OR, 4.449, 95% CI, 2.855-6.932, p<0.001), acute liver failure (OR, 8.195, 95% CI, 3.998-16.797, p<0.001), and device complications (OR, 6.087, 95% CI, 1.315-28.176, p=0.021).

Length of stay (LOS)

Demographic factors associated with higher odds of longer LOS were Medicaid insurance (vs. private) (OR, 1.192, 95% CI, 1.114-1.276, p<0.001), other insurance programs (vs. private) (OR, 1.129, 95% CI, 1.032-1.235, p=0.008), household income first quartile (vs. fourth quartile) (OR, 1.083, 95% CI, 1.024-1.145, p=0.005). In addition, comorbidity index (OR, 1.014, 95% CI, 1.011-1.016, p<0.001), and hepatic lobectomy (vs. partial hepatectomy) (OR, 1.062, 95% CI, 1.020-1.105, p=0.004) were also associated with increased odds of longer LOS. Postoperative complications associated with longer LOS included cardiovascular complications (OR, 1.132, 95% CI, 1.027-1.248, p=0.013), bleeding complications/transfusion (OR, 1.063, 95% CI, 1.005-1.124, p=0.033), pulmonary complications/pneumonia (OR, 1.442, 95% CI, 1.354-1.535, p<0.001), infection/sepsis (OR, 1.728, 95% CI, 1.598-1.868, p<0.001), digestive system complications (OR, 1.314, 95% CI, 1.216-1.419, p<0.001), wound complications (OR, 1.220, 95% CI, 1.051-1.416, p=0.009), deep vein thrombosis/pulmonary embolism (OR, 1.756, 95% CI, 1.542-2.000, p<0.001), and acute renal failure (OR, 1.366, 95% CI, 1.280-

1.457, p<0.001). NAFLD and male gender were associated with decreased length of stay (OR, 0.907, 95% CI, 0.842-0.976, p=0.009 and OR, 0.946, 95% CI, 0.908-0.986, p=0.008 respectively) (Table 4.7).

DISCUSSION

Using the Nationwide Inpatient database, we estimated the annual prevalence of NAFLD in hospitalized patients with HCC from 2005 to 2014, described prevalence trends during the 10-year period, and investigated the impact of NAFLD on postoperative outcomes including increased occurrence of complications, in-hospital mortality and length of hospital stay. In the cohort of 31,015 patients who were diagnosed with HCC, depending on specific subgroups, up to 18.0% of patients had coexisting NAFLD. Overall, the prevalence of NAFLD increased at an average rate of 3.6% per year from 2005 to 2014. This continuous rise in the prevalence of NAFLD in hospitalized patients with HCC throughout the entire study period is consistent with a recent study focusing on economic burden of NAFLD among hospitalized adults (Hirode et al., 2019). In addition, we found that prevalence of NAFLD increased more in patients 65 years and older than younger patients where an annual increase of 4.2% was observed in the older groups compared to the annual increase of 2.4% in the younger group. NAFLD prevalence increased 4.4% annually in females while it only increased 3.1% annually in males. Moreover, prevalence increased by 121% in male patients 45 years and older compared to patients 45 and younger. Meanwhile, prevalence jumped 206% between the same age groups in women indicating higher NAFLD prevalence in postmenopausal women. This might be related to the loss of protective effect of estrogen in women after menopause. Risk factors of NAFLD such as insulin resistance, hyperlipidemia and visceral fat accumulation increase in women after menopause (Lovejoy et al., 2008). Our data showed that the highest prevalence rate of NAFLD was among Hispanics followed by non-Hispanic white. Non-

Hispanic black had the lowest prevalence rate. Noticing this race disparities in NAFLD prevalence, researchers have focused on epigenetic and genome-wide association studies and proposed that PNPLA3 I148M rs738409 variant might be a major determinant of race-related differences in hepatic fat accumulation (Xu et al., 2015). Similar to NAFLD/NASH incidence rates, the highest rate of I148M presence of 49% was among Hispanics followed by non-Hispanic white (23%) and non-Hispanic black (17%) (Romeo et al., 2008).

Parallel to the epidemic of obesity and type 2 diabetes, the prevalence of NAFLD in both children and adults is rapidly rising (Tanaka et al., 2019) and has become the most common cause of chronic liver disease worldwide. Prior research indicated that NAFLD-related HCC is increasing gradually, accounting for approximately 35% of HCC cases in 2010 (Dyson et al., 2014). Although there is a lot of ongoing NAFLD research, few studies have been conducted to compare the surgical outcomes in HCC patients with coexisting NAFLD and those without NAFLD. Our study revealed that despite being older and having more comorbidities, only postoperative complication of acute renal failure was higher in NAFLD group than non-NAFLD group. This may be related to the significant higher proportions of obesity and diabetes in NAFLD patients. Diabetes is a major cause of chronic kidney disease and obesity is associated with aggravated course and poor outcomes of chronic kidney disease (Eknoyan, 2011). Acute kidney disease is a risk factor of chronic kidney disease and vice versa (Chawla, Eggers, Star, & Kimmel, 2014). Moreover, in multivariable analysis, NAFLD was not associated with increased occurrence of postoperative complications. Although mortality was higher in NAFLD group, NAFLD itself was not an independent risk factor of mortality. Interestingly, NAFLD was found to be associated with shortened hospital LOS in the present study. Similar findings were reported in a study using the same NIS database, which indicated a shorter length of stay in NAFLD patients undergoing bariatric surgery (Mavilia, Wakefield, & Karagozian, 2019).

Although the study did not explain why NAFLD was associated with a shorter length of stay, we believe that this might reflect the impact of obesity. Hauck and Hollingsworth have showed that for surgical patients, obese was associated with shorter hospital stay and the researchers postulated that obesity seemed to have a protective effect on a range of medical conditions that could improve health outcomes resulting in shorter hospital stay (Hauck & Hollingsworth, 2010).

Our data showed that NAFLD was neither associated with increased odds of the occurrence of postoperative complications nor risks of in-hospital mortality. Furthermore, NAFLD was associated with 9% reduced hospital LOS. Conflicting findings of the impact of NAFLD on postoperative outcomes have been reported. Results from a previous single center-based study showed that steatosis was an independent predictor of complications (Kooby et al., 2003). However, another study evaluated perioperative risk in 437 sequential patients undergoing bariatric surgery and found that NAFLD was not predictive of postoperative complications (Ribeireiro et al., 2011). A similar retrospective study comparing postoperative outcomes in patients with and without NAFLD reported no significant differences in postoperative complication and mortality (Wu et al., 2011). Comparable perioperative and long-term outcomes were also reported between HCC patients with NAFLD and patients with other etiologies following liver resection (Yang et al., 2020). Moreover, studies have reported better overall outcomes in HCC patients with NAFLD following liver resection. In a prospective study that followed 247 NAFLD-cirrhosis patients and 267 hepatitis C-cirrhosis patients, lower cumulative incidence of liver-related complications was observed in patients with NAFLD-cirrhosis (Bhala et al., 2011). In a separate study, Reddy and research team (Reddy et al., 2012) compared the long-term survival outcomes after curative therapy between HCC patients with NASH and patients with HCV and/or alcoholic liver disease. Results from the study indicated that HCC patients with NASH had less severe liver dysfunction at the time when the HCC was

diagnosed. The study further revealed that HCC patients with NASH had better overall survival than patients with HCV and/or alcoholic liver disease. Although, no prior study had reported what we have found in our study that NAFLD was associated with a reduced LOS, Ma and colleagues had reported that prolonged LOS was significantly associated with reduced rates of overall survival (Ma et al., 2015). This may indicate that a reduced LOS was associated with favorable long-term survival, which had been proved in patients following elective colorectal cancer resection (Curtis et al., 2016). Therefore, we believe in patients with either HCC or cirrhosis, coexistence of NAFLD is not a negative factor in terms of its impact on postoperative outcomes.

Literature has highlighted that NAFLD is strongly associated with features of the metabolic syndrome (MS), particularly abdominal obesity and type 2 diabetes (Anstee et al., 2013). In our study approximately 19% of patients with NAFLD were obese compared to only 6% of patients in non-NAFLD group. Prior studies have reported different scenarios of the impact of obesity on postoperative complications. Wong and colleagues have reported that patients with NAFLD-related HCC were less likely to receive grafts because of the higher proportion of noncirrhotic patients or compensated cirrhotic patients with low Model for End-Stage Liver Disease (MELD) score below thresholds required to receive prioritization for liver transplantation (Wong et al., 2017). The decreased occurrence of postoperative complication in HCC patients with NAFLD may be partially explained by obesity paradox where obese patients with prevalent chronic disease show lower mortality and survival benefit (Curcic et al., 2019; Karagozian et al., 2016). It was postulated that obese individuals may have good nutritional and physiological reserves and demonstrate enhanced inflammatory response to injury, which may offset comorbidity and mortality among obese patients undergoing hepatectomy (Guo et al., 2015).

Our study showed that comorbidity index and surgical procedure were independent predictors of increased occurrence of postoperative complications, in-hospital mortality,

and hospital LOS. Cirrhosis was only associated with in-hospital mortality. Similar findings were reported in a retrospective study reviewing HCC patients undergoing liver resection between 1983 and 2015, which indicated that major surgical procedures were significantly associated with major complications and early mortality after liver resection (Lee et al., 2016). An earlier study also showed that the number of comorbid factors and cirrhosis were the significant predictors of 30-day mortality after hepatic resection (Bolder et al., 1999). Our study also identified acute liver failure as the most significant risk factor of in-hospital mortality followed by device and pulmonary complications. Eight postoperative complications showed significant impact on hospital LOS. Prior reviews have summarized available literature regarding the occurrence of postresection liver failure and exclusively concluded that liver failure is the major cause of mortality after liver resection (Hammond et al., 2011; Kauffmann & Fong, 2014). A recent population-based retrospective study with a large sample size of 2,461 patients undergoing hepatectomy in Sweden also proved that post-hepatectomy liver failure is the single most important cause of mortality after hepatectomy (Gilg et al., 2018). Regarding postoperative LOS, Lorenzo and colleagues believed LOS is most influenced by comorbidities (Lorenza et al., 2005). Another study estimated the impact of major complications on postresection outcomes and financial burden and found that the occurrence of a major complication increased mean LOS by 8.7 days and increased risk of death by 9.3% (Idrees et al., 2019).

Our study has several limitations, most of which are related to the use of administrative database. Incomplete coding (Haut, Pronovost, & Schneider, 2012) and concerns over the clinical accuracy of ICD-9 diagnosis code (Campbell et al., 2011) are the major ones. In addition, the database does not provide information on HCC stage, severity of liver disease, tumor grade, and tumor size which may affect postoperative outcomes. Despite these limitations, findings from this study provided national level estimates for the prevalence trends of NAFLD across 10 years and evaluated the impact

of NAFLD on postoperative complications in HCC patients undergoing liver resection. In summary, our data indicated the significant increase in the prevalence of NAFLD in hospitalized HCC patients over the course of the study. However, NAFLD was associated with neither increased occurrence of postoperative complications nor in-hospital mortality. Furthermore, NAFLD was found to be associated with 9% reduced hospital LOS. Given the comparable risk of postoperative adverse outcomes in HCC patients with and without NAFLD, HCC with NAFLD may not be considered carrying higher surgical risks of postoperative complications, in-hospital mortality and prolonged hospital LOS when compared to HCC occurring on classical liver diseases.

