The Impact of Complications of Cirrhosis in Patients Undergoing Cardiac Surgery: A Propensity Matched Cohort Study

By

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Abstract

Background: Patients with cirrhosis and concomitant coronary/valvular heart disease present a clinical dilemma. Cardiac surgeons often are reluctant to operate in this high-risk population, potentially diminishing survival/potential for liver transplant. This study aimed to identify associations between the severity of cirrhosis and post-cardiac surgical outcomes. Methods: We performed a retrospective study of propensity matched cohorts of patients undergoing cardiac surgery from APPROACH database at the University of Alberta Hospital from January 2004 to December 2014. The relationship between severity of liver disease, medical comorbidity and surgical factors on survival to hospital discharge were evaluated. Key summary: Among 60 subjects with cirrhosis, the overall mortality was 40%. Compared with non-cirrhotic patients (n=310), cirrhotics had more postoperative complications (respiratory and renal failure), longer cardiopulmonary bypass time [128 (99 - 200) vs 116 (83 - 161) minutes, p=0.02] and required more blood products during surgery (58% vs 43%, p=0.03). Cirrhotics also had longer median length of stay in ICU [5 (3 -11) vs 2 (1 - 4), p=0.00001] and were more likely to be on mechanical ventilation [2 (1 - 5) vs 1(0.5 -1.2), p=0.00001] and renal replacement therapy (15% vs 6%, p=0.02) post-operatively. After adjusting for other covariates, presence of cirrhosis [aOR: 2.2 (95%CI: 1.10 - 4.22)], increased CCI [aOR: 1.4 (95%CI: 1.18 - 1.60)] and the need for any intraoperative transfusion [aOR: 2.6 (95%CI: 1.28 - 5.04)] were independently associated with increased mortality. Conclusion: Mortality rates were significantly high in cirrhotics undergoing cardiac surgery compared to their non-cirrhotic counterparts despite having lower median MELD scores. Compared with non-cirrhotic patients, cirrhotics undergoing surgery had more postoperative complications, had a higher overall burden on preoperative illness (CCI) and required more medical services and organ support post-operatively.

Preface

This thesis is an original work done by Sagaya Jeya sheela Maria Xavier. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Cardiac Surgery in patients with cirrhosis: A retrospective cohort study”, Pro00038965, April 11, 2013.

Dedication

I dedicate this thesis to *my parents* who keep teaching me...

"There is gold, and a multitude of rubies: but the lips of knowledge are a precious jewel"

(Proverbs 20:15, Old Testament, King James Version)

…and *my 7 and 4 year old daughters, Anenya & Olivia,* for actually showing me how to put that to practice ☺

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List of Symbols, Abbreviations and Nomenclature

aOR	adjusted Odds Ratio
APPROACH	Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease
ARDS	Adult Respiratory Distress Syndrome
BBB	Blood Brain Barrier
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CPB	Cardio Pulmonary Bypass
CCI	Charlson's Comorbidity Index
CI	Confidence Interval
CTP	Child Turcotte Pugh
CVD	CardioVascular Disease
CVICU	CardioVascular Intensive Care Unit
ESLD	End-Stage Liver Disease
FFP	Fresh Frozen Plasma
GI	Gastro Intestinal
HRS	Hepato Renal Syndrome
ICU	Intensive Care Unit
INR	International Normalized Ratio
IQR	Inter Quartile Range
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fraction
MELD	Model for End Stage Liver Disease
MI	Myocardial Infarction
MV	Mechanical Ventilation
NYHA	New York Heart Association
OPTN	Organ Procurement and Transplantation Network
OR	Odds Ratio

PCI	Percutaneous Coronary Index
RAAS	Renin Angiotensin Aldosterone System
RBC	Red Blood Cell
RRT	Renal Replacement Therapy
SBP	Spontaneous Bacterial Peritonitis
SD	Standard Deviation
UNOS	United Network for Organ Sharing
UTI	Urinary Tract Infection
VD	Vessel Disease

Chapter One: Background

Cardiac surgery in patients with cirrhosis induced end stage liver disease (ESLD) presents significant challenges. In the presence of cirrhosis, the therapeutic outcome of major cardiac surgeries is significantly limited (1). Previous uncontrolled studies have demonstrated that cirrhotic patients have high rates of post cardiopulmonary bypass (CPB) morbidity and mortality (2-4). Nutritional compromise, immune system dysfunction, weakened coagulation, renal system failure and cardiomyopathy secondary to portal hypertension have been considered responsible for the poor patient prognosis (1, 2, 5). Considering these poor outcomes and limited success rates after cardiac surgery, cardiac surgeons traditionally have been hesitant to perform elective cardiac surgeries in patients with advanced liver disease. This in turn reduces the likelihood of successful future liver transplantation and the possibility for improved survival in cirrhotic patients with concomitant coronary/valvular heart disease (6, 7). Adequate cardiac function (ejection fraction > 50%) is critical for cirrhotic patients to be considered for liver transplantation. This necessitates carefully planned correction of pre-existing cardiac conditions prior to being referred for liver transplantation (8, 9). However, post cardiac surgical outcomes in cirrhotic patients have been demonstrated to be poorer in patients with high Child Turcotte Pugh (CTP) and MELD (Model for End Stage Disease) scores. Interestingly, a few groups have evaluated a different treatment approach which combined elective cardiac surgery and liver transplantation for this high risk population (6,

8, 10, 11). Outcomes described in these reports appear encouraging only if patients have normal ventricular function of the heart, no previous history of cardiac surgeries, uncomplicated cardiac pathology and CTP score not more than class B. However, if all the above characteristics were considered for patient selection, it is likely that very few patients will qualify for combined cardiac surgery and liver transplantation. Majority of patients with concomitant cirrhosis and heart disease, on the other hand, have a wide range of cardiac abnormalities resulting in poor ventricular function (ejection fraction < 50%). And importantly, this is the cohort of patients that could most benefit from cardiac surgery prior to liver transplantation. Therefore, it is crucial to identify the risk factors that impact outcomes after cardiac surgery in this high risk patient subset. This, in turn, will permit better post-surgical outcomes and successful future liver transplantation.

1.1 Purpose of the Thesis

In existing practice, CTP class B or C and MELD score > 20 have been considered as contraindications for cardiac surgery using CPB (12-18). However evidence based recommendations are currently not available to support this practice. Therefore, more detailed studies recruiting a larger number of cirrhotic patients (cases) and non-cirrhotic controls are mandatory to determine therapeutic strategies for the improvement of clinical outcomes in cirrhotic patients. As an effort in this direction, we conducted this single center study where we compared a large group of cirrhotic patients undergoing cardiac surgery (n = 60) to non-cirrhotic controls (n = 310) using propensity matching to examine:

- Survival following cardiac surgery
- Pre/perioperative factors that are independently associated with increased mortality (multivariate analysis)
- The association between severity of liver disease (MELD score) and post-surgical outcomes

1.2 Specific Objectives

The objectives of the study are:

1. To determine if cirrhosis is independently associated with higher mortality in propensity matched analysis
2. To determine the association between cirrhosis and post-surgical outcomes such as complications, lengths of stay and requirement of organ support

1.3 Hypothesis

The primary hypotheses are that patients with advanced cirrhosis will have greater in-hospital and overall mortality and a greater incidence of postoperative complications following cardiac surgery. Secondary hypotheses of our study are that cirrhotic patients will require greater surgical and postoperative support compared to control patients requiring cardiac surgeries.

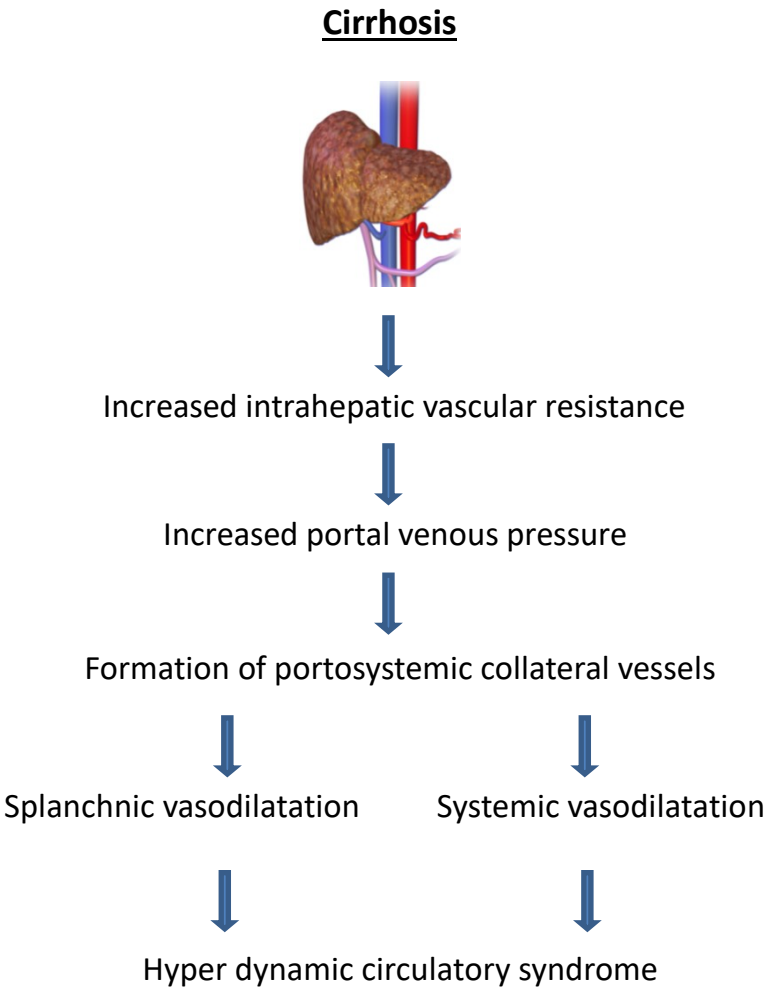
Chapter Two: Literature Review

Cirrhosis is the endpoint of many liver diseases and is the 13th leading cause of death worldwide (19). It is defined pathologically as the irreversible replacement of healthy liver cells into scar tissue. Although there are many causes for cirrhosis, the most common ones around the world are hepatitis C, alcoholic hepatitis and non-alcoholic fatty liver disease (20-22). Other relatively less common causes of cirrhosis are primary biliary cirrhosis, primary sclerosing cholangitis and genetic diseases such as Wilson's disease, alpha-1 antitrypsin deficiency, hemochromatosis and hepatocellular carcinoma.