Table 4.1. Prevalence of NAFLD among hospitalized HCC patients from 2005 to 2014

	2005 n (%)	2006 n (%)	2007 n (%)	2008 n (%)	2009 n (%)	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)
Total hospitalized	2805	2470	2955	3582	3288	3224	3446	3046	3135	3064
Total NAFLD	264 (9.4)	209 (8.5)	249 (8.4)	333 (9.3)	286 (8.7)	313 (9.7)	337 (9.8)	304 (10.0)	343 (10.9)	357 (11.7)
Age group (years)										
<65	96 (6.4)	78 (5.5)	106 (6.3)	132 (6.3)	104 (5.4)	109 (5.7)	127 (6.4)	113 (6.3)	127 (7.0)	127 (7.1)
≥65	168 (12.9)	131 (12.6)	143 (11.2)	201 (13.5)	182 (13.4)	204 (15.4)	208 (14.4)	191 (15.2)	216 (16.4)	230 (18.0)
Gender										
Male	173 (8.7)	133 (7.3)	161 (7.4)	209 (8.1)	179 (7.5)	191 (8.1)	216 (8.4)	205 (9.3)	219 (9.5)	227 (10.0)
Female	91 (11.3)	75 (11.5)	87 (11.3)	124 (12.5)	107 (11.9)	122 (14.3)	121 (13.8)	99 (11.6)	124 14.7)	130 (16.2)
Race/ethnicity										
White	139 (11.9)	87 (9.7)	113 (9.2)	156 (9.6)	155 (10.5)	173 (10.4)	200 (11.3)	184 (11.6)	209 (12.7)	209 (12.8)
Black	16 (5.7)	11 (3.7)	10 (3.1)	20 (5.1)	24 (5.4)	14 (3.2)	28 (5.2)	32 (6.4)	27 (5.2)	25 (5.2)
Hispanic	42 (11.3)	42 (11.5)	41 (10.5)	64 (13.9)	38 (9.0)	60 (13.3)	63 (12.7)	49 (11.3)	63 (14.3)	70 (16.3)
Other	19 (5.5)	20 (6.2)	38 (9.7)	34 (6.1)	27 (5.4)	39 (9.8)	23 (5.6)	27 (6.6)	34 (8.8)	39 (10.0)
Unknown	48 (7.5)	49 (8.3)	47 (7.6)	59 (10.7)	42 (9.5)	27 (10.3)	23 (10.6)	12 (9.8)	10 (6.9)	14 (10.5)

Note: NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

NAFLD prevalence trends were estimated using multivariate log-binomial regression model with NAFLD as outcome and calendar year as a predictor. Gender, age and race/ethnicity were added to the model. Adjusted prevalence ratio (PR) of year: 1.036, 95% CI 1.022 – 1.049, p<0.001.

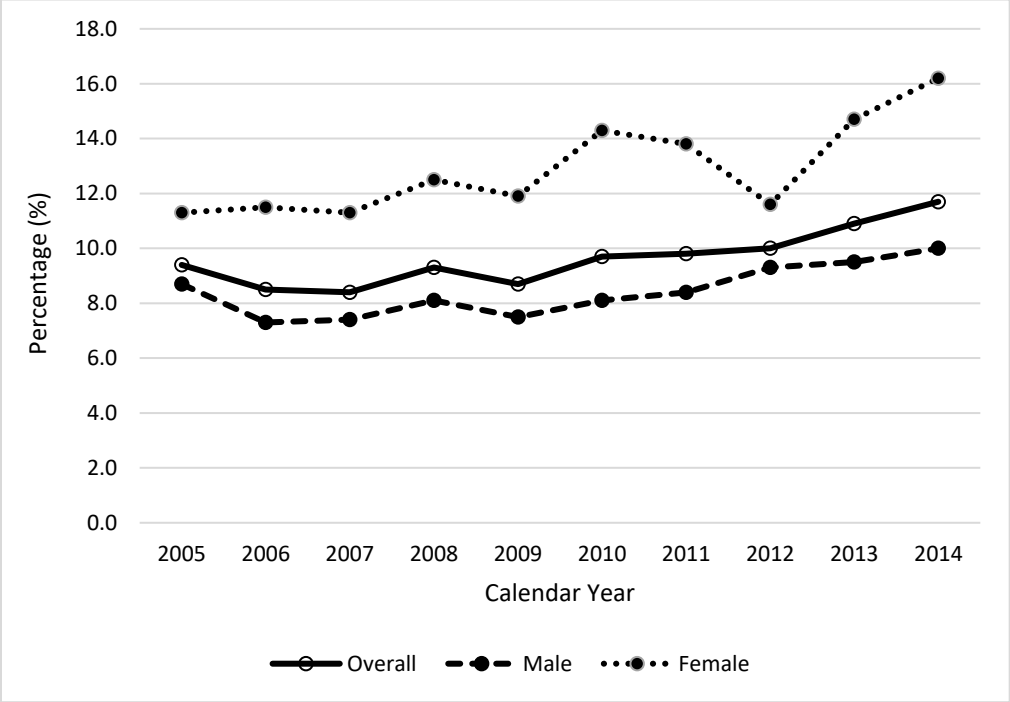

Figure 4. 1. Prevalence of non-alcoholic fatty liver disease overall and by gender from 2005 to 2014 among hospitalized patients with hepatocellular carcinoma

Table 4. 2. Demographic and hospital characteristics associated with NAFLD status in hospitalized patients with HCC and underwent liver resection, 2005-2014

	Total n (%)	NAFLD n (%)	Non-NAFLD n (%)	p-value
Total	283	3081		
Mean age, y	63 (±13)	67 (±11)	62 (±13)	<0.001
Gender				0.758
Male	2212 (65.8)	186 (65.7)	2026 (65.8)	
Female	1146 (34.1)	97 (34.3)	1049 (34.1)	
Unknown	6 (0.2)	0 (0)	6 (0.2)	
Race				<0.001
White	1743 (51.8)	167 (59.0)	1576 (51.2)	
Black	331 (9.8)	17 (6.0)	314 (10.2)	
Hispanic	291 (9.7)	35 (12.4)	256 (8.3)	
Other	564 (16.8)	30 (10.6)	534 (17.3)	
Unknown	435 (12.9)	34 (12.0)	401 (13.0)	
Insurance status				<0.001
Medicare	1533 (45.6)	172 (60.8)	1361 (44.2)	
Medicaid	377 (11.2)	19 (6.7)	358 (11.6)	
Private	1258 (37.4)	77 (27.2)	1181 (38.3)	
Other	191 (5.7)	15 (5.3)	176 (5.7)	
Unknown	5 (0.1)	0 (0.0)	5 (0.2)	
Household income (quartile)				0.701
Frist	786 (23.4)	75 (26.5)	711 (23.1)	
Second	775 (23.0)	64 (22.6)	711 (23.1)	
Third	829 (24.6)	70 (24.7)	759 (24.6)	
Fourth	861 (25.6)	65 (23.0)	796 (25.8)	
Unknown	113 (3.4)	9 (3.2)	104 (3.4)	
Hospital region	0.092			
Northeast	861 (25.6)	85 (30.0)	776 (25.2)	
Midwest	651 (19.4)	55 (19.4)	596 (19.3)	
South	1074 (31.9)	93 (32.9)	981 (31.8)	
West	778 (23.1)	50 (17.7)	728 (23.6)	
Hospital location/ teaching status				0.643
Rural	41 (1.2)	3 (1.1)	38 (1.2)	
Urban/nonteaching	286 (8.5)	28 (9.9)	258 (8.4)	
Urban/teaching	3024 (89.9)	250 (88.3)	2774 (90.1)	
Unknown	13 (0.4)	2 (0.7)	11 (0.4)	
Hospital bed size				0.103
Small	176 (5.2)	14 (5.0)	162 (5.3)	
Medium	477 (14.2)	53 (18.7)	424 (13.8)	
Large	2698 (80.2)	214 (75.6)	2484 (80.6)	
Unknown	13 (0.4)	2 (0.7)	11 (0.4)	
Surgical procedure				0.005
Partial hepatectomy	2105 (62.6)	199 (70.3)	1906 (61.9)	
Hepatic lobectomy	1259 (37.4)	84 (29.7)	1175 (38.1)	

NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

Table 4. 3. Comorbidities associated with NAFLD status in hospitalized patients with HCC and underwent liver resection, 2005-2014

	Total n (%)	NAFLD n (%)	Non-NAFLD n (%)	p-value
Total	3364	283	3081	
AIDS	17 (0.5)	1 (0.4)	16 (0.5)	0.706
Alcohol abuse	274 (8.1)	0 (0)	274 (8.9)	<0.001
Deficiency anemias	398 (11.8)	33 (11.7)	365 (11.8)	0.926
Rheumatoid arthritis/collagen vascular diseases	55 (1.6)	4 (1.4)	51 (1.7)	0.759
Chronic blood loss anemia	35 (1.0)	6 (2.1)	29 (0.9)	0.061
Congestive heart failure	139 (4.1)	17 (6.0)	122 (4.0)	0.098
Chronic pulmonary disease	517 (15.4)	50 (17.7)	467 (15.2)	0.262
Coagulopathy	420 (12.5)	52 (18.4)	368 (11.9)	0.002
Depression	213 (6.3)	25 (8.8)	188 (6.1)	0.071
Diabetes, uncomplicated	831 (24.7)	106 (37.5)	725 (23.5)	<0.001
Diabetes with chronic complications	92 (2.7)	12 (4.2)	80 (2.6)	0.105
Drug abuse	77 (2.3)	1 (0.4)	76 (2.5)	0.023
Hypertension	1839 (54.7)	166 (58.7)	1673 (54.3)	0.159
Hypothyroidism	269 (8.0)	30 (10.6)	239 (7.8)	0.091
Liver disease	1540 (45.8)	283 (100.0)	1257 (40.8)	<0.001
Lymphoma	22 (0.7)	2 (0.7)	20 (0.6)	0.908
Fluid and electrolyte disorders	795 (23.6)	71 (25.1)	724 (23.5)	0.547
Metastatic cancer	301 (8.9)	14 (4.9)	287 (9.3)	0.014
Other neurological disorders	102 (3.0)	9 (3.2)	93 (3.0)	0.879
Obesity	246 (7.3)	53 (18.7)	193 (6.3)	<0.001
Paralysis	22 (0.7)	4 (1.4)	18 (0.6)	0.098
Peripheral vascular disorders	136 (4.0)	23 (8.1)	113 (3.7)	<0.001
Psychoses	75 (2.2)	9 (3.2)	66 (2.1)	0.258
Pulmonary circulation disorders	63 (1.9)	5 (1.8)	58 (1.9)	0.891
Renal failure	173 (5.1)	22 (7.8)	151 (4.9)	0.036
Solid tumor without metastasis	135 (4.0)	16 (5.7)	119 (3.9)	0.142
Valvular disease	123 (3.7)	13 (4.6)	110 (3.6)	0.380
Weight loss	247 (7.3)	17 (6.0)	230 (7.5)	0.368
Cirrhosis	1191 (35.4)	225 (79.5)	966 (31.4)	<0.001

NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma, AIDS=acquired immune deficiency syndrome

Table 4. 4. Postoperative outcomes by NAFLD status in hospitalized patients with HCC, 2005-2014