2.1 Complications of Cirrhosis

The presence of persistent liver injury is an essential component in the pathogenesis of cirrhosis when normal liver tissue is progressively replaced by scar tissue over time. Extensive liver fibrosis leads to increased resistance to blood flow through the liver. The resulting higher blood pressure in the portal venous system leads to portal hypertension (23, 24) and the consequent formation of porto-systemic collaterals. These low resistance collateral vessels in turn contribute to increased portal blood flow via arterial vasodilation in the splanchnic and systemic circulations and further aggravate portal venous pressure. This ultimately results in development of hyperkinetic circulatory syndrome (25). Figure 1 highlights the pathophysiology of portal hypertension and the consequent hyperdynamic circulation.

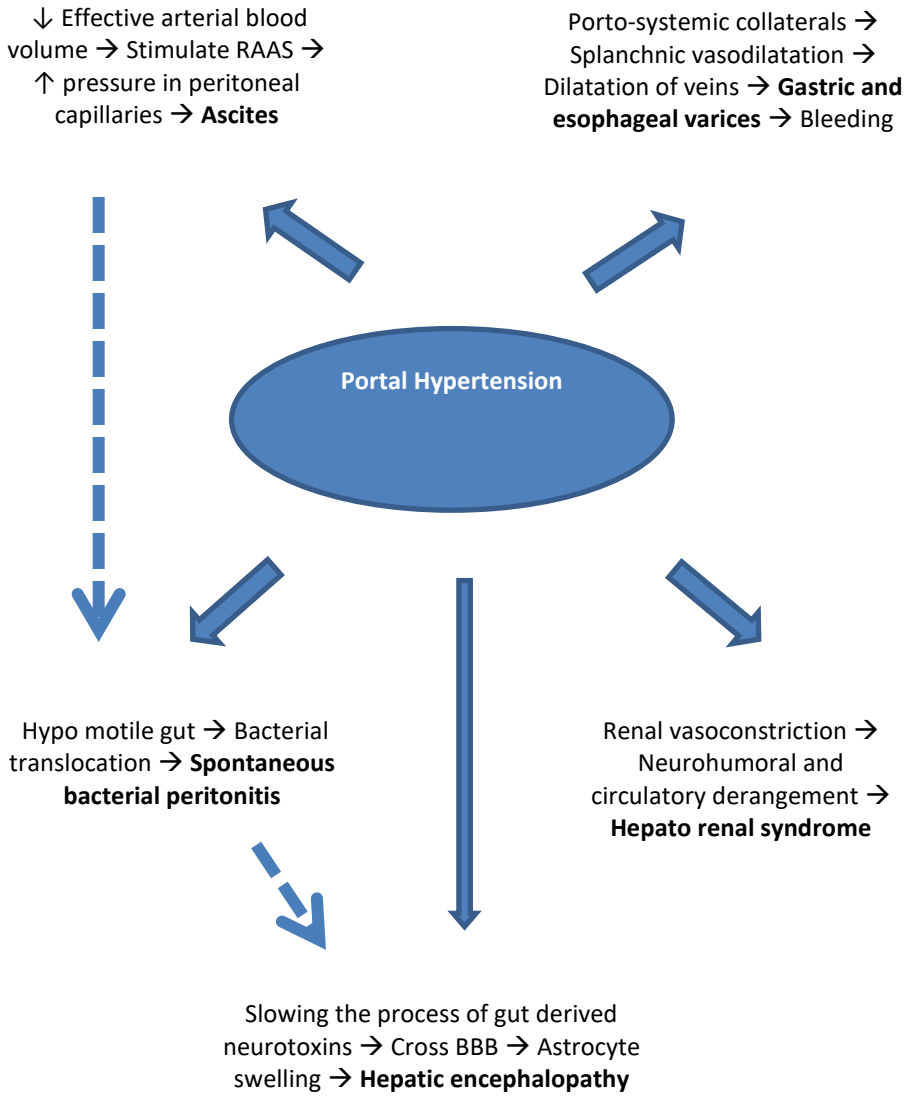
Figure 1 Pathophysiology of Portal Hypertension.



This figure illustrates the development and pathogenesis of portal hypertension and hyper dynamic circulatory syndrome. Cirrhosis produces in increased intra hepatic vascular resistance and increased portal vein pressure. As a result, porto-systemic collaterals are formed and vasodilatation of splanchnic and systemic circulation occurs. This leads to develop hyper dynamic circulation in the body (Liver clipart courtesy: Wikimedia commons).

With increasing portal vein pressure and decreasing liver function, patient develops signs of decompensated cirrhosis such as ascites, gastrointestinal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy and hepatorenal syndrome (HRS) (26-29). The pathophysiology of these complications is illustrated in figure 2.

Figure 2 Sequelae of Portal Hypertension.



The above figure explains how portal hypertension results in the following serious complications in cirrhotic patients. Portal hypertension causes hyperdynamic circulation and therefrom decreased effective arterial blood volume. This activates renin angiotensin aldosterone system (RAAS) and produces **ascites**. **Gastric and esophageal varices** result from the formation of portosystemic collaterals and splanchnic vasodilatation. **Spontaneous Bacterial Peritonitis** develops from infected ascetic fluid and bacterial translocation. **HepatoRenal Syndrome** is caused by the mechanism similar to the formation of ascites and severe renal vasoconstriction. **Hepatic encephalopathy** results from accumulation of neuro toxic substances in the brain.

2.1.1 Ascites

Splanchnic and peripheral vasodilatation occurring as a consequence of portal hypertension results in decreased effective arterial blood volume and subsequent stimulation of the renin angiotensin aldosterone system (RAAS). This in turn results in expansion of plasma volume and overflow of fluid into peritoneal cavity, termed ascites (30).

2.1.2 Esophageal and Gastric Varices

As a result of portal hypertension, porto systemic collaterals are formed in some specific places of gastrointestinal tract where the venous pressure is low. With progressively increasing portal pressure, these collaterals become dilated, forming varices which carry a high tendency to rupture and bleed massively (31).

2.1.3 Spontaneous Bacterial Peritonitis

Cirrhotic patients with ascites develop spontaneous bacterial peritonitis due immune dysfunction. Bacterial translocation is considered the primary contributory mechanism for this complication. In addition, ascites and decreased gut motility promote bacterial growth in the peritoneum, further contributing to the propensity for bacterial peritonitis (27, 32).

2.1.4 Hepatorenal Syndrome

Hepatorenal syndrome is the impairment of renal function (decreased glomerular filtration rate secondary to compromised renal perfusion) that results from

advanced liver disease, with no other identifiable cause for renal failure. This condition is characterized by marked renal vasoconstriction in the presence of significant peripheral vasodilatation. Hepatorenal syndrome is life-threatening and often warrants renal transplant (33, 34).

2.1.5 Hepatic Encephalopathy

Hepatic encephalopathy comprises a group of neuropsychiatric symptoms in patients with cirrhosis and prolonged portal hypertension. Protracted portosystemic shunting results in the accumulation of neurotoxins such as ammonia that are capable of crossing the blood brain barrier. The resultant astrocyte swelling and neurotransmitter dysfunction are considered responsible for the clinical manifestations of hepatic encephalopathy (35).

The multifarious complications described above are essentially responsible for the increased morbidity and mortality seen in patients with decompensated cirrhosis (36-39). Compared to the general population, cirrhosis significantly increases all-cause mortality in cirrhotic patients (40). It is also observed that mortality after having elective surgery is increased in patients with both compensated and decompensated liver cirrhosis (41). In particular, presence of concomitant heart disease is associated with increased mortality in cirrhotic patients (42, 43).

2.2 Diagnostic Challenges in Cirrhosis

Since the damage of the liver is irreversible, it is important for physicians to diagnose it early and manage appropriately in order to limit further insult to liver

and for better quality of life for patients with cirrhosis. The diagnosis of cirrhosis can be confirmed by noninvasive methods such as radiological (Magnetic Resonance Elastography, Magnetic Resonance Image and Computed Tomography) and ultrasound evidence of signs of liver cirrhosis (44, 45). But, liver biopsy and histological evidence remains the gold standard to diagnose cirrhosis when clinical findings are not typical and for the estimation of cirrhosis severity (44, 46).

2.3 Assessment of Cirrhosis Severity

Once diagnosed, patients are assessed for the risk prediction of cirrhosis using many prognostic models. Despite many models in the last twenty years, child turcotte pugh (CTP) and model for end stage liver disease (MELD) scores are globally the most widely used (47-52). These two scores predict the severity of cirrhosis and provide a useful guide to physicians in choosing the safe mode of treatment for patients with ESLD (53).

2.3.1 Child Pugh Score

CTP is calculated from 5 clinical parameters. They are:

A. Three laboratory parameters:
    a. Total bilirubin
    b. Serum albumin
    c. Prothrombin time
B. Two signs:
    a. Ascites

b. Hepatic encephalopathy

Each parameter scores one to three points. Based on the added number of points, the patients are classified as: A (5 – 6 points), B (7 – 9 points) and C (10 – 15 points) (54, 55).

Table 1 Child Turcotte Pugh Score.

Clinical parameters	1 point	2 points	3 points
Serum albumin (g/L)	>35	28 - 35	< 28
Bilirubin (μmol/L)	<34	34 - 50	> 50
INR	< 1.7	1.71 – 2.30	> 2.30
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I or II	Grade II or III

CTP is calculated from the five clinical parameters shown in the table. Each parameter scores one to three points. Abbreviations: INR, International normalized ratio.

Table 2 Interpretation of CTP.

Points	Class	1 year survival	2 year survival
5 - 6	A	100%	85%
7 - 9	B	81%	57%
10 - 15	C	45%	35%

The above table illustrates the interpretation of CTP score to assess the prognosis of cirrhosis and chronic liver disease. Based on the added number of points, the patients are classified as: A (5 – 6 points), B (7 – 9 points) and C (10 – 15 points). Patients in child class A and B have better 1 year survival. Class C patients unfortunately have poor 1 year survival rates.

2.3.1.1 Evidence for Child Pugh Score Applicability

Child Pugh scoring system has been a very useful tool in assessing the prognosis of cirrhotic patients for more than 4 decades now (56). Child Pugh class B and C patients have been shown to have higher mortality rates following cardiac surgeries (14). Komoda *et al* showed that survival rates after radical pericardiectomy were bad in child pugh class C than class A (57). More recently, Lee and colleagues described that the greater risk of bleeding immediately after polypectomy was increased in cirrhotic patients with CTP B or C (58). Modification of the CTP score by introduction of an additional class D makes it as effective as the MELD score in predicting prognostic outcomes in cirrhotic patients (59). Although MELD is considered to provide a more objective assessment of cirrhosis severity, CTP score continues to be an intuitive tool that is easier to use in the bedside (56, 60).

2.3.2 MELD Score

Nowadays, physicians calculate MELD score using the formula proposed by UNOS/OPTN 2016, around the world. MELD uses laboratory parameters such as international normalized ratio, serum creatinine, serum bilirubin, serum sodium and whether dialysis was done at least twice in the past week. The allocated points are added up to constitute a score ranging from 6 to 40. In liver failure patients waiting for liver transplantation, authors (61, 62) have predicted 90-day mortality using MELD score as follows:

- 40 or more — 71.3% mortality
- 30 – 39 — 52.6% mortality
- 20 – 29 — 19.6% mortality
- 10 – 19 — 6.0% mortality
- < 9 — 1.9% mortality

2.3.2.1 Evidence for MELD Score Applicability

Ishigami *et al* demonstrated that MELD helps stratify patients who would gain most from living donor liver transplantation (63). In cirrhotic patients undergoing tricuspid valve surgery, MELD score has been shown to provide a simple and effective method for risk stratification (64). In this study, Ailawadi and colleagues found that MELD score greater than 15 was strongly associated with increased mortality. Interestingly, a report in 2005 showed that MELD was also useful in predicting mortality from surgery in cirrhotic patients undergoing a wide range of other non-transplant surgical procedures (65). Reddy *et al* described that cirrhotic patients with MELD score greater than 15 are the candidates to be referred by the internist to the transplant center for liver transplant evaluation (66). It is also interesting to note that MELD scoring system may be a useful tool for liver transplant allocation in patients with end stage liver failure (67).

2.4 Challenges in the Treatment of Cirrhosis:

In order to decrease morbidity and mortality rates, cirrhosis should be diagnosed early, screened for predictors of poor prognosis and treated appropriately. To date,

there is no specific treatment to completely cure cirrhosis. However, strategies exist, to limit or delay the progression of further liver damage. This includes conservative medical management approaches for patients with compensated cirrhosis (68). Nevertheless, liver transplantation is the only available lifesaving procedure for patients with decompensated cirrhosis (69-72).

2.5 Cirrhosis and Concomitant Heart Disease:

Heart and liver are known to interact and influence each other's function (73). Despite this, until a few decades ago, heart disease was considered a rare occurrence in patients with cirrhosis. With increasing numbers of ESLD patients being treated with liver transplantation, it is becoming obvious that successful liver transplantation results in measurable hemodynamic improvement in transplant recipients (74-77). Although there was improvement in hemodynamic circulation, mortality outcomes post liver transplantation were poor (78). This increased mortality could be partly explained by cardiovascular diseases and its complications such as myocardial infarction, arrhythmias, congestive heart failure, pericardial effusion, pulmonary hypertension and edema postsurgical (79-86). This suggests that better outcomes are possible if such cardiac conditions are surgically corrected prior to being listed for liver transplantation.

2.6 Summary and Rationale:

Surgical correction of heart diseases using CPB in patients with cirrhosis, however, has been a great challenge to cardiologists until now (87). In fact, it has been empirically agreed that cardiac surgery is contraindicated in patients with ESLD due to high mortality after cardiac operations. Therefore, it is paramount to identify the risk factors that predict the outcomes following cardiac surgery, in order to achieve better postsurgical outcomes and a successful liver transplantation in the future. To date, existing published experience with cardiac surgical procedures in cirrhotic patients with high rates of morbidity and mortality is based on relatively small study cohorts. To address this, we considered studying a large group of cirrhotic patients who underwent cardiac surgery (cases) compared to non-cirrhotic cardiac surgery patients (controls) using a propensity matched case-control approach.

Chapter Three: METHODS AND MATERIALS

3.1 Study Design

In our analysis, we conducted a retrospective study of propensity matched cohorts (cirrhotics and non-cirrhotics, termed 'cases' and 'controls' respectively, henceforth in the thesis) who underwent cardiac operations between January 2004 and December 2014 at University of Alberta Hospital and Mazankowski Heart Institute, Edmonton, Alberta.

3.2 Propensity Score Matching

Non-cirrhotic controls were propensity matched (~ 5 to 1) to cirrhotic patients based on multiple variables including age, sex, medical comorbidities such as CVD, congestive heart failure, chronic obstructive pulmonary disease, renal disease, diabetes mellitus, dialysis, hypertension, hyperlipidemia, malignancy, peripheral vascular disease and smoking history, previous myocardial infarction, previous coronary artery bypass surgery, previous percutaneous coronary intervention, previous thrombolytic therapy, indication for catheterization, coronary anatomy, and ejection fraction and stringent matching techniques were applied to select the patients with the nearest propensity score for each case (i.e. within 3 decimal places of the propensity score for each case). Overlap of propensity scores between patients in both cohorts were evaluated using histograms, $\chi 2$ values, and probability values. Differences in baseline factors between groups were calculated before and after propensity adjustment to assess

balance. After the match, t tests were used to determine if there were statistically significant differences between cirrhotics and non-cirrhotics that underwent cardiac surgery. The distribution of propensity scores between cohorts is displayed in the Appendix.

3.3 Study Population

Our patient cohort includes a total of 370 patients who received cardiac surgery. Among them, 60 patients were diagnosed with cirrhosis of liver and the remaining 310 patients had various cardiac diseases without cirrhosis. These patients were compared with regard to demographics, risk factors for cardiac disease, surgical operative variables and postoperative complications. A subgroup retrospective analysis was also performed on the 60 cirrhotic patients undergoing cardiac surgery to look for association between severity of liver disease and their survival to hospital discharge.

3.3.1 Inclusion Criteria

The following are eligible criteria for the inclusion of cases:

(1) Patients who were > 18 years of age admitted to the adult CVICU

(2) Having a diagnosis of cirrhosis made by pathological and radiological evidence

(3) Underwent cardiac surgery

Eligible criteria for inclusion of controls:

(1) Patients who were > 18 years of age admitted to the adult CVICU

(2) Absence of any evidence of cirrhosis

(3) Underwent cardiac surgery

3.3.1.1 Cardiac surgeries included in the cohort:

We included the following types of cardiac surgeries performed on the cirrhotics and non-cirrhotics. They were coronary artery bypass graft (CABG), uni or multi valvular repair and/or replacement, congenital heart disease repair (Fontan revision, ventricular septal defect and atrioventricular septal defect repair), pericardiectomy, aortic dissection repair, thromboendarterectomy, pulmonary embolectomy and placement of ventricular assist device.

3.3.2 Exclusion Criteria

(1) Patients who were < 18 years of age admitted to adult CVICU

(2) Patients who underwent heart transplantation

3.4 Data Source

Required data (January 2004 to December 2014) was collected from APPROACH database (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease). This registry has statistics on all cardiac patients undergoing any cardiac procedures in Alberta, Canada since 1995 (88, 89). It provides detailed patient information which includes demographics, medical, surgical and postoperative clinical parameters. Preoperative and postoperative variables were extracted from charts by experts and abstracters (90).

3.4.1 Study Variables in matched cohort Study:

3.4.1.1 Preoperative variables

a. Demographics:

Age, gender of a patient, body weight and height and BMI were included in the study for baseline demographics.

b. Risk factors for cardiac diseases:

Presences of any of the following risk factors were included. They were hypertension, hyperlipidemia, diabetes type I and II, previous history of myocardial infarction, percutaneous coronary intervention, congestive heart failure with New York Heart Association class and prior CABG and history of smoking.

c. Charlson comorbidity score components:

It was developed to predict the ten year mortality among hospitalized patients with a range of comorbid conditions (91, 92). In addition, studies from Denmark and the United Kingdom have shown the strong association of CCI with mortality in patients with liver disease (40, 93). This index has 19 comorbid conditions and each condition is allocated with a point of 1, 2, 3 and 6 depending on the risk of dying associated with each condition. The following table explains the comorbidity scoring system (Table 3).

Table 3 Charlson Comorbidity Index.

1 point	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2 points	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia

	Lymphoma
3 points	Moderate or severe liver disease
6 points	Metastatic solid tumor
	AIDS

The above table describes the allocated points for a variety of comorbid conditions. Abbreviations: AIDS, acquired immune deficiency syndrome

In our matched cohort study, we excluded mild, moderate and severe liver disease from the total in order to balance the score between cirrhotics and non-cirrhotics.

d. Extent of coronary artery disease:

This involves angiographic determination of involvement of number of coronary arteries with the percentage of obstruction. We divided this variable into one or two vessel disease with > 75% of obstruction of coronary artery, three vessel disease with > 75% of obstruction and presence of left main disease.

e. Left ventricular ejection fraction:

Ejection fraction in echocardiography determines the pumping ability of the heart and is an important parameter to define heart failure. Left ventricular ejection fraction of > 55% is considered as normal in adults. We had variables with ejection fractions > 50%, 35-50%, 20-34%, <20%. Some of the patients did not have measurable ejection fraction.