	Total n (%)	NAFLD n (%)	Non-NAFLD n (%)	p-value
Total	3364	283	3081	
Complications				
Cardiovascular complications	122 (3.6)	11 (3.9)	111 (3.6)	0.807
Bleeding complications/transfusion	527 (15.7)	49 (17.3)	478 (15.5)	0.425
Pulmonary complications/pneumonia	364 (10.8)	38 (13.4)	326 (10.6)	0.140
Infection/sepsis	206 (6.1)	17 (6.0)	189 (6.1)	0.932
Digestive system complications	199 (5.9)	14 (4.9)	185 (6.0)	0.470
Intra-abdominal abscess	107 (3.2)	9 (3.2)	98 (3.2)	1.000
Wound complications	49 (1.5)	3 (1.1)	46 (1.5)	0.561
Deep vein thrombosis/ pulmonary embolism	57 (1.7)	2 (0.7)	55 (1.8)	0.179
Device complications	85 (2.5)	9 (3.2)	76 (2.5)	0.464
Acute renal failure	340 (10.1)	40 (14.1)	300 (9.7)	0.019
Acute liver failure	72 (2.1)	9 (3.2)	63 (2.0)	0.207
Other complications	72 (2.1)	9 (3.2)	63 (2.0)	0.207
Mortality	165 (4.9)	23 (8.1)	142 (4.6)	0.009
LOS (median day, IQR)	6 (4)	6 (4)	6 (4)	0.473

NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

Table 4.5. Negative binomial regression analysis of increased occurrence of complications in hospitalized patients with HCC and underwent liver resection, 2005-2014

	Unadjusted		Adjusted		
Variable	OR	95% CI	OR	95% CI	p-value
NAFLD	1.133	0.918-1.399	0.994	0.806 -1.224	0.952
Age	1.008	1.003-1.013			NS
Male	1.102	0.969-1.253			NS
Insurance status					
Medicaid vs. private	1.138	0.925-1.398			NS
Medicare vs. private	1.219	1.066-1.395			NS
Other vs. private	1.267	0.972-1.650			NS
Household income (quartile)					
First vs. fourth	1.304	1.096-1.551			NS
Second vs. fourth	1.158	0.970-1.382			NS
Third vs. fourth	1.258	1.059-1.494			NS
Hepatic lobectomy vs partial hepatectomy	1.423	1.260-1.607	1.338	1.191-1.504	<0.001
Comorbidity index	1.052	1.046-1.057	1.049	1.044-1.055	<0.001
Cirrhosis	1.220	1.078-1.382			NS

OR = odds ratio; CI = confidence interval; NS = non-significant, NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

Table 4. 6. Risk factors for mortality in hospitalized patients with HCC and underwent liver resection, 2005-2014

	Unadjusted		Adjusted		
Variable	OR	95% CI	OR	95% CI	p-value
NAFLD	1.830	1.157-2.892	1.176	0.615-2.249	0.625
Age	1.029	1.015-1.043	1.026	1.007-1.045	0.006
Male	1.318	0.933-1.863			NS
Hepatic lobectomy vs partial hepatectomy	2.372	1.727-3.256	1.770	1.164-2.694	0.008
Comorbidity index	1.107	1.092-1.123	1.049	1.030-1.069	<0.001
Cirrhosis	2.603	1.895-3.575	1.870	1.193-2.932	0.006
Complication					
Cardiovascular complications	3.132	1.806-5.433			NS
Bleeding complications/transfusion	2.982	2.129-4.176			NS
Pulmonary complications/ pneumonia	21.199	15.027-29.908	5.695	3.698-8.771	<0.001
Infection/sepsis	16.590	11.652-23.620	2.805	1.668-4.718	<0.001
Device complications	6.176	3.611-10.561	6.087	1.315-28.176	0.021
Acute renal failure	17.404	13.126-25.805	4.449	2.855-6.932	<0.001
Acute liver failure	44.041	26.427-73.396	8.195	3.998-16.797	<0.001
Other complications	5.511	3.049 -9.960			NS

OR = odds ratio; CI = confidence interval; NS = non-significant, NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

Table 4. 7. Negative binomial regression analysis of LOS in hospitalized patients with HCC and underwent liver resection, 2005-2014

	Unadjusted		Adjusted		
Variable	OR	95% CI	OR	95% CI	p-value
NAFLD	0.948	0.872-1.031	0.907	0.842-0.976	0.009
Age	1.003	1.001-1.005			NS
Male	1.020	0.971-1.071	0.946	0.908-0.986	0.008
Insurance status					
Medicaid vs. private	1.268	1.174-1.369	1.192	1.114-1.276	<0.001
Medicare vs. private	1.133	1.077-1.192			NS
Other vs. private	1.158	1.045-1.283	1.129	1.032-1.235	0.008
Household income (quartile)					
Frist vs. fourth	1.193	1.117-1.274	1.083	1.024-1.145	0.005
Second vs. fourth	1.119	1.048-1.196			NS
Third vs. fourth	1.116	1.046-1.191			NS
Hospital bed size					
Small vs. large	0.871	0.784-0.968			NS
Medium vs. large	0.932	0.872-0.996			NS
Comorbidity index	1.027	1.025-1.029	1.014	1.011-1.016	<0.001
Hepatic lobectomy vs. partial hepatectomy	1.161	1.108-1.217	1.062	1.020-1.105	0.004
Cirrhosis	1.111	1.060-1.166			NS
Complications					
Cardiovascular complications	1.359	1.206-1.530	1.132	1.027-1.248	0.013
Bleeding complications/transfusion	1.310	1.232-1.393	1.063	1.005-1.124	0.033
Pulmonary complications/pneumonia	2.194	2.058-2.338	1.442	1.354-1.535	<0.001
Infection/sepsis	2.721	2.513-2.947	1.728	1.598-1.868	<0.001
Digestive system complications	1.653	1.509-1.811	1.314	1.216-1.419	<0.001
Wound complications	1.807	1.510-2.163	1.220	1.051-1.416	0.009
Deep vein thrombosis/ pulmonary embolism	2.545	2.169-2.987	1.756	1.542-2.000	<0.001
Device complications	1.619	1.409-1.859			NS
Acute renal failure	2.085	1.950-2.230	1.366	1.280-1.457	<0.001
Acute liver failure	2.121	1.833-2.453			NS
Other complications	1.530	1.315-1.780			NS

LOS = length of stay; NS = non-significant, NAFLD=non-alcoholic fatty liver disease, HCC=hepatocellular carcinoma

CHAPTER 5 DISCUSSION AND CONCLUSIONS

Hepatectomy, the only curative treatment for HCC, is a major surgery and associated with increased risks of postoperative early mortality, readmission, and other adverse outcomes. This dissertation project focused on the adverse outcomes which included 90-day mortality, 30-day unplanned readmission, complications, and hospital length of stay in HCC patients undergoing hepatectomies. The dissertation project included three studies.

Summary of current research

In the first study which was described in chapter 2, we reported the 90-day mortality rate of 10.2%, which was at the higher end of the mortality range. We identified 10 risk factors including age, sex, race/ethnicity, insurance status, education, Charlson/Deyo score, annual hospital volume, and surgical procedure that were significantly associated with 90-day mortality. We also reported 90-day mortality rates of 2.47%, 5.88%, 12.58%, and 24.67% in low, medium, high, and excessive risk groups respectively. To test the discriminatory ability of the risk score model, we used receiver operating characteristic (ROC) and got the area under the curve (AUC) of 0.69. We compared our model with several models reported from previous research. Our model had similar discriminatory ability to a study conducted with the widely used P-POSSUM predictive scoring system for perioperative care (AUC=0.68) (Knoblich et al., 2020). Our study also was comparable to two studies that used MELD scores to predict postoperative mortality, which showed the AUC of 0.71 and 0.69 respectively (Fromer et al., 2016; Ghamarnejad et al., 2020). Studies that incorporated laboratory test variables showed higher AUC values (Hyder et al., 2013), however, information for these variables are not available for over 60% of the

cases in NCDB. Among the ten identified risk factors in our study, eight are available before the surgery and two are available either before the surgery if a biopsy is conducted or immediately after the surgery. This risk score can quantify patients' risks for 90-day mortality after hepatectomy without acknowledgement of detailed information on postoperative complications and laboratory test values, which could be a useful tool in improving 90-day mortality after hepatectomy.

In the second study which was included in chapter 3, we described 30-day unplanned readmission rate in HCC patients following a hepatectomy, identified associated risk factors and addressed the impact of 30-day unplanned readmission on conditional 90-day mortality. We reported the 30-day unplanned readmission of 5.2% and found male gender, Hispanic ethnicity, facility with high hospital hepatectomy volume, and higher Charlson-Deyo scores were associated with significant higher odds of 30-day unplanned readmission. Patients with a history of 30-day readmission was associated with approximately 2.3-fold increased odds of conditional 90-day mortality. The significant impact of 30-day unplanned readmission on conditional 90-day mortality had demonstrated in 15 subgroups. The finding of 30-day unplanned readmission rate of 5.2% is much lower than reports from prior studies. One of the reasons for the low readmission rate may be partially due to the way that readmission is captured in NCDB where only readmissions to the same treatment facility are recorded. Our findings that higher Charlson-Deyo scores were associated with increased odds of 30-day unplanned readmission were consistent with all previous study indicating the consensus that higher comorbidities had negative impact on 30-day unplanned readmission. The major goal of the current study was to evaluate how 30-day unplanned readmission affects conditional 90-day mortality. In subgroup analysis, in terms of age groups, we found that the impact of 30-day unplanned readmission on conditional 90-day mortality was only significant in patients 75 years and older. Another interesting finding was that even though male gender

was associated with higher odds of 30-day unplanned readmission, females had higher odds of 90-day mortality than males once they were readmitted within 30 days of discharge. For the current study, we were the first to investigate the association between 30-day unplanned readmission on 90-day mortality by AFP level and extent of fibrosis. AFP is highly expressed in the fetal yolk sac and liver, but not in normal adults' tissues (Tilghman, & Belayew, 1982). The elevation of AFP has been shown to correlate with unfavorable prognosis (Nomura, & Tanabe, 1989). We found that 30-day unplanned readmission affected 90-day mortality only in patients with an elevated AFP and in patients with severe liver fibrosis, which may indicate elevated AFP is an indicator of poor prognosis as reported previously (Peng et al., 2004). The current study was the first to provide national level estimate for 30-day unplanned readmission and address the impact of readmission on conditional 90-day mortality. This study might be helpful in improving 30-day unplanned readmission and 90-day mortality in HCC patients undergoing hepatectomies.

Consistent with previous reports on NAFLD, we found that from 2005 to 2014, the prevalence of NAFLD increased by 24.5% and admissions to hospitals with NAFLD increased approximately 35.2%. Each increasing year was associated with 3.6% increased prevalence. Patients 65 years and older had twice the prevalence as those younger than 65 years. Due to multiple age-related physiological mechanisms, elderly individuals are more likely to develop intra-abdominal obesity and metabolic syndrome which consist of obesity, insulin resistance, dyslipidemia, and hypertension (Bechtold, Palmer, Valtos, Lasiello, & Sowers, 2006). The greatest increase in annual prevalence of NAFLD was among females followed by Hispanics. We noted that proportion of female HCC patients younger than 55 years of age dropped from 21.9% in 2005 to 16.2% in 2015 while that in female HCC patients 55 years and older increased from 78.1% in 2005 to 83.8% in 2014. Previous study speculated that circulating levels of estrogen might have a protective effect on the development of hepatic steatosis (Carulli et al., 2006). This may