3.4.1.2 Operative variables

a. Priority of surgery:

Surgical priority variables were whether they emergent, urgent in-hospital, urgent out of hospital and not urgent out of hospital

b. Incidence of surgery:

This variable indicates how many times surgery was performed on the patient. These were divided into first cardiac operation, second operation and three or more reoperations.

c. Type of cardiac surgery:

We grouped cardiac surgeries into four variables. They were isolated coronary artery bypass graft (CABG), CABG and valvular surgery, valve repair or replacement and other surgeries.

d. Hemodynamic data:

These included CPB time and aortic cross clamp time in minutes. CPB time indicates how long a heart lung machine maintains the circulation of blood and oxygen of the body during open heart surgery, whereas aortic cross clamp time indicates how long the systemic circulation separates from the outflow of heart during cardiac surgery.

e. Blood product transfusion:

These variables were how many number of packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate transfused intraoperatively.

3.4.1.3 Postoperative variables

a. Postoperative complications:

This was one of the primary outcomes in our study. We included all complications that may be expected from each system. Our cases and controls had the following systemic complications.

(i) Cardiac complications:

Cardiac tamponade, cardiac arrest, atrial fibrillation and heart failure

(ii) Respiratory complications:

Pneumonia, prolonged ventilation, pleural effusion, chest tube insertion and acute respiratory distress syndrome (ARDS)

(iii)Neurological complications

Delirium

(iv)Renal complications:

Acute kidney injury

(v) Gastrointestinal complications:

GI bleeding, mesenteric ischemia

(vi)Infections:

Superficial and deep sternal wound infections, harvest site infection and urinary tract infection.

b. CVICU length of stay:

This variable was a secondary outcome in our study. This was calculated between admission to CVICU and discharge to ward.

c. Mortality:

This variable was one of the primary outcomes. The in-hospital mortality was calculated from the number of patients who died prior to discharge. Overall mortality was calculated from the number of patients in our study cohort who died between January 2004 and December 2014 inclusive.

d. Organ support:

Postoperative requirement of medical services such as renal replacement therapy and mechanical ventilation were included in our study. They were our secondary outcomes of interest.

3.4.2 Additional Study Variables and Data Collection:

In addition to the above mentioned variables, we collected more data on etiology and complications of cirrhosis, comorbidities before surgery (CCI) and relevant clinical laboratory parameters during, before and after surgery from the medical charts of 60 patients and estimated the severity of cirrhosis prior to cardiac surgery using MELD score.

a. Etiology of cirrhosis:

We included the most common and other causes of liver diseases. The diagnosis of cirrhosis was confirmed by the evidence from histopathology and radiology. The causes of cirrhosis included were hepatitis B and C, alcoholic hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary/secondary sclerosing cholangitis, nonalcoholic steatohepatitis, Budd-Chiari syndrome, hepatocellular carcinoma, alpha-1 antitrypsin, Wilson's disease, hemochromatosis and congestive cirrhosis secondary to cardiovascular disease.

b. Complications of cirrhosis:

Preoperative complications of cirrhosis were included under this heading. They were ascites, esophageal and gastric variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis and having a transjugular intrahepatic portosystemic shunt.

c. CCI:

We included all indices of CCI including mild, moderate and severe liver disease and added up the values together.

d. MELD score:

The MELD score was calculated according to the 2016 United Network for Organ Sharing /Organ Procurement and Transplantation Network policy formula (94, 95), using laboratory parameters and the online MELD calculator: (https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older)

e. Length of stay in hospital and ICU:

These were counted from the date and time of appropriate admissions to the date and time of discharges.

f. Postoperative organ support:

Postoperative need for vasopressors such as epinephrine, norepinephrine, vasopressin, milrinone, dobutamine and phenylephrine were recorded. Similarly postoperative need of mechanical ventilation and renal replacement therapy were documented.

The relationship between severity of liver disease, medical comorbidity and surgical factors on survival to hospital discharge was evaluated and the results were compared between survivors and nonsurvivors following cardiac surgery.

3.5 Outcomes

3.5.1 Primary Outcome

The primary outcomes of interest for our study were in-hospital mortality, overall mortality and postoperative complications.

3.5.2 Secondary Outcomes

Secondary outcomes of interest included CVICU length of stay, postoperative organ support and health resource utilization.

3.6 Statistical Analyses

3.6.1 Descriptive Analyses

Statistical analysis was carried out using Stata/MP 13.0 for Windows (StataCorp LP, Texas). Continuous variables were described as median and interquartile range (IQR) and mean, standard deviation where appropriate. Categorical variables were reported as numbers and proportions. Univariate analyses for categorical variables were analyzed with chi square test and Fisher's exact test for cells with a number less than five. Continuous variables were tested with Mann Whitney test for nonparametric and student t test for normally distributed variables. Chi square test for trend used to test a group of perioperative categorical variables such as extent of coronary artery disease, left ventricular ejection fraction, surgical priority, surgical incidence and types of surgery (96). Statistical significance was reported for a p value < 0.05 with 95% confidence interval.

3.6.2 Multivariable Analyses:

In order to adjust for covariates, multivariate analysis was used to analyze the association between cirrhosis and mortality with covariates included based on a p value < 0.10 from univariable analysis. After exclusion of collinear, non-significant and not clinically important variables, final model was built using purposeful selection method. Univariate logistic regression and conditional logistic regression were performed to analyze the association between overall mortality and other variables such as presence of cirrhosis, CCI, blood transfusion

during surgery and CPB time, in the final model. Results were reported as unadjusted and adjusted odds ratio with 95% confidence interval and p value < 0.05. The diagnostic accuracy of logistic regression was estimated using the area under the receiver operator curve (AUROC). It measures the goodness of fit for the binary outcome variable in the final model. This test is also capable of differentiating the diseased population from healthy ones (97).

3.6.3 Kaplan Meier Curve:

It is a non-parametric test used to estimate survival time between two different groups. When creating a Kaplan Meier (KM) curve, each subject should have three variables such as serial time, event (1= event; 0= censored) and study group (cases and controls) (98). Using Stata™, KM curve was created and results between cases and controls were compared using log rank test. This test estimates the chi-square for each event time for each group and sums the results.

In our analysis, the three variables for each subject were

(1) Time after cardiac surgery in months

(2) Event of interest: 1= death any time after cardiac surgery, 0= censored and alive until December 2014

(3) Study group: Cirrhotics and non cirrhotics

Chapter Four: Results

4.1 Baseline Demographics, Clinical and Preoperative Characteristics in Cases and Controls

In our final study population, a total of 60 cirrhotic patients were propensity matched approximately 1:5 to 310 non-cirrhotic patients undergoing cardiac surgery. The cirrhotic and noncirrhotic patient cohorts were well balanced for age, gender, body mass index, risk factors for cardiac diseases and preoperative variables (Table: 4). In terms of CCI (excluding liver disease from the total score), the median score in cirrhotics was higher (median [IQR] 3 [1 - 5] vs 2 [1 - 4], p= 0.10) than in controls.

Table 4 Univariate analysis of baseline demographics, clinical and preoperative characteristics in cases and controls.

Variables:	n	Cirrhosis	n	Non-Cirrhosis	P- value
AGE	60	54 (13.4)	310	52.5 (17)	0.45
Gender (Male)	60	42 (70%)	310	218 (70%)	0.96
BMI	45	27.4 (24-32)	236	28.4 (25-33)	0.15
Cardiac risk factors					
Hypertension	60	35 (58.3%)	310	176 (56.8%)	0.82
Dyslipidemia	60	38 (63.3%)	310	186 (60%)	0.63
Type 1 diabetes		0		0	
Type 2 diabetes	60	16 (26.7%)	310	78 (25.2%)	0.81
Prior MI	60	22 (36.7%)	310	105 (33.8%)	0.67
Heart failure	60	16 (26.7%)	310	67 (21.6%)	0.39
NYHA class					0.37
Class 1	60	6 (10%)	310	16 (5.2%)	
Class 2	60	5 (8.3%)	310	44 (14.2%)	
Class 3	60	9 (15%)	310	36 (11.7%)	
Class 4	60	3 (5%)	310	24 (7.7%)	
Not entered	60	37 (61.7%)	310	190 (61.3%)	
Current smoker	60	26 (43.3%)	310	127 (41.2%)	0.73
Preoperative renal failure	60	3 (5%)	310	13 (4.2%)	0.73
CCI	60	3 (1 - 5)	310	2 (1 - 4)	0.10

Preoperative investigations					
Extent of Coronary artery disease (>75%)					0.57
1 or 2 VD	60	6 (10%)	310	30 (9.7%)	
3 VD	60	13 (21.7%)	310	61 (19.7%)	
Left main	60	11 (18.3%)	310	54 (17.4%)	
Normal angiogram	60	10 (16.7%)	310	65 (21%)	
Not available	60	15 (25%)	310	83 (26.8%)	
< 50%	60	5 (8.3%)	310	17 (5.5%)	
LVEF, %:					0.20
>50%	60	10 (16.7%)	310	81 (26.1%)	
>35-50%	60	9 (15%)	310	44 (14.2%)	
>20-34%	60	3 (5%)	310	12 (3.9%)	
<20%	60	1 (1.7 %)	310	0	
Not available	60	37 (61.7%)	310	173 (55.8%)	

Values presented as mean (standard deviation), median (interquartile range) and proportion (percentage). BMI: Body Mass Index, MI: Myocardial Infarction, NYHA: New York Heart Association, CCI: Charlson Comorbidity Index, CAD: Coronary Artery Disease, VD: Vessel Disease, LVEF: Left Ventricular Ejection Fraction

4.2 Operative Variables Between Cirrhotics and Non-cirrhotics

Operative variables shown in table 5 were also balanced between cases and controls in terms of surgical priority, procedures and incidence. Cardiac surgeries were done either as an emergent, urgent in-hospital, urgent out-of-hospital procedure or non-urgent out-of-hospital procedure. 91.7% of cirrhotics underwent cardiac surgery as an urgent or emergent procedure compared to 86.6% of non-cirrhotics.

Majority of patients in our cohort received cardiac surgery using CPB and we found cirrhotic patients had statistically significant longer cardiopulmonary bypass time (median minutes, 128 [99 - 200] vs 116 [83 - 161], p=0.02) compared to the control patients. Similarly, the aortic cross clamp time was also greater in cirrhotics (median minutes, 82 [48 - 115] vs 75 [46 - 115], p=0.13) than in controls, but not statistically significant. The likelihood of receiving any blood product transfusions (red blood cell, fresh frozen plasma or platelets) was significantly greater in cirrhotics during surgery (58.3% vs 43.2%, p=0.03).

Table 5 Univariate analysis on operative variables between cirrhotics and non cirrhotics.

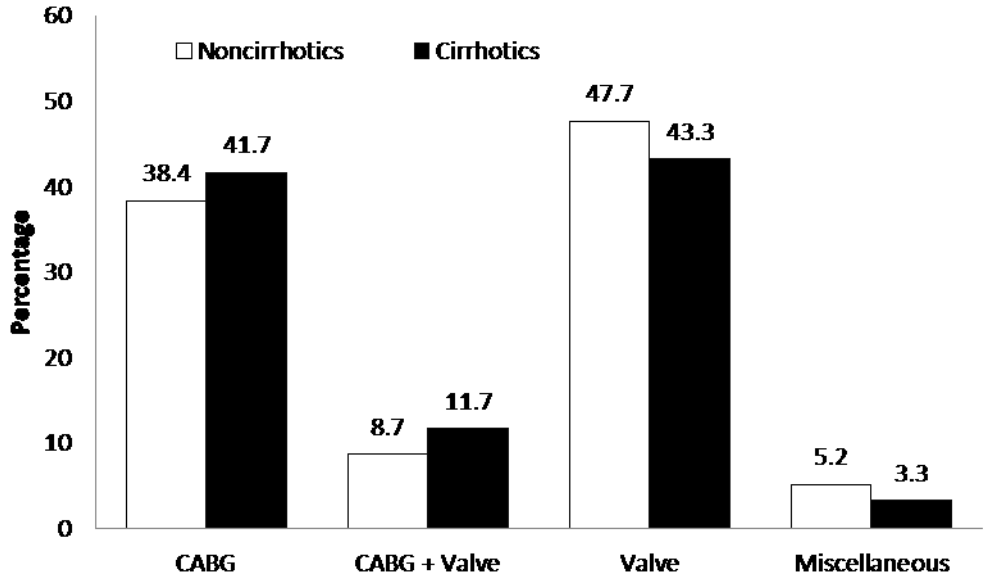
Variables:	n	Cirrhosis	n	non-cirrhosis	P value
Operative variables:					
Surgical priority, % :					0.29
Emergent	60	6 (10%)	310	25 (8.1%)	
Urgent in-hospital	60	27 (45%)	310	130 (42%)	
Urgent out of hospital	60	22 (36.7%)	310	113 (36.5%)	
Not urgent out of hospital	60	5 (8.3%)	310	42 (13.6%)	
Surgical incidence, %					0.56
First operation	60	48 (80%)	310	240 (77.7%)	
Second operation	60	11 (18.3%)	310	58 (18.8%)	
Third or greater	60	1 (1.7%)	310	11 (3.6%)	
Surgery, %					0.42
CABG	60	25 (41.7%)	310	119 (38.4%)	
CABG + valve	60	7 (11.7%)	310	27 (8.7%)	
Valve	60	26 (43.3%)	310	148 (47.7%)	

Miscellaneous	60	2 (3.3%)	310	16 (5.2%)	
Intraoperative variables:					
Cardiopulmonary Bypass time, minutes	60	128 (99-200)	310	116 (83 - 161)	0.02
Aortic cross clamp time, minutes	60	82 (48-115)	310	75 (46 - 115)	0.13
Any transfusion	60	35 (58.3%)	310	134 (43.2%)	0.03
Intraoperative RBC	60	1 (0 - 3)	310	0 (0 - 1)	0.0001
Intraoperative FFP	60	0 (0 - 2)	310	0 (0 - 0)	0.002
Intraoperative cryoprecipitate	60	0 (0 - 0)	310	0 (0 - 0)	0.08
Intraoperative Platelet	60	0 (0 - 1)	310	0 (0 - 1)	0.01

Values presented as median (interquartile range) and proportion (percentage). CABG: Coronary Artery Bypass Graft, RBC: Red Blood Cell, FFP: Fresh Frozen Plasma

In terms of types of cardiac surgeries performed, nearly 53.4% of cirrhotics underwent CABG and CABG + valve procedures compared to 47.1% among controls. Control patients underwent valvular surgeries more often than cirrhotic patients. This data is illustrated in figure 3.

Figure 3 Types of Surgery Performed.



This figure shows the percentage of types of surgery performed on cirrhotics and non cirrhotics. There were no significant difference noted in between cases and controls (p=0.43). CABG: Coronary artery bypass graft

4.3 Postoperative Outcome and Complications in Cases and Controls

Postoperative outcomes such as mortality, length of stay in hospital/ICU and complications after surgery are shown in table 6. The overall mortality in patients with cirrhosis undergoing cardiac surgery was significantly greater than the propensity matched controls ([40%, n = 60] vs [20%, n = 310], p value 0.001). The in-hospital mortality was also higher in people with liver cirrhosis (15% vs 5% in controls, p = 0.04). The median length of stay in intensive care unit in patients with cirrhosis was significantly longer compared to matched controls (median days [IQR], 5 [3-11] vs 2[1- 4], p = 0.00001). Major postoperative complications were significantly greater in patients with liver cirrhosis (63.3% vs 48%, p = 0.03) compared to controls.

Table 6 Postoperative outcome and complications in cases and controls.

Variables:	n	cirrhosis	n	non-cirrhosis	P value
Overall mortality	60	24 (40%)	310	63 (20%)	0.001
In hospital mortality	60	9 (15%)	310	15 (5%)	0.04
CVICU LOS -days	60	5 (3 - 11)	309	2 (1 - 4)	0.00001
Any Complications	60	38 (63.3%)	310	148 (48%)	0.03
Cardiac complications	60	22 (36.7%)	310	87 (28%)	0.18
Cardiac tamponade	60	2 (3.3%)	310	13 (4.2%)	0.76
Re-operation	60	12 (20%)	310	69 (22.3%)	0.7
Cardiac arrest	60	5 (8.3%)	310	4 (1.3%)	0.007
Atrial fibrillation	60	14 (23.3%)	310	52 (16.8%)	0.27
Respiratory complications	60	31 (51.7%)	310	85 (27%)	0.0002
Intubation days	60	2 (1 - 5)	310	1 (0.5 - 1.2)	0.00001
Prolonged ventilation (> 24 hours)	60	20 (33.3%)	310	67 (22%)	0.05
Pneumonia	60	14 (23.3%)	310	30 (9.7%)	0.003

Pleural effusion	60	9 (15%)	310	16 (5.2%)	0.005
Chest tube insertion	60	6 (10%)	310	10 (3.2%)	0.02
ARDS	60	4 (6.7%)	310	18 (5.8%)	0.77
Neurological complications	60	2 (3.3%)	310	14 (5%)	1
Delirium	60	2 (3.3%)	310	14 (4.5%)	1
Renal complications	60	14 (23.3%)	310	29 (9%)	0.002
Acute kidney injury	60	13 (21.7%)	310	24 (7.7%)	0.001
Postoperative renal replacement therapy	60	9 (15%)	310	19 (6.1%)	0.02
Gastrointestinal complications	60	5 (8.3%)	310	17(6%)	0.37
Bleeding	60	5 (8.3%)	310	13 (4.2%)	0.19
Mesenteric ischemia	60	0	310	3 (1%)	1
Infectious complications	60	4 (6.7%)	310	27 (9%)	0.8
Superficial sternal wound infection	60	3 (5%)	310	14 (4.5%)	0.75

Deep sternal wound infection	60	1 (1.7%)	310	5 (1.6%)	1
Harvest site infection	60	1 (1.7%)	310	10 (3.2%)	1
UTI	60	1 (1.6%)	310	3 (1%)	0.51

Values presented as median (interquartile range) and proportion (percentage). CVICU: Cardio Vascular Intensive Care Unit, LOS: Length of Stay, ARDS: Acute Respiratory Distress Syndrome, UTI: Urinary Tract Infection

Among the various cardiac complications that were compared, only cardiac arrest was significantly more often observed in cirrhotics (8.3% vs 1.3% in controls, p = 0.007). Atrial fibrillation and cardiac tamponade were the only other complications that were noted in the study population and were not statistically different between cases and controls (Figure 4).

Figure 4 Cardiac Complications after Surgery.

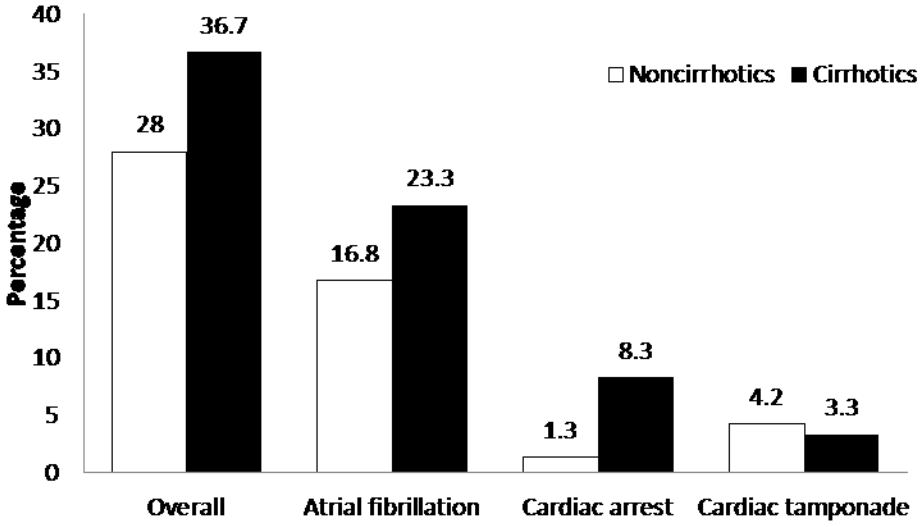


Figure 4 displays the percentage of overall cardiac complications following cardiac surgery, atrial fibrillation, cardiac arrest and cardiac tamponade. Among them, cirrhotics were more likely to have cardiac arrest compared to controls (p=0.007).