imply that women have a relatively lower risk of developing NAFLD before menopause, but the risk increases in postmenopausal women. In contrast, there are no such risk changes in men. In addition, literature has reported that prevalence of overall obesity and class 3 obesity had showed significant increasing linear trends among women but not among men (Flegal et al., 2016). It is expected that the prevalence of NAFLD increases more rapidly in women. Prevalence of NAFLD also increases greatly in Hispanics. Overall, Hispanic population has reached nearly 58 million in 2016 accounting for almost half of the national population growth since 2000 (Flores, 2017). Hispanics had the greatest increase in the annual prevalence of obesity from 1999-2000 to 2011-2012 than any other race/ethnicity groups (An, 2014). Also, the greatest increase in the newly diagnosed elderly individuals with type 2 diabetes between 1994 and 2010 was found in Hispanic population (McBean, Li, Gilbertson, & Collins, 2004). Given the increase of obesity and type 2 diabetes, the two main risk factors of NAFLD, it is likely that the prevalence of NAFLD would increase significantly among hospitalized Hispanic patients with HCC. Compared to HCC patients without NAFLD, patients with NAFLD had more comorbidities including obesity, higher complication of acute renal failure, and higher mortality. On the other hand, more alcohol abuse, drug abuse and metastatic cancer were observed in non-NAFLD group. As discussed previously, NAFLD is closely associated with metabolic syndromes which include the manifestations of hypertension, dyslipidemia, obesity and diabetes. Diabetes is a major cause of chronic kidney disease which is also significantly associated with acute kidney disease. In multivariable analysis, NAFLD did not show to be independent predictor of increased occurrence of postoperative complications and in-hospital mortality. Regarding the impact of NAFLD on postoperative outcome in HCC patients, literature has not been consistent. Several studies have reported that NAFLD especially NASH was associated with worse outcomes. However, comparable amount of studies indicated that NAFLD was not predictive of postoperative complications and

mortality (Wu et al., 2011), or the outcome between patients with and without NAFLD were similar (Yang et al., 2020), or NAFLD even showed favorable impact on incidence of liver-related complications (Bhala et al., 2011) and better overall survival (Reddy et al., 2012). It has been reported that HCC patients with NASH had less severe liver dysfunction at the time when the HCC was diagnosed (Reddy et al., 2012). Lower proportion of cirrhotic individuals and lower MELD score in compensated cirrhotic individuals were noted in HCC patients with NAFLD (Wong et al., 2017). Interestingly, in the current study, NAFLD was found to be associated with 9% reduced hospital length of stay. It was noted that HCC with NAFLD had a significant higher proportion of obesity than those without NAFLD (19% vs. 6%). Previous study had postulated that individuals with obesity may have a good nutritional and physiological reserves and demonstrate enhanced inflammatory response to injury, which may offset comorbidity and mortality among obese patients undergoing hepatectomy (Guo et al., 2015). The current study found that comorbidity index and surgical procedure were independent predictors of increased occurrence of postoperative complications, in-hospital mortality, and hospital LOS while cirrhosis was only associated with in-hospital mortality. These findings were in consistent with prior studies.

To further verify the impact of NAFLD on increased occurrence of postoperative complications, in-hospital mortality as well as hospital LOS, we also performed propensity score (PS) analysis with 1: 1 matching using the nearest neighbor matching method to obtain matched sets of non-NAFLD patients to each NAFLD patient based on PS scores. PS is the probability derived through a logistic regression model in which NAFLD was set as function of patients' age, gender, race/ethnicity and comorbidities. The PS matched dataset was then used in multivariable logistic regression and negative binomial regression analyses. The results from applying PS methods indicated that NAFLD was not indicative of increased occurrence of postoperative complications, in-hospital mortality, and prolonged LOS.

Research Implications

Findings from this dissertation indicated that 90-day mortality after hepatectomy in HCC patients undergoing hepatectomies was around 10%, though 30-day unplanned readmission rate was lower at 5.2%, patients with a history of 30-day unplanned readmission carried higher risk of conditional 90-day mortality. There is room for improvement of these two important postoperative outcomes. In the first study, we developed a useful tool – integer valued risk score model that can be applied to predict 90-day mortality, This model quantified the risks of 90-day mortality for each of the subgroups within respective risk factors by assigning an integer score derived from the weighting of β coefficients of a logistic regression model, so that total risk score can be calculated for each individual. Based on total risk score, patients were grouped into low, medium, high, and excessive risk groups. The corresponding mortality rate in the low risk group was 2.47% and each increase in the level of risk was associated with approximately doubled mortality rate, and the highest risk group reached the mortality rate close to 25%. Clearly, with this this risk score, clinicians can easily identify those who are at more than the average risk of 90-day mortality immediately after or even before the surgery, so that special attention may be payed to focus on these high-risk patients in regard to perioperative care. This useful tool may also be helpful in facilitating communications between patients and clinicians where a patient should be aware of his/her risk level of 90-day mortality and be more prepared to and compliant with treatment protocols.

Our second study identified higher Charson/Deyo score as the most important risk factor of 30-day unplanned readmission. This emphasized the significance of comorbidity management in the post-discharge period as most of readmissions were not related to the index hospitalization diagnosis but rather to comorbidities (Donzé et al., 2013). It is estimated that 5% to 79% (median proportion of 27.1%) of readmissions are potentially

avoidable although the true proportion remains unclear (Van Walraven et al., 2011). Therefore, careful management and control of common comorbidities after discharge could improve patients' overall health condition and reduce early, unplanned readmission. The finding that a history of 30-day unplanned readmission was associated with 2.3-fold increased odds of conditional 90-day mortality strengthened the necessity of control for comorbidities in the post-discharge period to prevent mortality once readmitted.

Even though NAFLD did not seem to affect the frequencies of postoperative complications or in-hospital mortality, this finding does not imply that the burdens in public health resulting from NAFLD should be ignored. Rather, the results may just indicate that liver resection is as safe in HCC patients with NAFLD as in HCC patients with other etiologies. Since results regarding the impact of NAFLD on postoperative outcomes are still under debate, more research is needed to truly understand the mechanism that NAFLD affects human body.

Future Research

Findings of this dissertation increased the knowledge on 90-day mortality, 30-day unplanned readmission as well as the role of NAFLD in the occurrence of outcomes after hepatectomy. Given the growing burden of HCC and NAFLD in the US and around the world, more research should be conducted to address the knowledge gaps and make the effort to reduce 90-day mortality, 30-day unplanned readmission, and other adverse outcomes. We suggest that future research may be focused on improving our prediction model for 90-day mortality by linking mutually beneficial databases. Specifically, we can link NCDB database with Midwest multi-institutional CoC accredited hospitals. All these hospitals provide demographic and clinical information to NCDB. We can test the accuracy/discriminatory ability of our model first by directly applying model algorithms to patient population queried from linked hospital database. Then, we can add more

information including detailed preoperative comorbidities, detailed laboratory test values and perioperative complications to the model. We will observe if, with additional information, the model will increase its discriminatory ability of predicting predict 90-day mortality.

For the second study, we believe any research that could follow up comorbidity management, patients' care at home and social/psychological support received would be beneficial. We have demonstrated comorbidity score was most important indicator of 30-day unplanned readmission. By comparing readmission outcome between patients with better management and control of the comorbidities and those without, we will be able to understand how many readmissions can be avoided due to the management of comorbidities.

To examine the impact of NAFLD on postoperative outcomes including occurrence of complications, in-hospital mortality and hospital LOS, we may consider using case-control study to investigate the effect of NAFLD on postoperative outcomes. Specifically, to evaluate the impact of NAFLD on postoperative complications, we can set up the case as HCC patients with postoperative complication and control as HCC patients without postoperative complications and then assess how much case and control have exposure of NAFLD. The case control study could also apply to evaluate the impact of NAFLD on in-hospital mortality and prolonged hospital LOS. Another suggestion is to evaluate this association in cross-sectional, large scale research involving multiple centers to increase the power to detect the difference since current hospital-based studies on the impact of NAFLD are single-center-based with limited sample size. Research is also needed to determine how much the impact of NAFLD is affected by obesity paradox, which can be addressed by examination of NAFLD separately in obese group and no-obese group. Although we believe obese information is most accurately described in hospital-based studies while administrative databases often under code this variable, we performed the

analyses stratified by obesity status for the current study. The results for increased occurrence of complications indicated that p values and odds ratios of NAFLD were very close in obese and non-obese patients (p=0.832 and p=0.827; OR=0.951 and OR=0.975 respectively). For the logistic regression models that evaluated the impact of NAFLD on mortality, the ORs were 0.629 in obese patients and 1.428 in non-obese patients. However, both were not significant (p=0.801 and p=0.303 respectively). Regarding hospital LOS, the OR of 0.901 was significant (p=0.013) in non-obese patients while OR of 0.922 was not significant (p=0.294) in obese patients. Since the sample size of obese HCC patients was small, we may not have adequate power to detect the effect of NAFLD to LOS in obese patients.

Conclusion

In summary, based on the β coefficients of risk factors identified by the logistic regression model, we developed and tested an integer-valued risk score for predicting 90-day mortality in HCC patients undergoing hepatectomies. We found this risk score model could easily quantify each of the patients' risk level and its discriminatory ability was comparable to some previously established models derived from the information not available in NCDB such as MELD scores. We also identified four risk factors of 30-day unplanned readmission in HCC patients undergoing hepatectomies. Furthermore, we demonstrated that patients with a history of 30-day unplanned readmission was associated with 2.3 times higher odds of conditional 90-day mortality and the extent of this association varied in different subgroups. Lastly, we showed the significant increase in the prevalence of NAFLD in hospitalized patients with HCC over the 10-year period between 2005 and 2014. However, we noted the similar postoperative adverse outcomes in HCC patients with and without NAFLD. This finding does not imply that the burdens of NAFLD

should be ignored. Rather, the results may just indicate that liver resection is as safe in HCC patients with NAFLD as in HCC patients with other etiologies.

REFERENCES

Adami, H. O., Hunter, D. J., & Trichopoulos, D. (Eds.). (2008). *Textbook of cancer epidemiology.* Oxford University Press, USA.

Adams, L. A., & Lindor, K. D. (2007). Nonalcoholic fatty liver disease. *Annals of epidemiology*, 17(11), 863-869.

Adejumo, A. C., Samuel, G. O., Adegbala, O. M., Adejumo, K. L., Ojelabi, O., Akanbi, O., ... & Pani, L. (2019). Prevalence, trends, outcomes, and disparities in hospitalizations for nonalcoholic fatty liver disease in the United States. *Annals of gastroenterology*, 32(5), 504.

Akinyemiju, T., Abera, S., Ahmed, M., Alam, N., Alemayohu, M. A., Allen, C., ... & Ayele, T. A. (2017). The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA oncology*, 3(12), 1683-1691.

Al-alem, F., Mattar, R. E., Fadl, O. A., Alsharabi, A., Al-Saif, F., & Hassanain, M. (2016). Morbidity, mortality and predictors of outcome following hepatectomy at a Saudi tertiary care center. *Annals of Saudi medicine*, 36(6), 414-421.

Alkhouri, N., & McCullough, A. J. (2012). Noninvasive diagnosis of NASH and liver fibrosis within the spectrum of NAFLD. *Gastroenterology & hepatology*, 8(10), 661.

Allen, A. M., Therneau, T. M., Larson, J. J., Coward, A., Somers, V. K., & Kamath, P. S. (2018). Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. *Hepatology*, 67(5), 1726-1736.

American College of Surgeons, American Cancer Society. National Cancer Database. *Natl Cancer Database*. 2017.

Amitrano, L., Guardascione, M. A., Brancaccio, V., & Balzano, A. (2002). Coagulation disorders in liver disease. In *Seminars in liver disease* (Vol. 22, No. 01, pp. 083-096). Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.:+ 1 (212) 584-4662.

An, R. (2014). Prevalence and trends of adult obesity in the US, 1999–2012. *International Scholarly Research Notices*, *2014*.

Andreou, A., Vauthey, J. N., Cherqui, D., Zimmitti, G., Ribero, D., Truty, M. J., ... & Belghiti, J. (2013). Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. *Journal of gastrointestinal surgery*, *17*(1), 66-77.

Anstee, Q. M., Targher, G., & Day, C. P. (2013). Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nature reviews Gastroenterology & hepatology*, 10(6), 330.

Armstrong, M. J., Houlihan, D. D., Bentham, L., Shaw, J. C., Cramb, R., Olliff, S., ... & Newsome, P. N. (2012). Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *Journal of hepatology*, 56(1), 234-240.