Respiratory complications were observed more commonly in cases as compared to control patients. Incidence of overall respiratory complications was 51.7% in cirrhotic patients compared to a 27% incidence in controls (p=0.0002). Individual complications such as pneumonia (23.3% vs 9.7%, p = 0.003) and pleural effusion (15% vs 5.2%, p = 0.005) were significantly higher in cases compared to controls (Figure 5). As a consequence, cirrhotic patients required more chest tube insertions (10% vs 3.2%, p = 0.02), prolonged ventilation more than 24 hours (33.3% vs 22%, p = 0.05) and had longer median days on mechanical ventilation (2[1 - 5] vs 1[0.5 -1.2], p=0.00001). Similarly, the incidence of overall renal complications (cases, 23.3% vs controls, 9%; p=0.002) and acute kidney injury (21.7% vs 7.7%, p = 0.001) were greater in cirrhotic patients compared to controls, with a greater likelihood to be on renal replacement therapy (15% vs 6.1%, p = 0.02), postoperatively (Figure 6).

Figure 5 Respiratory Complications Post Surgery.

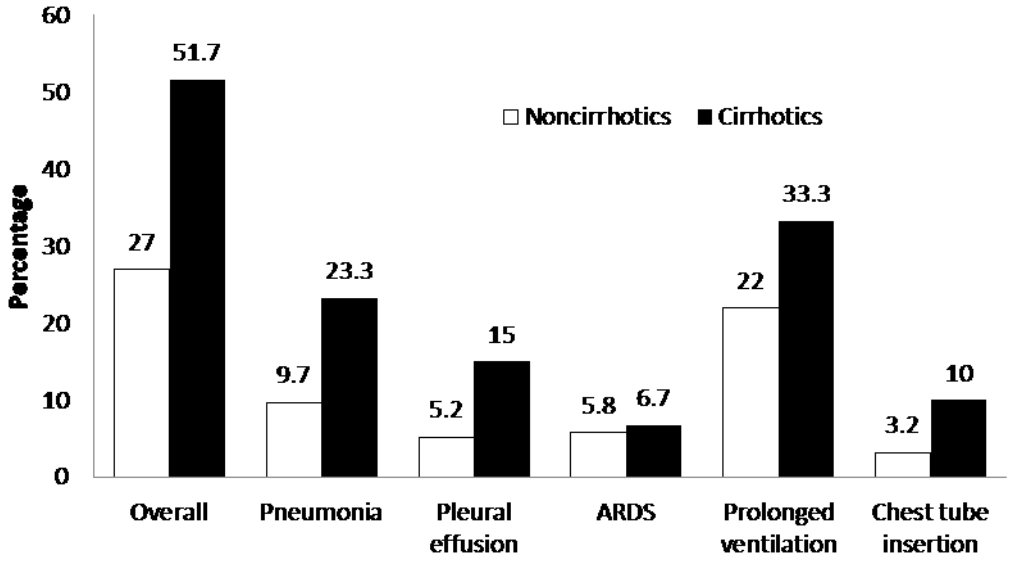


Figure 5 illustrates the percentage of overall respiratory complications after cardiac surgery, pneumonia, pleural effusion, acute respiratory distress syndrome (ARDS), prolonged ventilation, chest tube insertion. Cirrhotics were more likely to have overall respiratory complications (p=0.0002), pneumonia (p=0.003), pleural effusion (p=0.005) and needed prolonged ventilation (p=0.05) and chest tube insertion (p=0.02).

Figure 6 Renal Complications Post Surgery.

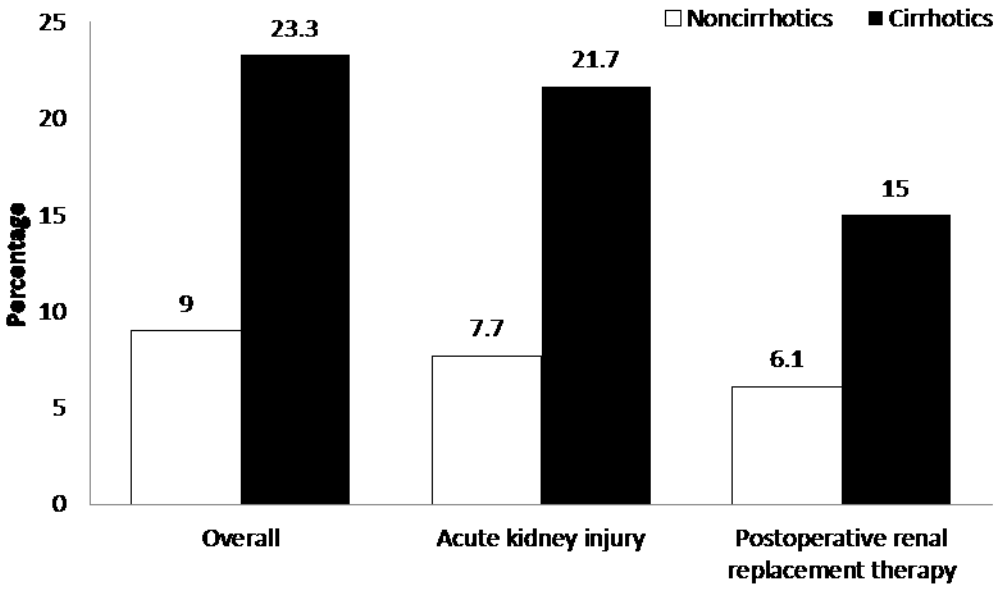


Figure 6 shows the percentage of overall renal complications after cardiac surgery, acute kidney injury and require of renal replacement therapy. Cirrhotics had greater incidence of overall renal complications (p=0.002), acute kidney injury (p=0.001) and required more renal replacement therapy (p=0.02)

4.4 Independent Association of Factors that Predict Increased Mortality in Propensity Matched Cases and Controls

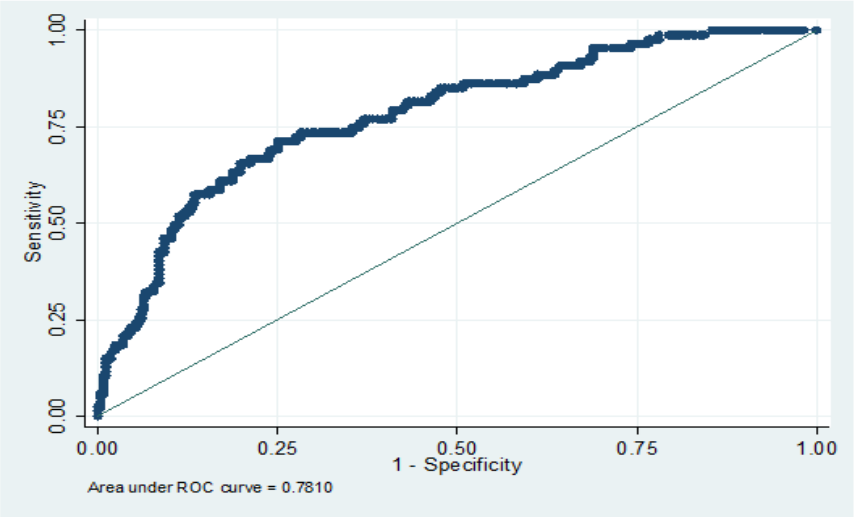
Multivariable logistic regression was performed to adjust for potential confounders in the final model which included 286 subjects. The results of this analysis are shown in table 7. After adjusting other covariates in the model, cirrhosis [aOR 2.2 (95% CI 1.10 - 4.22)], CCI [aOR 1.4 (95% CI 1.18 - 1.60)] and any intraoperative transfusions [aOR 2.7 (95% CI 1.42 - 5.11)] were independently associated with increased overall mortality. CPB time was not independently associated with mortality. The final model performance was estimated by area under the receiver operator curve (AUROC) and was 0.78 (Figure 7).

Table 7 Multivariable analysis for the independent association of factors with increased mortality in propensity matched cases and controls.

Variables	Unadjusted OR (95%CI) (n=310)	P value	Adjusted OR (95%CI) (n=286)	P value
Overall mortality:				
Cirrhosis	2.6 (1.45 - 4.69)	0.002	2.2 (1.10 -4.22)	0.03
CCI	1.5 (1.33 - 1.71)	0.0001	1.4 (1.18 -1.60)	0.0001
Any transfusion	2.4 (1.25 – 4.62)	0.00001	2.6 (1.28 -5.04)	0.007
Cardiopulmonary bypass time	1.005 (1.002 - 1.007)	0.002	1.0008 (0.99 - 1.004)	0.63

Values reported as unadjusted odds ratio and adjusted odds ratio with 95% confidence interval. CCI: Charlson Comorbidity Index

Figure 7 Area under the receiver operator curve.

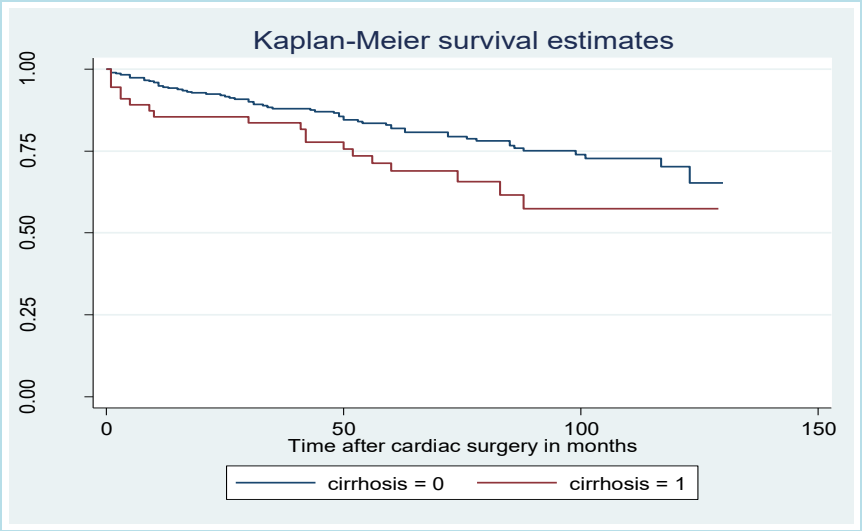


This figure illustrates area under the receiver operator curve and describes the diagnostic accuracy of final model in logistic regression. P = 0.781 shows strong model in terms of accuracy.

4.5 Survival Estimates in Cirrhotics and Non-cirrhotics

Kaplan Meier curve was created to analyse the survival estimates of cases and controls undergoing cardiac surgery. We found in our analysis that there was a significant difference in cumulative survival rates between the two groups using log rank test (p = 0.01). The cumulative survival in cirrhotics at 12 months was 78% in cases versus 92% in controls. At the end of 60 months and 120 months, cumulative survival was 65% and 52% in cases compared to 82% and 70% in controls (Figure 8).

Figure 8 Survival estimates in cases and controls.



The above graph shows Kaplan-Meier cumulative survival after cardiac operations stratified by cirrhosis (n = 60) vs controls (n = 310); Log rank test: P = 0.01

4.6 Subgroup Analysis: 60 Cirrhotic Patients Undergoing Cardiac Surgery

Univariable analysis was performed on 60 patients with cirrhosis to compare the results between survivors and nonsurvivors. The results are shown in table 8. In comparing survivors, non survivors were significantly older [mean years (SD), 59.5 (12.5) vs 50.7 (13), p = 0.01] and majority of them were males. There was no significant difference in types of surgeries performed on both survivors and nonsurvivors. The etiological profile of cirrhosis was predominantly similar in cirrhotics and non-cirrhotics with a few minor differences as noted in figure 9. The incidence of cirrhosis-related complications were not remarkably different between the two groups preoperatively (Figure 10), with the exception of a greater preoperative incidence of ascites in survivors (45.8% vs 13.9%, p=0.008). As anticipated, nonsurvivors had higher median CCI (5 [3-6.5] vs 2 [1-3], p=0.00001), MELD scores (12.1 [8.6 - 20.3] vs 8.8 [4.4 - 15.4], p=0.03), and higher median creatinine (108 [83 - 144] vs 79 [58 - 93], p=0.0008) preoperatively. In addition, they had significantly longer ICU (median days, 10.5 [4.5 - 25] vs 4 [2 - 5],p=0.0001) and in hospital (median days, 32 [17.5 - 51] vs 9 [6 - 14],p=0.00001) stay and required more medical organ support including vasopressors (87.5% vs 61.1%,p=0.03), mechanical ventilation (median days, 4.5 [2 - 17.5] vs 2 [1 - 2],p=0.004), and renal replacement therapy (45.8% vs 2.8%,p=0.0001) as compared to survivors.

Table 8 Univariable analysis of demographic details, types of surgery, etiology and complications of cirrhosis among survivors and nonsurvivors.

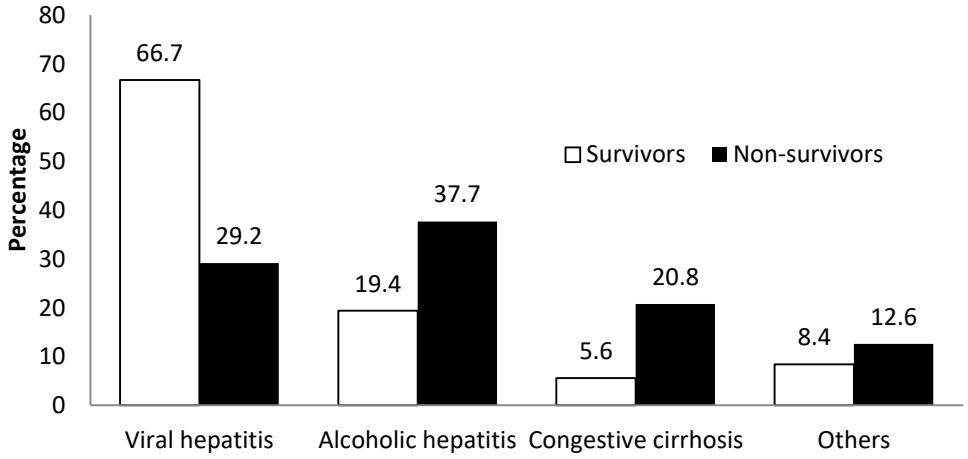
	n	Survivors	n	Non-survivors	P Value
AGE	36	50.7 (13)	24	59.5 (12.5)	0.01
Types of surgery					
1.CABG	36	20 (55.6%)	24	12 (50%)	0.67
2.Valve	36	15 (41.7%)	24	11 (45.8%)	0.74
4.Miscellaneous	36	1 (2.78%)	24	1 (4.1%)	1
Etiology of Liver disease					
1. Viral hepatitis	36	24 (66.7%)	24	7 (29.2%)	0.004
2.Alcoholic cirrhosis	36	7 (19.4%)	24	9 (37.7 %)	0.12
3.Congestive cirrhosis	36	2 (5.6%)	24	5 (20.8%)	0.10
4. Other causes	36	3 (8.4%)	24	3 (12.6%)	0.67
Complications					
1.Ascites	36	5 (13.9%)	24	11 (45.8%)	0.008
2.Variceal bleeding	36	6 (16.7%)	24	2 (8.3%)	0.45

3.Encephalopathy	36	3 (8.3%)	24	4 (16.7%)	0.42
4.Hepatorenal syndrome	36	1 (2.8%)	24	0	1
5.Spontaneous Bacterial Peritonitis	36	0	24	2 (8.3%)	0.15
CCI	36	2 (1-3)	24	5 (3- 6.5)	0.00001
MELD	22	8.8 (4.4-15.4)	16	12.1 (8.6-20.3)	0.03
Preoperative Creatinine	36	79 (58 - 93)	24	108 (83 - 144)	0.0008
Organ support-Post surgery					
1. Vasopressors	36	22 (61.1%)	24	21 (87.5%)	0.03
2. RRT	36	1 (2.8%)	24	11 (45.8%)	0.0001
ICU LOS	36	4 (2-5)	24	10.5 (4.5-25)	0.0001
Days on MV	36	2 (1-2)	24	4.5 (2-17.5)	0.004
Hospital LOS	36	9 (6-14)	24	32 (17.5-51)	0.00001

Values presented as mean (standard deviation), median (interquartile range) and proportion (percentage). CABG: Coronary Artery Bypass Graft, CCI: Charlson Comorbidity Index, MELD: Model for End Stage Liver Disease, RRT: Renal

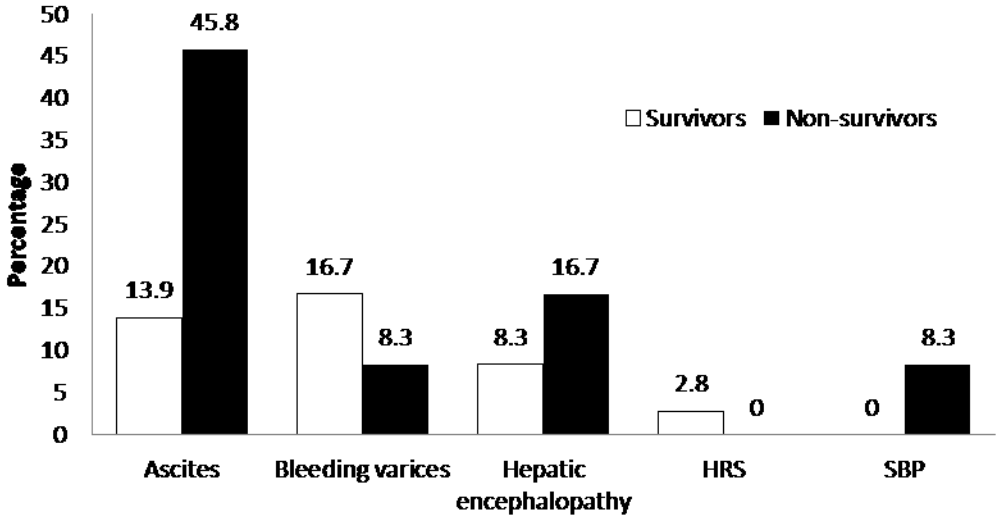
replacement therapy, ICU: Intensive Care Unit, LOS: Length of Stay, MV: Mechanical ventilation

Figure 9 Etiology of Cirrhosis.



This bar chart illustrates the percentage of most common causes of cirrhosis among survivors and nonsurvivors. Survivors were more likely to have viral hepatitis compared to non survivors (p=0.004). Non survivors had alcoholic cirrhosis as a common cause, but not statistically significant (p=0.12). The other causes including nonalcoholic steatohepatitis, hemochromatosis, primary biliary cirrhosis, hepatocellular carcinoma were balanced between survivors and nonsurvivors (p=0.67).

Figure 10 Complications of Cirrhosis.



The above graph shows the percentage of complications due to cirrhosis prior to cardiac surgery. Survivors were more likely to have ascites than nonsurvivors (p=0.008). The incidence of hepatic encephalopathy (p=0.42) and spontaneous bacterial peritonitis (p=0.15) were slightly more in survivors, but not statistically significant. Abbreviations: HRS, Hepatorenal Syndrome; SBP, Spontaneous Bacterial Peritonitis

Chapter Five: Discussion

5.1 Key Findings

We present a large series of cirrhotic patients with concomitant heart disease in whom we evaluated the important determining factors for poor postsurgical outcomes compared to non-cirrhotic surgical patients. Overall mortality was significantly higher in cirrhotic patients undergoing cardiac surgery compared to non-cirrhotic controls (40% vs 20%). In addition, cirrhotics suffered more postoperative complications, which significantly lengthened their ICU stay and increased their requirement for postoperative mechanical organ support. After adjusting for significant covariates, cirrhosis, medical comorbidity (high CCI) and requirement for intraoperative transfusions were independently associated with increased mortality.

5.2 Association between MELD Score and Mortality

Incidence of perioperative morbidity and mortality are generally very high in cirrhotic patients undergoing surgery. Ever since its development in 2001, the MELD score has proven to be a very useful tool to risk stratify cirrhotic patients and instruct treatment choices in a wide variety of clinical scenarios (99). The inherent objective nature and the use of continuous numerical values in MELD scoring provide convenience in predicting mortality following surgical procedures including liver transplantation (65, 100-102).