Asiyanbola, B., Chang, D., Gleisner, A. L., Nathan, H., Choti, M. A., Schulick, R. D., & Pawlik, T. M. (2008). Operative mortality after hepatic resection: are literature-based rates broadly applicable?. *Journal of Gastrointestinal Surgery*, 12(5), 842-851.

Babadjouni, R., Wen, T., Donoho, D. A., Buchanan, I. A., Cen, S. Y., Friedman, R. A., ... & Attenello, F. J. (2019). Increased hospital surgical volume reduces rate of 30- and 90-day readmission after acoustic neuroma surgery. *Neurosurgery*, 84(3), 726-732.

Bachellier, P., Rosso, E., Pessaux, P., Oussoultzoglou, E., Nobili, C., Panaro, F., & Jaeck, D. (2011). Risk factors for liver failure and mortality after hepatectomy associated with portal vein resection. *Annals of surgery*, 253(1), 173-179.

Bagnardi, V., Blangiardo, M., La Vecchia, C., & Corrao, G. (2001). A meta-analysis of alcohol drinking and cancer risk. *British journal of cancer*, 85(11), 1700-1705.

Balzan, S., Belghiti, J., Farges, O., Ogata, S., Sauvanet, A., Delefosse, D., & Durand, F. (2005). The “50-50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Annals of surgery*, 242(6), 824.

Baydar, T., Engin, A. B., Girgin, G., Aydin, S., & Sahin, G. (2005). Aflatoxin and ochratoxin in various types of commonly consumed retail ground samples in Ankara, Turkey. *Annals of agricultural and environmental medicine*, 12(2), 193-197.

Bechtold, M., Palmer, J., Valtos, J., Iasiello, C., & Sowers, J. (2006). Metabolic syndrome in the elderly. *Current diabetes reports*, *6*(1), 64-71.

Becker's Healthcare. Average hospital readmission costs for 18 diagnoses. Retrieved November 27, 2019, from https://www.beckershospitalreview.com/rankings-and-ratings/average-hospital-readmission-costs-for-18-diagnoses.html

Bedogni, G., Miglioli, L., Masutti, F., Tiribelli, C., Marchesini, G., & Bellentani, S. (2005). Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*, 42(1), 44-52.

Bennett, J. W., & Klich, M. Mycotoxins.(2003). *Clin Microbiol Rev*, 16(497.516).

Berman, K., Tandra, S., Forssell, K., Vuppalanchi, R., Burton Jr, J. R., Nguyen, J., ... & Chalasani, N. (2011). Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. *Clinical Gastroenterology and Hepatology*, 9(3), 254-259.

Bhala, N., Angulo, P., van der Poorten, D., Lee, E., Hui, J. M., Saracco, G., ... & Day, C. P. (2011). The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology*, 54(4), 1208-1216.

Boffa, D. J., Rosen, J. E., Mallin, K., Loomis, A., Gay, G., Palis, B., ... & Facktor, M. A. (2017). Using the National Cancer Database for outcomes research: a review. *JAMA oncology*, 3(12), 1722-1728.

Boffetta, P., Boccia, S., & La Vecchia, C. (2014). A quick guide to cancer epidemiology.

Bolder, U., Brune, A., Schmidt, S., Tacke, J., Jauch, K. W., & Löhlein, D. (1999). Preoperative assessment of mortality risk in hepatic resection by clinical variables: a multivariate analysis. *Liver Transplantation and Surgery*, 5(3), 227-237.

Bosch, F. X., Ribes, J., Díaz, M., & Cléries, R. (2004). Primary liver cancer: worldwide incidence and trends. *Gastroenterology*, 127(5), S5-S16.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 68(6), 394-424.

Bressac, B., Kew, M., Wands, J., & Ozturk, M. (1991). Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. *Nature*, 350(6317), 429-431.

Brudvik, K. W., Mise, Y., Conrad, C., Zimmitti, G., Aloia, T. A., & Vauthey, J. (2015). Definition of Readmission in 3,041 Patients Undergoing Hepatectomy. *Journal of the American College of Surgeons*, 221(1), 38-46.

Bruix, J., Qin, S., Merle, P., Granito, A., Huang, Y. H., Bodoky, G., ... & Gerolami, R. (2017). Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 389(10064), 56-66.

Campbell, P. G., Malone, J., Yadla, S., Chitale, R., Nasser, R., Maltenfort, M. G., ... & Ratliff, J. K. (2011). Comparison of ICD-9–based, retrospective, and prospective assessments of perioperative complications: assessment of accuracy in reporting. *Journal of Neurosurgery: Spine*, 14(1), 16-22.

Carulli, L., Lonardo, A., Lombardini, S., Marchesini, G., & Loria, P. (2006). Gender, fatty liver and GGT. *Hepatology*, *44*(1), 278-279.

Chacko, S., & Samanta, S. (2016). Hepatocellular carcinoma: A life-threatening disease. *Biomedicine & Pharmacotherapy*, 84, 1679-1688.

Chalasani, N., Younossi, Z., Lavine, J. E., Diehl, A. M., Brunt, E. M., Cusi, K., ... & Sanyal, A. J. (2012). The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*, 55(6), 2005-2023.

Chang, C. M., Yin, W. Y., Su, Y. C., Wei, C. K., Lee, C. H., Juang, S. Y., ... & Lee, C. C. (2014). Preoperative risk score predicting 90-day mortality after liver resection in a population-based study. *Medicine*, 93(12).

Chirapongsathorn, S., Poovorawan, K., Soonthornworasiri, N., Pan-ngum, W., Phaosawasdi, K., & Treeprasertsuk, S. (2020). Thirty-Day Readmission and Cost Analysis in Patients With Cirrhosis: A Nationwide Population-Based Data. *Hepatology Communications*, 4(3), 453-460.

Clavien, P. A., Lesurtel, M., Bossuyt, P. M., Gores, G. J., Langer, B., & Perrier, A. (2012). Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *The lancet oncology*, 13(1), e11-e22.

Couto, O. F. M., Dvorchik, I., & Carr, B. I. (2007). Causes of death in patients with unresectable hepatocellular carcinoma. *Digestive diseases and sciences*, *52*(11), 3285-3289.

Curcic, I. B., Berkovic, M. C., Kuna, L., Roguljic, H., Smolic, R., Varzic, S. C., ... & Smolic, M. (2019). Obesity Paradox in Chronic Liver Diseases: Product of Bias or a Real Thing?. *Journal of clinical and translational hepatology*, 7(3), 275.

Curtis, N., Noble, E., Salib, E., Awad, M., Hipkiss, R., Dalton, R., ... & Francis, N. (2016). Impact of laparoscopic surgery and length of stay on long term survival following colorectal cancer resection within an Enhanced Recovery Programme. *Clinical nutrition ESPEN*, 12, e51-e51.

Davila, J. A., Duan, Z., McGlynn, K. A., & El-Serag, H. B. (2012). Utilization and outcomes of palliative therapy for hepatocellular carcinoma: a population-based study in the United States. *Journal of clinical gastroenterology*, 46(1).

Davis, G. L., Alter, M. J., El–Serag, H., Poynard, T., & Jennings, L. W. (2010). Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*, 138(2), 513-521.

Delis, S. G., & Dervenis, C. (2008). Selection criteria for liver resection in patients with hepatocellular carcinoma and chronic liver disease. *World Journal of Gastroenterology: WJG*, 14(22), 3452.

Dhir, M., Melin, A. A., Douaiher, J., Lin, C., Zhen, W. K., Hussain, S. M., ... & Are, C. (2016). A review and update of treatment options and controversies in the management of hepatocellular carcinoma. *Annals of surgery*, 263(6), 1112-1125.

Dimick, J. B., Wainess, R. M., Cowan, J. A., Upchurch Jr, G. R., Knol, J. A., & Colletti, L. M. (2004). National trends in the use and outcomes of hepatic resection. *Journal of the American College of Surgeons*, 199(1), 31-38.

Donato, F., Tagger, A., Gelatti, U., Parrinello, G., Boffetta, P., Albertini, A., ... & Porru, S. (2002). Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *American journal of epidemiology*, 155(4), 323-331.

Donzé, J., Lipsitz, S., Bates, D. W., & Schnipper, J. L. (2013). Causes and patterns of readmissions in patients with common comorbidities: retrospective cohort study. *Bmj*, 347.

Dyson, J., Jaques, B., Chattopadyhay, D., Lochan, R., Graham, J., Das, D., ... & Sumpter, K. (2014). Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. *Journal of hepatology*, 60(1), 110-117.

Egal, S., Hounsa, A., Gong, Y. Y., Turner, P. C., Wild, C. P., Hall, A. J., ... & Cardwell, K. F. (2005). Dietary exposure to aflatoxin from maize and groundnut in young children from Benin and Togo, West Africa*. International Journal of Food Microbiology*, 104(2), 215-224.

Egger, M. E., Squires III, M. H., Kooby, D. A., Maithel, S. K., Cho, C. S., Weber, S. M., ... & Scoggins, C. R. (2015). Risk stratification for readmission after major hepatectomy: development of a readmission risk score. *Journal of the American College of Surgeons*, 220(4), 640-648.

Eguchi, S., Kanematsu, T., Arii, S., Omata, M., Kudo, M., Sakamoto, M., ... & Liver Cancer Study Group of Japan. (2011). Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. *British journal of surgery*, 98(4), 552-557.

Eknoyan, G. (2011). Obesity and chronic kidney disease. *Nefrología (English Edition)*, *31*(4), 397-403.

El-Serag, H. B. (2012). Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*, 142(6), 1264-1273.

El-serag, H. B., Tran, T., & Everhart, J. E. (2004). Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology*, *126*(2), 460-468.

Ertle, J., Dechêne, A., Sowa, J. P., Penndorf, V., Herzer, K., Kaiser, G., ... & Canbay, A. (2011). Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *International Journal of Cancer*, 128(10), 2436-2443.

Etra, J. W., Squires III, M. H., Fisher, S. B., Rutz, D. R., Martin, B. M., Kooby, D. A., ... & Russell, M. C. (2014). Early identification of patients at increased risk for hepatic

insufficiency, complications and mortality after major hepatectomy. *HPB*, 16(10), 875-883.

Fan, S. T., Lai, E. C., Lo, C. M., Ng, I. O., & Wong, J. (1995). Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Archives of surgery*, 130(2), 198-203.

Fink-Grernmels, J. (1999). Mycotoxins: their implications for human and animal health. *Veterinary Quarterly*, 21(4), 115-120.

Flegal, K. M., Kruszon-Moran, D., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2016). Trends in obesity among adults in the United States, 2005 to 2014. *Jama*, *315*(21), 2284-2291.

Flores, A. (2017). How the US Hispanic population is changing. *Pew Research Center*, *18*.

Forner A., Reig M., & Bruix J. (2018). Hepatocellular carcinoma. *The Lancet*, 391, 1301-1314.

Fromer, M. W., Aloia, T. A., Gaughan, J. P., Atabek, U. M., & Spitz, F. R. (2016). The utility of the MELD score in predicting mortality following liver resection for metastasis. *European Journal of Surgical Oncology (EJSO)*, 42(10), 1568-1575.

Ghamarnejad, O., Khajeh, E., Rezaei, N., Afshari, K., Adelian, A., Nikdad, M., ... & Mehrabi, A. (2020). Comparative Analysis of the Discriminatory Performance of Different Well-Known Risk Assessment Scores for Extended Hepatectomy. *Scientific Reports*, 10(1), 1-9.

Gilg, S., Sandström, P., Rizell, M., Lindell, G., Ardnor, B., Strömberg, C., & Isaksson, B. (2018). The impact of post-hepatectomy liver failure on mortality: a population-based study. *Scandinavian journal of gastroenterology*, 53(10-11), 1335-1339.

Giuliante, F., Ardito, F., Pinna, A. D., Sarno, G., Giulini, S. M., Ercolani, G., ... & Pulitanò, C. (2012). Liver resection for hepatocellular carcinoma≤ 3 cm: results of an Italian multicenter study on 588 patients. *Journal of the American College of Surgeons*, 215(2), 244-254.

Global Burden of Disease Cancer Collaboration. (2019). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. *JAMA oncology*, 5(12), 1749-1768.

Greenblatt, D. Y., Weber, S. M., O'Connor, E. S., LoConte, N. K., Liou, J. I., & Smith, M. A. (2010). Readmission after colectomy for cancer predicts one-year mortality. *Annals of surgery*, 251(4), 659

Groopman, J. D., Kensler, T. W., & Wild, C. P. (2008). Protective interventions to prevent aflatoxin-induced carcinogenesis in developing countries. *Annu. Rev. Public Health*, 29, 187-203.

Guo, Z., Zhang, J., Jiang, J. H., Li, L. Q., & Xiang, B. D. (2015). Obesity does not influence outcomes in hepatocellular carcinoma patients following curative hepatectomy. *PLoS One*, 10(5).

Guzman, N. J. (2012). Epidemiology and management of hypertension in the hispanic population. *American Journal of Cardiovascular Drugs*, 12(3), 165-178.

Hammond, J. S., Guha, I. N., Beckingham, I. J., & Lobo, D. N. (2011). Prediction, prevention and management of postresection liver failure. *British journal of surgery*, 98(9), 1188-1200.

Hasan, O., Meltzer, D. O., Shaykevich, S. A., Bell, C. M., Kaboli, P. J., Auerbach, A. D., ... & Schnipper, J. L. (2010). Hospital readmission in general medicine patients: a prediction model. *Journal of general internal medicine*, 25(3), 211-219.

Hauck, K., & Hollingsworth, B. (2010). The impact of severe obesity on hospital length of stay. *Medical care*, 335-340.

Haut, E. R., Pronovost, P. J., & Schneider, E. B. (2012). Limitations of administrative databases. *Jama*, *307*(24), 2589-2590.

Hernandez-Meza, G., McKee, S., Carlton, D., Yang, A., Govindaraj, S., & Iloreta, A. (2019). Association of Surgical and Hospital Volume and Patient Characteristics With 30-Day Readmission Rates. *JAMA Otolaryngology–Head & Neck Surgery*, 145(4), 328-337.

Hirode, G., Vittinghoff, E., & Wong, R. J. (2019). Increasing clinical and economic burden of nonalcoholic fatty liver disease among hospitalized adults in the United States. *Journal of clinical gastroenterology*, 53(10), 765-771.

Horwitz, L. I., Lin, Z., Herrin, J., Bernheim, S., Drye, E. E., Krumholz, H. M., & Ross, J. S. (2015). Association of hospital volume with readmission rates: a retrospective cross-sectional study. *bmj*, 350, h447.

Hu, Y., McMurry, T. L., Isbell, J. M., Stukenborg, G. J., & Kozower, B. D. (2014). Readmission after lung cancer resection is associated with a 6-fold increase in 90-day postoperative mortality. *The Journal of Thoracic and Cardiovascular Surgery*, 148(5), 2261-2267.e1.

Hucke, F., Sieghart, W., Schöniger-Hekele, M., Peck-Radosavljevic, M., & Müller, C. (2011). Clinical characteristics of patients with hepatocellular carcinoma in

Austria–is there a need for a structured screening program?. *Wiener klinische Wochenschrift*, 123(17-18), 542-551.

Hyder, O., Pulitano, C., Firoozmand, A., Dodson, R., Wolfgang, C. L., Choti, M. A., ... & Pawlik, T. M. (2013). A risk model to predict 90-day mortality among patients undergoing hepatic resection. *Journal of the American College of Surgeons*, 216(6), 1049-1056.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (2010). Alcohol consumption and ethyl carbamate. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, 96, 3.

Idrees, J. J., Johnston, F. M., Canner, J. K., Dillhoff, M., Schmidt, C., Haut, E. R., & Pawlik, T. M. (2019). Cost of major complications after liver resection in the United States: are high-volume centers cost-effective?. *Annals of surgery*, 269(3), 503-510.

Inokuchi, M., Kato, K., Sugita, H., Otsuki, S., & Kojima, K. (2014). Impact of comorbidities on postoperative complications in patients undergoing laparoscopy-assisted gastrectomy for gastric cancer. *BMC surgery*, 14(1), 97.

Ishak, K., Baptista, A., Bianchi, L., Callea, F., De Groote, J., Gudat, F., ... & Phillips, M. J. (1995). Histological grading and staging of chronic hepatitis. *Journal of hepatology*, 22(6), 696-699.

Ishizawa, T., Hasegawa, K., Aoki, T., Takahashi, M., Inoue, Y., Sano, K., ... & Makuuchi, M. (2008). Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology*, 134(7), 1908-1916.

Kalogeridi, M. A., Zygogianni, A., Kyrgias, G., Kouvaris, J., Chatziioannou, S., Kelekis, N., & Kouloulias, V. (2015). Role of radiotherapy in the management of hepatocellular carcinoma: A systematic review. *World journal of hepatology*, 7(1), 101.

Kamiyama, T., Nakanishi, K., Yokoo, H., Kamachi, H., Tahara, M., Yamashita, K., ... & Todo, S. (2010). Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. *Journal of the American College of Surgeons*, 211(4), 443-449.

Kansagara, D., Papak, J., Pasha, A. S., O'Neil, M., Freeman, M., Relevo, R., ... & Jou, J. H. (2014). Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Annals of internal medicine*, 161(4), 261-269.

Kanwal, F., Kramer, J. R., Ilyas, J., Duan, Z., & El-Serag, H. B. (2014). HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of US Veterans with HCV. *Hepatology*, 60(1), 98-105.

Kanwal, F., Kramer, J. R., Mapakshi, S., Natarajan, Y., Chayanupatkul, M., Richardson, P. A., ... & Chu, J. (2018). Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology*, 155(6), 1828-1837.

Karagozian, R., Bhardwaj, G., Wakefield, D. B., & Baffy, G. (2016). Obesity paradox in advanced liver disease: obesity is associated with lower mortality in hospitalized patients with cirrhosis. *Liver international*, 36(10), 1450-1456.

Kattakuzhy, S., Levy, R., Rosenthal, E., Tang, L., Wilson, E., & Kottilil, S. (2016). Hepatitis C genotype 3 disease. *Hepatology international*, 10(6), 861-870.

Kauffmann, R., & Fong, Y. (2014). Post-hepatectomy liver failure. *Hepatobiliary surgery and nutrition*, 3(5), 238.

Kew, M. C. (2013). Aflatoxins as a cause of hepatocellular carcinoma. *Journal of Gastrointestinal & Liver Diseases*, 22(3).

Kew, M. C. (2015). Obesity as a cause of hepatocellular carcinoma. *Annals of Hepatology*, *14*(3), 299-303.

Kim, S., Maynard, E. C., Shah, M. B., Daily, M. F., Tzeng, C. W. D., Davenport, D. L., & Gedaly, R. (2015). Risk factors for 30-day readmissions after hepatectomy: analysis of 2444 patients from the ACS-NSQIP database. *Journal of Gastrointestinal Surgery*, 19(2), 266-271.

Kimbrough, C. W., Agle, S. C., Scoggins, C. R., Martin, R. C., Marvin, M. R., Davis, E. G., ... & Jones, C. M. (2014). Factors predictive of readmission after hepatic resection for hepatocellular carcinoma. *Surgery*, 156(4), 1039-1048.

Knoblich, T., Hinz, U., Stravodimos, C., Schön, M. R., Mehrabi, A., Büchler, M. W., & Hoffmann, K. (2020). Comparison of score-based prediction of 90-day mortality after liver resection. *BMC surgery*, 20(1), 19.

Kooby, D. A., Fong, Y., Suriawinata, A., Gonen, M., Allen, P. J., Klimstra, D. S., ... & Jarnagin, W. R. (2003). Impact of steatosis on perioperative outcome following hepatic resection. *Journal of Gastrointestinal Surgery*, 7(8), 1034-1044.

Krumholz, H. M. (2013). Post-hospital syndrome–a condition of generalized risk. The *New England journal of medicine*, 368(2), 100.

Kudo, M., Finn, R. S., Qin, S., Han, K. H., Ikeda, K., Piscaglia, F., ... & Blanc, J. F. (2018). Lenvatinib versus sorafenib in first-line treatment of patients with

unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet*, 391(10126), 1163-1173.

Kwok, J., Langevin, S. M., Argiris, A., Grandis, J. R., Gooding, W. E., & Taioli, E. (2010). The impact of health insurance status on the survival of patients with head and neck cancer. *Cancer*, 116(2), 476-485.

Lawson, D. H., Gray, J. M. B., McKillop, C., Clarke, J., Lee, F. D., & Patrick, R. S. (1986). Diabetes mellitus and primary hepatocellular carcinoma. *QJM: An International Journal of Medicine*, 61(1), 945-955.

Ledda, C., Loreto, C., Zammit, C., Marconi, A., Fago, L., Matera, S., ... & Costa, C. (2017). Non-infective occupational risk factors for hepatocellular carcinoma: A review. *Molecular medicine reports*, 15(2), 511-533.

Lee, C. W., Tsai, H. I., Sung, C. M., Chen, C. W., Huang, S. W., Jeng, W. J., ... & Chen, M. F. (2016). Risk factors for early mortality after hepatectomy for hepatocellular carcinoma. *Medicine*, 95(39).

Lee, H. Y., Shin, J. Y., Lee, S. A., Ju, Y. J., & Park, E. C. (2019). The 30-day unplanned readmission rate and hospital volume: a national population-based study in South Korea. *International Journal for Quality in Health Care*.

Liu, Y., & Wu, F. (2010). Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. *Environmental health perspectives*, 118(6), 818-824.

Llovet, J. M., & Bruix, J. (2003). Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*, 37(2), 429-442.

Llovet, J. M., Real, M. I., Montaña, X., Planas, R., Coll, S., Aponte, J., ... & Rodés, J. (2002). Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *The Lancet*, 359(9319), 1734-1739.

Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J. F., ... & Schwartz, M. (2008). Sorafenib in advanced hepatocellular carcinoma. *New England journal of medicine*, 359(4), 378-390.

Lok, A. S., Everhart, J. E., Wright, E. C., Di Bisceglie, A. M., Kim, H. Y., Sterling, R. K., ... & Dienstag, J. L. (2011). Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology*, 140(3), 840-849.

Lopez, C., Ramos, L., Bulacio, L., Ramadan, S., & Rodriguez, F. (2002). Aflatoxin B1 content in patients with hepatic diseases. *MEDICINA-BUENOS AIRES-*, 62(4), 313-316.

Lorenzo, C. S., Whitney, M. L., Lurie, F., & Wong, L. L. (2005). Factors affecting outcome in liver resection. *HPB*, 7(3), 226-230.

Lovejoy, J. C., Champagne, C. M., De Jonge, L., Xie, H., & Smith, S. R. (2008). Increased visceral fat and decreased energy expenditure during the menopausal transition. *International journal of obesity*, 32(6), 949-958.

Lucas, D. J., Sweeney, J. F., & Pawlik, T. M. (2014). The timing of complications impacts risk of readmission after hepatopancreatobiliary surgery. *Surgery*, 155(5), 945-953.

Ma, L., Li, J., Shao, L., Lin, D., & Xiang, J. (2015). Prolonged postoperative length of stay is associated with poor overall survival after an esophagectomy for esophageal cancer. *Journal of thoracic disease*, 7(11), 2018.

Maluccio, M., & Covey, A. (2012). Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. *CA: a cancer journal for clinicians*, 62(6), 394-399.

Margonis, G. A., Sasaki, K., Andreatos, N., Nishioka, Y., Sugawara, T., Amini, N., ... & Pawlik, T. M. (2017). Prognostic impact of complications after resection of early stage hepatocellular carcinoma. *Journal of surgical oncology*, 115(7), 791-804.

Martinez, B. A. F., Leotti, V. B., Nunes, L. N., Machado, G., & Corbellini, L. G. (2017). Odds ratio or prevalence ratio? an overview of reported statistical methods and appropriateness of interpretations in cross-sectional studies with dichotomous outcomes in veterinary medicine. *Frontiers in veterinary science*, 4, 193.

Martínez-Mier, G., Esquivel-Torres, S., Alvarado-Arenas, R. A., Ortiz-Bayliss, A. B., Lajud-Barquín, F. A., & Zilli-Hernandez, S. (2016). Liver resection morbidity, mortality, and risk factors at the departments of hepatobiliary surgery in Veracruz, Mexico. *Revista de Gastroenterología de México (English Edition)*, 81(4), 195-201.

Mavilia, M. G., Wakefield, D., & Karagozian, R. (2019). Nonalcoholic fatty liver disease does not predict worse perioperative outcomes in bariatric surgery. *Obesity research & clinical practice*, *13*(4), 416-418.

Mayo, S. C., Shore, A. D., Nathan, H., Edil, B. H., Hirose, K., Anders, R. A., ... & Pawlik, T. M. (2011). Refining the definition of perioperative mortality following

hepatectomy using death within 90 days as the standard criterion. *HPB*, 13(7), 473-482.

Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulvirenti, A., Bozzetti, F., ... & Gennari, L. (1996). Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New England Journal of Medicine*, 334(11), 693-700.

McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, Hispanics, and Asians. *Diabetes care*, *27*(10), 2317-2324.

Mikolasevic, I., Milic, S., Wensveen, T. T., Grgic, I., Jakopcic, I., Stimac, D., ... & Orlic, L. (2016). Nonalcoholic fatty liver disease-A multisystem disease?. *World journal of gastroenterology*, 22(43), 9488.

Mittal, S., & El-Serag, H. B. (2013). Epidemiology of HCC: consider the population. *Journal of clinical gastroenterology*, 47, S2.

Mochari-Greenberger, H., Cohen, L. P., Liao, M., & Mosca, L. (2015). Racial and Ethnic Differences in 30-Day Readmission and 1-Year Mortality among Patients Hospitalized for Heart Failure. *J Clin Exp Cardiolog,* 6(3)

Montero, A. J., Stevenson, J., Guthrie, A. E., Best, C., Goodman, L. M., Shrotriya, S., ... & Kalaycio, M. E. (2016). Reducing unplanned medical oncology readmissions by improving outpatient care transitions: A process improvement project at the Cleveland Clinic. *Journal of oncology practice*, 12(5), e594-e602.

Moore, B. J., White, S., Washington, R., Coenen, N., & Elixhauser, A. (2017). Identifying increased risk of readmission and in-hospital mortality using hospital administrative data. *Medical care*, 55(7), 698-705.

Mullen, J. T., Ribero, D., Reddy, S. K., Donadon, M., Zorzi, D., Gautam, S., ... & Vauthey, J. N. (2007). Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *Journal of the American College of Surgeons*, 204(5), 854-862.

Nagasue, N., Kohno, H., Chang, Y. C., Taniura, H., Yamanoi, A., Uchida, M., ... & Yukaya, H. (1993). Liver resection for hepatocellular carcinoma. Results of 229 consecutive patients during 11 years. *Annals of surgery*, 217(4), 375.

Namasivayam, S., Martin, D. R., & Saini, S. (2007). Imaging of liver metastases: MRI. *Cancer Imaging*, 7(1), 2.

Narula, N., Kim, B. J., Davis, C. H., Dewhurst, W. L., Samp, L. A., & Aloia, T. A. (2018). A proactive outreach intervention that decreases readmission after hepatectomy. *Surgery*, 163(4), 703-708.

Nomura, F., Ohnishi, K., & Tanabe, Y. (1989). Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. *Cancer*, *64*(8), 1700-1707.

Ostrovsky, A., O'Connor, L., Marshall, O., Angelo, A., Barrett, K., Majeski, E., ... & Levy, J. (2016). Predicting 30-to 120-day readmission risk among Medicare fee-for-service patients using nonmedical workers and mobile technology. *Perspectives in health information management*, 13(Winter).

Pais, R., Barritt 4th, A. S., Calmus, Y., Scatton, O., Runge, T., Lebray, P., ... & Conti, F. (2016). NAFLD and liver transplantation: current burden and expected challenges. *Journal of hepatology*, 65(6), 1245-1257.

Parkin, D. M. (2006). The global health burden of infection-associated cancers in the year 2002. *International journal of cancer*, 118(12), 3030-3044.

Pekow, J. R., Bhan, A. K., Zheng, H., & Chung, R. T. (2007). Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Cancer*, 109(12), 2490-2496.

Peng, S. Y., Chen, W. J., Lai, P. L., Jeng, Y. M., Sheu, J. C., & Hsu, H. C. (2004). High α-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and β-catenin mutations. *International journal of cancer*, 112(1), 44-50.

Peng, Y., Qi, X., & Guo, X. (2016). Child–Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. *Medicine*, 95(8).

Persson, E. C., Schwartz, L. M., Park, Y., Trabert, B., Hollenbeck, A. R., Graubard, B. I., ... & McGlynn, K. A. (2013). Alcohol consumption, folate intake, hepatocellular carcinoma, and liver disease mortality. *Cancer Epidemiology and Prevention Biomarkers*, 22(3), 415-421.

Piscaglia, F., Svegliati-Baroni, G., Barchetti, A., Pecorelli, A., Marinelli, S., Tiribelli, C., ... & HCC-NAFLD Italian Study Group. (2016). Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. *Hepatology*, *63*(3), 827-838.

Poon, R. T. P., Fan, S. T., Lo, C. M., Liu, C. L., & Wong, J. (2002). Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Annals of surgery*, 235(3), 373

Puri, P., & Sanyal, A. J. (2012). Nonalcoholic fatty liver disease: definitions, risk factors, and workup. *Clinical Liver Disease*, 1(4), 99.

Raimondi, S., Bruno, S., Mondelli, M. U., & Maisonneuve, P. (2009). Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *Journal of hepatology*, 50(6), 1142-1154.

Ramacciato, G., D'angelo, F., Baldini, R., Petrucciani, N., Antolino, L., Aurello, P., ... & Cucchetti, A. (2012). Hepatocellular carcinomas and primary liver tumors as predictive factors for postoperative mortality after liver resection: a meta-analysis of more than 35,000 hepatic resections. *The American Surgeon*, 78(4), 456-467.

Rau J. Kaiser Health News. New round of Medicare readmission penalties hits 2,583 hospitals. 2019. https://khn.org/news/hospital-readmission-penalties-medicare-2583-hospitals/. Accessed November 29, 2019.

Reddy, S. K., Steel, J. L., Chen, H. W., DeMateo, D. J., Cardinal, J., Behari, J., ... & Tsung, A. (2012). Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology*, *55*(6), 1809-1819.

Resende, V., Rezende-Neto, J. B. D., Fernandes, J. S., & Cunha-Melo, J. R. D. (2011). Assessment of morbidity and mortality after hepatic resections. *Revista do Colegio Brasileiro de Cirurgioes*, 38(5), 323-326.

Ribeireiro, T., Swain, J., Sarr, M., Kendrick, M., Que, F., Sanderson, S., ... & Charlton, M. (2011). NAFLD and insulin resistance do not increase the risk of postoperative complications among patients undergoing bariatric surgery—a prospective analysis. *Obesity surgery*, 21(3), 310-315.

Rinella, M. E. (2015). Nonalcoholic fatty liver disease: a systematic review. *Jama*, 313(22), 2263-2273.

Romeo, S., Kozlitina, J., Xing, C., Pertsemlidis, A., Cox, D., Pennacchio, L. A., ... & Hobbs, H. H. (2008). Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nature genetics*, 40(12), 1461-1465.

Sangro, B., Carpanese, L., Cianni, R., Golfieri, R., Gasparini, D., Ezziddin, S., ... & Maria Ettorre, G. (2011). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology*, 54(3), 868-878.

Sapisochin, G., & Bruix, J. (2017). Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nature Reviews Gastroenterology & Hepatology*, 14(4), 203.

Saunders, R. S., Fernandes-Taylor, S., Kind, A. J., Engelbert, T. L., Greenberg, C. C., Smith, M. A., ... & Kent, K. C. (2014). Rehospitalization to primary versus different facilities following abdominal aortic aneurysm repair. *Journal of vascular surgery*, 59(6), 1502-1510.

Schiergens, T. S., Dörsch, M., Mittermeier, L., Brand, K., Küchenhoff, H., Lee, S. M., ... & Thasler, W. E. (2015). Thirty-day mortality leads to underestimation of postoperative death after liver resection: a novel method to define the acute postoperative period. *Surgery*, 158(6), 1530-1537.

Schneider, E. B., Hyder, O., Wolfgang, C. L., Hirose, K., Choti, M. A., Makary, M. A., ... & Pawlik, T. M. (2012). Patient readmission and mortality after surgery for hepato-pancreato-biliary malignancies. *Journal of the American College of Surgeons*, 215(5), 607-615

Schwartz, M., Roayaie, S., & Konstadoulakis, M. (2007). Strategies for the management of hepatocellular carcinoma. *Nature clinical practice Oncology*, 4(7), 424-432.

Shi, J., Zhu, L., Liu, S., & Xie, W. F. (2005). A meta-analysis of case–control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *British journal of cancer*, 92(3), 607-612.

Shi, M., Guo, R. P., Lin, X. J., Zhang, Y. Q., Chen, M. S., Zhang, C. Q., ... & Li, J. Q. (2007). Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Annals of surgery*, 245(1), 36.

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: a cancer journal for clinicians*, 69(1), 7-34.

Simmons, O. L., Feng, Y., Parikh, N. D., & Singal, A. G. (2019). Primary care provider practice patterns and barriers to hepatocellular carcinoma surveillance. *Clinical Gastroenterology and Hepatology*, 17(4), 766-773.

Simon, T. G., King, L. Y., Chong, D. Q., Nguyen, L. H., Ma, Y., VoPham, T., ... & Khalili, H. (2018). Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. *Hepatology*, 67(5), 1797-1806.

Simons, J. P., Hill, J. S., Ng, S. C., Shah, S. A., Zhou, Z., Whalen, G. F., & Tseng, J. F. (2009). Perioperative mortality for management of hepatic neoplasm: a simple risk score. *Annals of surgery*, 250(6), 929-934.

Simons, J. P., Ng, S. C., Hill, J. S., Shah, S. A., Zhou, Z., & Tseng, J. F. (2010). In-hospital mortality from liver resection for hepatocellular carcinoma: a simple risk score. *Cancer*, 116(7), 1733-1738.

Slatore, C. G., Au, D. H., & Gould, M. K. (2010). An official American Thoracic Society systematic review: insurance status and disparities in lung cancer practices and outcomes. *American journal of respiratory and critical care medicine*, 182(9), 1195-1205.

Spolverato, G., Ejaz, A., Kim, Y., Weiss, M., Wolfgang, C. L., Hirose, K., & Pawlik, T. M. (2014). Readmission incidence and associated factors after a hepatic resection at a major hepato-pancreatico-biliary academic centre. *HPB*, 16(11), 972-978.

Starley, B. Q., Calcagno, C. J., & Harrison, S. A. (2010). Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology*, *51*(5), 1820-1832.

Strosnider, H., Azziz-Baumgartner, E., Banziger, M., Bhat, R. V., Breiman, R., Brune, M. N., ... & Henry, S. H. (2006). Workgroup report: public health strategies for reducing aflatoxin exposure in developing countries. *Environmental health perspectives*, 114(12), 1898-1903.

Stuver, S. H. E. R. R. I., & Trichopoulos, D. I. M. I. T. R. I. O. S. (2008). Cancer of the liver and biliary tract. *Cancer epidemiology*, 2, 308-332.

Tamandl, D., Butte, J. M., Allen, P. J., D'Angelica, M. I., DeMatteo, R. P., Groeger, J. S., ... & Fong, Y. (2015). Hospital readmissions after liver surgery for metastatic colorectal cancer. *Surgery*, 157(2), 231-238.

Tanaka, A., Uegaki, S., Kurihara, H., Aida, K., Mikami, M., Nagashima, I., ... & Takikawa, H. (2007). Hepatic steatosis as a possible risk factor for the development of hepatocellular carcinoma after eradication of hepatitis C virus with antiviral therapy in patients with chronic hepatitis C. *World Journal of Gastroenterology: WJG*, 13(39), 5180.

Tanaka, N., Kimura, T., Fujimori, N., Nagaya, T., Komatsu, M., & Tanaka, E. (2019). Current status, problems, and perspectives of non-alcoholic fatty liver disease research. *World journal of gastroenterology*, 25(2), 163.

Tang, N., Maselli, J. H., & Gonzales, R. (2014). Variations in 30-day hospital readmission rates across primary care clinics within a tertiary referral center. *Journal of hospital medicine*, 9(11), 688-694.

Tapper, E. B., Halbert, B., & Mellinger, J. (2016). Rates of and reasons for hospital readmissions in patients with cirrhosis: a multistate population-based cohort study. *Clinical Gastroenterology and Hepatology*, 14(8), 1181-1188.

Testino, G., Leone, S., & Borro, P. (2014). Alcohol and hepatocellular carcinoma: a review and a point of view. *World journal of gastroenterology*: WJG, 20(43), 15943.

Thalheimer, U., Triantos, C. K., Samonakis, D. N., Patch, D., & Burroughs, A. K. (2005). Infection, coagulation, and variceal bleeding in cirrhosis. *Gut*, 54(4), 556-563.

Thompson, H. H., Tompkins, R. K., & Longmire Jr, W. P. (1983). Major hepatic resection. A 25-year experience. *Annals of surgery*, 197(4), 375.

Tilghman, S. M., & Belayew, A. (1982). Transcriptional control of the murine albumin/alpha-fetoprotein locus during development. *Proceedings of the National Academy of Sciences*, *79*(17), 5254-5257.

Torzilli, G., Belghiti, J., Kokudo, N., Takayama, T., Capussotti, L., Nuzzo, G., ... & Morenghi, E. (2013). A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West study group. *Annals of surgery*, 257(5), 929-937.

Tsai, T. C., Joynt, K. E., Orav, E. J., Gawande, A. A., & Jha, A. K. (2013). Variation in surgical-readmission rates and quality of hospital care. *New England Journal of Medicine*, 369(12), 1134-1142.

Tsim, N. C., Frampton, A. E., Habib, N. A., & Jiao, L. R. (2010). Surgical treatment for liver cancer. *World Journal of Gastroenterology: WJG*, 16(8), 927.

Tzeng, C. W. D., Cooper, A. B., Vauthey, J. N., Curley, S. A., & Aloia, T. A. (2014). Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. *HPB*, 16(5), 459-468.

Van Walraven, C., Bennett, C., Jennings, A., Austin, P. C., & Forster, A. J. (2011). Proportion of hospital readmissions deemed avoidable: a systematic review. *Cmaj*, 183(7), E391-E402.

Vauthey, J. N., Chaoui, A., Do, K. A., Bilimoria, M. M., Fenstermacher, M. J., Charnsangavej, C., ... & Caridi, J. (2000). Standardized measurement of the

future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*, 127(5), 512-519.

Verloh, N., Haimerl, M., Rennert, J., Müller-Wille, R., Nießen, C., Kirchner, G., ... & Wiggermann, P. (2013). Impact of liver cirrhosis on liver enhancement at Gd-EOB-DTPA enhanced MRI at 3 Tesla. *European journal of radiology*, 82(10), 1710-1715.

Viganò, L., Conci, S., Cescon, M., Fava, C., Capelli, P., D'Errico, A., ... & Salizzoni, M. (2015). Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: A multicenter matched analysis with HCV-related HCC. *Journal of hepatology*, *63*(1), 93-101.

Virani, S., Michaelson, J. S., Hutter, M. M., Lancaster, R. T., Warshaw, A. L., Henderson, W. G., ... & Tanabe, K. K. (2007). Morbidity and mortality after liver resection: results of the patient safety in surgery study. *Journal of the American College of Surgeons*, 204(6), 1284-1292.

Wakai, T., Shirai, Y., Sakata, J., Korita, P. V., Ajioka, Y., & Hatakeyama, K. (2011). Surgical outcomes for hepatocellular carcinoma in nonalcoholic fatty liver disease. *Journal of Gastrointestinal Surgery*, *15*(8), 1450-1458.

Wang, P., Kang, D., Cao, W., Wang, Y., & Liu, Z. (2012). Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes/metabolism research and reviews*, 28(2), 109-122.

Wang, Q., Fiel, M. I., Blank, S., Luan, W., Kadri, H., Kim, K. W., ... & Hiotis, S. P. (2013). Impact of liver fibrosis on prognosis following liver resection for hepatitis B-associated hepatocellular carcinoma. *British journal of cancer*, 109(3), 573.

Weaver, C., Schiech, L., Held-Warmkessel, J., Kedziera, P., Haney, E., DiLullo, G., ... & Barsevick, A. (2006, May). Risk for unplanned hospital readmission of patients with cancer: results of a retrospective medical record review. *In Oncology Nursing Forum* (Vol. 33).

Weller, W. E., Rosati, C., & Hannan, E. L. (2007). Relationship between surgeon and hospital volume and readmission after bariatric operation. *Journal of the American College of Surgeons*, 204(3), 383-391.

Welzel, T. M., Graubard, B. I., Quraishi, S., Zeuzem, S., Davila, J. A., El-Serag, H. B., & McGlynn, K. A. (2013). Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. *The American journal of gastroenterology*, 108(8), 1314.

White, D. L., Kanwal, F., & El–Serag, H. B. (2012). Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clinical gastroenterology and hepatology*, 10(12), 1342-1359.

White, D. L., Thrift, A. P., Kanwal, F., Davila, J., & El-Serag, H. B. (2017). Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology*, 152(4), 812-820.

Williams, C. D., Stengel, J., Asike, M. I., Torres, D. M., Shaw, J., Contreras, M., ... & Harrison, S. A. (2011). Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*, 140(1), 124-131.

Williams, J. H., Phillips, T. D., Jolly, P. E., Stiles, J. K., Jolly, C. M., & Aggarwal, D. (2004). Human aflatoxicosis in developing countries: a review of toxicology,

exposure, potential health consequences, and interventions. *The American journal of clinical nutrition*, 80(5), 1106-1122.

Wong, C. R., Njei, B., Nguyen, M. H., Nguyen, A., & Lim, J. K. (2017). Survival after treatment with curative intent for hepatocellular carcinoma among patients with vs without non-alcoholic fatty liver disease. *Alimentary pharmacology & therapeutics*, 46(11-12), 1061-1069.

Wong, J. A., & Devereaux, P. J. (2019). Cardiac Device Implantation Complications: A Gap in the Quality of Care?. *Annals of internal medicine*, *171*(5), 368-369.

Wong, R. J., Cheung, R., & Ahmed, A. (2014). Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the US. *Hepatology*, 59(6), 2188-2195.

World Health Organization. (2014). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012.

Woz, S., Mitchell, S., Hesko, C., Paasche-Orlow, M., Greenwald, J., Chetty, V. K., ... & Jack, B. (2012). Gender as risk factor for 30 days post-discharge hospital utilisation: a secondary data analysis. *BMJ* open, 2(2), e000428.

Wu, T. H., Yu, M. C., Chan, K. M., Lee, C. F., Chen, T. C., Chang, H. C., ... & Lee, W. C. (2011). Prognostic effect of steatosis on hepatocellular carcinoma patients after liver resection. *European Journal of Surgical Oncology (EJSO)*, 37(7), 618-622.

Xu, J. (2018). *Trends in liver cancer mortality among adults aged 25 and over in the United States, 2000-2016*. US Department of Health & Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.

Xu, R., Tao, A., Zhang, S., Deng, Y., & Chen, G. (2015). Association between patatin-like phospholipase domain containing 3 gene (PNPLA3) polymorphisms and

nonalcoholic fatty liver disease: a HuGE review and meta-analysis. *Scientific reports*, 5, 9284.

Yamazaki, S., & Takayama, T. (2017). Management strategies to minimize mortality in liver resection for hepatocellular carcinoma. *Japanese journal of clinical oncology*, 47(10), 899-908.

Yang, B., Liu, J. B., So, S. K., Han, S. S., Wang, S. S., Hertz, A., ... & Hsing, A. W. (2018). Disparities in hepatocellular carcinoma incidence by race/ethnicity and geographic area in C alifornia: Implications for prevention. *Cancer*, 124(17), 3551-3559.

Yang, J. D., Kim, B., Sanderson, S. O., Sauver, J. L. S., Yawn, B. P., Pedersen, R. A., ... & Kim, W. R. (2012, January). Hepatocellular carcinoma in olmsted county, Minnesota, 1976-2008. In *Mayo Clinic Proceedings* (Vol. 87, No. 1, pp. 9-16). Elsevier.

Yang, T., Hu, L. Y., Li, Z. L., Liu, K., Wu, H., Xing, H., ... & Gu, W. M. (2020). Liver resection for hepatocellular carcinoma in non-alcoholic fatty liver disease: A multicenter propensity matching analysis with HBV-HCC. *Journal of Gastrointestinal Surgery*, 24(2), 320-329.

Yao, F. Y., Ferrell, L., Bass, N. M., Watson, J. J., Bacchetti, P., Venook, A., ... & Roberts, J. P. (2001). Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*, 33(6), 1394-1403.

Yi, S. W., Choi, J. S., Yi, J. J., Lee, Y. H., & Han, K. J. (2018). Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: A prospective cohort study in Korea. *Cancer*, 124(13), 2748-2757.

Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*, 64(1), 73-84.

Younossi, Z. M., Stepanova, M., Afendy, M., Fang, Y., Younossi, Y., Mir, H., & Srishord, M. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clinical Gastroenterology and Hepatology*, *9*(6), 524-530.

Younossi, Z. M., Stepanova, M., Negro, F., Hallaji, S., Younossi, Y., Lam, B., & Srishord, M. (2012). Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine*, *91*(6), 319-327.

Zhan, K. Y., Graboyes, E. M., Nguyen, S. A., & Day, T. A. (2016). Risk Factors Associated With Unplanned Readmission in Patients Undergoing Parotid Cancer Surgery: A Study of the National Cancer Database. *JAMA Otolaryngology–Head & Neck Surgery*, 142(6), 544-550.

Zou, H., Tao, Y., & Wang, Z. M. (2017). Integration of Child-Pugh score with future liver remnant yields improved prediction of liver dysfunction risk for HBV-related hepatocellular carcinoma following hepatic resection. *Oncology letters*, 13(5), 3631-3637.