In the past 7 years, several observational studies show that patients with cirrhosis undergoing cardiac surgery had increased mortality. A systematic review in 2010 of 9 retrospective analyses of small study subject samples showed that the overall mortality after a wide range of cardiac operations in patients with liver cirrhosis was 17.1% with MELD score of > 13 (87). Vanhuyse *et al* in 2012 demonstrated that the in-hospital mortality rate after cardiac surgery in 34 patients with cirrhosis was 26% with mean MELD score 12 +/- 3.5. In this study, they also showed that both CTP and MELD scores predicted the occurrence of operative mortality (12). Another retrospective cohort study in 2013 reported that the in-hospital mortality following cardiac operations in 32 patients with liver disease was 16% with a MELD score greater than 15 (103). A prospective study in the same year reported 12% mortality immediately after cardiac surgery in 58 cirrhotic patients with MELD score of 18.5 (104). Both studies affirmed the usefulness of MELD in predicting in-hospital mortality. In 2014, Lin and colleagues reported a 19-year evaluation of 55 cirrhotic patients who underwent cardiac surgery. In this study, the in-hospital mortality rate of 16.4% was independently associated by preoperative serum bilirubin and if they underwent CABG. However, MELD score failed to predict the overall mortality (105).

Despite low median MELD scores, our study reconfirms the above reports by showing high in-hospital and overall mortality rates in patients with liver cirrhosis after cardiac surgeries. However, our propensity matched study design allowed us to compare the outcomes with a matched control population. In addition, the

relatively larger cohort size (n = 60) in our study further emphasizes the observed magnitude of mortality in the cirrhotic population.

5.3 Association between Cirrhosis and Postoperative Outcomes

Postoperative complications and associated mortality are more likely in cirrhotic patients undergoing surgery. The observed complications include: (1) *elevated portal hypertension*, and the resultant new onset ascites or aggravation of existing ascites, liver failure, coagulopathy, upper GI bleeding, acute renal failure, hepatorenal syndrome and hepatic encephalopathy; (2) *surgical wound complications* such as infection, dehiscence, eventration, fistulation, abscess formation and surgical site bleeding; and (3) *other system complications* such as pneumonia/ARDS, ventilation dependence, chronic obstructive pulmonary disease exacerbation, chronic heart failure, arrhythmia, myocardial infarction, UTI, paralytic ileus, pulmonary embolism and death (106).

In general, cardiac surgeries are high-risk surgeries with higher likelihood for complications in the context of cirrhosis. Several studies have shown the association between cirrhosis and serious postoperative complications including mortality, after cardiac surgery. A retrospective analysis by Hayashida *et al* of 18 cirrhotic patients reports the association between cirrhosis and development of major postoperative complications such as infection, gastrointestinal bleeding, pleural effusion, renal and respiratory failure after cardiac surgery in patients with any degree of cirrhosis. All CTP class B and C patients showed complications and

higher mortality in the end (15). Another retrospective case analysis in 2005 reports sternal wound infections, hepatic decompensation, bacteremia and massive bleeding in post cardiac surgery patients with advanced liver disease (107). Occurrence of pulmonary, renal and infectious complications were also reaffirmed in two other retrospective cohort studies in 2011 (108) and 2013 (109). More recently, a systematic review in 2015 demonstrates that presence of cirrhosis was associated with higher incidence acute kidney injury and sepsis in addition to the above mentioned complications following cardiac surgery (1). However, neither of the above mentioned studies have a matched control population. In our study, we compare patients undergoing cardiac surgery with propensity matched controls, and show that increased mortality in patients undergoing cardiac surgery was associated with the presence of cirrhosis. We demonstrate that having a diagnosis of cirrhosis increases the odds of overall death by 2.2 times in patients undergoing cardiac surgery. Preoperative cirrhosis was also associated with increased incidence rates of postoperative complications such as cardiac arrest, pneumonia, pleural effusion and acute kidney injury.

Consequent to greater incidence of postoperative complications in the cirrhotic post cardiac surgery population, existing literature consistently reports longer in-hospital and ICU stays and greater health care expenditure in these patients (110-112). This was reaffirmed by our study by recording significantly longer in-hospital and ICU stays for cirrhotic patients compared to non-cirrhotic controls. The requirement of special postoperative needs such as prolonged mechanical

ventilation and RRT after cardiac surgery probably prolonged their in-hospital and ICU stay.

5.4 Independent Association between Predicting Factors and Increased Mortality in Cirrhosis

Several studies have shown that factors such as Euroscore, MELD score, central venous pressure, preoperative bilirubin and CABG status were independently associated with increased mortality in cirrhotic patients undergoing cardiac surgeries. In 2012, Arif *et al* showed that Euroscore and MELD score were associated with increased overall mortality in cirrhotic patients undergoing CPB requiring cardiac surgeries (113). A year later, Lopez *et al* demonstrated that central venous pressure was also independently associated with short-term mortality in cirrhotic cardiac surgery patients (104). In a later report, Lin and colleagues showed that preoperative bilirubin and CABG status were independently associated with early and late mortality outcomes (105). Our study, on the other hand, failed to show association between mortality and any of the above predicting factors.

Charlson comorbidity index, on the other hand, has not consistently shown strong association with mortality in cirrhotic patients following cardiac surgery. For instance, the study by Jepsen et al on Danish cirrhosis patients demonstrated that, after excluding liver disease, CCI was strongly associated with increased mortality in the first year of being diagnosed with cirrhosis (93). On the contrary,

at least two other studies which evaluated mortality rates in cardiac surgery undergoing cirrhotic patients were unable to demonstrate a relationship between CCI and overall mortality (114, 115). Nonetheless, in our analysis, CCI was independently associated with overall mortality post cardiac surgery, after adjusting for the presence of cirrhosis. An additional observation made in our study was that patients with cirrhosis who had an intraoperative necessity for blood products were at greater risk for increased mortality overall. This was in agreement with a report in 2008 that showed independent association between the need for blood transfusion and increased mortality after cardiac surgery (116).

Hence, patients with cirrhosis and heart disease constitute a challenging population to cardiac surgeons. In order to improve the quality of life in patients with any degree of cirrhosis and concomitant heart disease, it is crucial to recognize the basic principles in the assessment, screening and treatment of patients in this high risk population. We suggest that early diagnosis of cirrhosis in heart disease patients, proper treatment of comorbidities and close monitoring of liver function using MELD score prior to surgery would improve the long-term mortality after cardiac surgery in patients with cirrhosis.

5.5 Limitations

The results of this study need to be considered within the context of the following limitations.

(1) Our study was a single centered and retrospective study potentially introducing sources of bias.

(2) In our institution, the decision to perform cardiac surgeries are made based on the cardiac surgeon's discretion and not based on standardized guideline. The majority of the cirrhotic patients undergoing cardiac surgery had low MELD scores (only 9 patients out of 60 with MELD > 20) which may be appropriate in the surgical setting, but may also introduce selection bias. To try and limit selection bias, we performed propensity score matching with non-cirrhotic patients (117).

(3) One of the limitations of the retrospective studies is a lack of sufficient data of recorded information in the medical charts. Even though data for the outcome variables of interest were available most cases, some preoperative clinical variables were missing.

Despite these limitations, we report one of the largest series of cirrhotic patients undergoing cardiac surgery (n=60) and believe that these results build on the current literature.

5.6 Future directions

Our study is single centered and understandably this places limits to the generalizability of our study results. We propose to address this in the future by expanding the study to include multiple participating centers in the presence of accepted consensus guidelines. This will increase the number of study participants across different geographic locations and offer scope for a balanced interpretation

of our results. In the subgroup analysis part of our study, patient information was reviewed retrospectively using patient charts as our source of data for study variables of interest. In this process, many-a-time, we were faced with unavailability or incompleteness of recorded information. A prospective study design will effectively circumvent these shortcomings and warrants future prospective trials with larger patient populations.

Chapter Six: Conclusion

This propensity matched study demonstrated that cirrhotic patients undergoing major cardiac surgeries have high mortality (40%). Preoperative cirrhosis was independently associated with an adjusted odds of 2.2 times increase in post-surgical mortality after adjusting for significant covariates (CCI: aOR 1.4). Identifying more refined cut-offs regarding severity of liver disease and medical comorbidity warrants further investigation.

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Appendix

Propensity matching of study cohorts:

Detailed output with balance statistics to assess achieved balance on observed covariates:

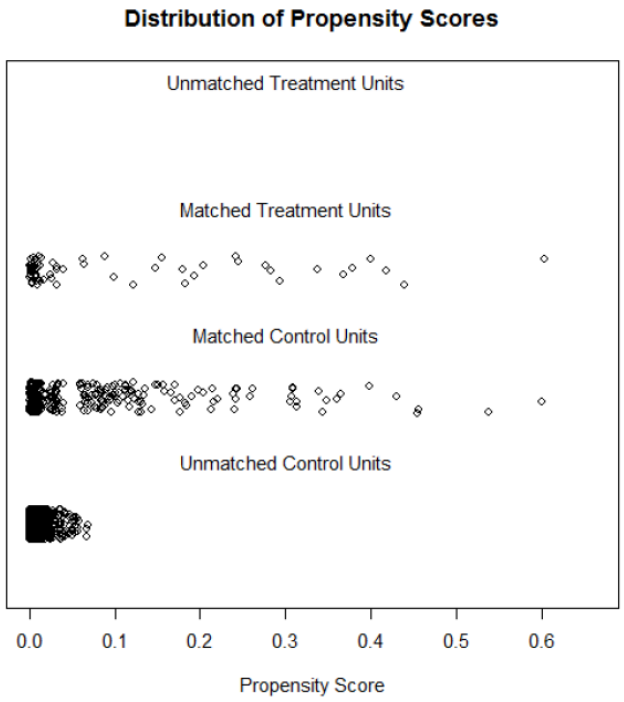
		Means Treated		Means Control		SD Control		Std. Mean Diff.	
Subsamples	Covariates	Before	After	Before	After	Before	After	Before	After
(all cases)	propensity	.100	.100	.004	.066	.018	.099	.664	.236
	sex0	.290	.290	.251	.297	.434	.458	.085	-.014
	sex1	.710	.710	.749	.703	.434	.458	-.085	.014
	priority1	.097	.097	.051	.081	.221	.273	.152	.054
	priority2	.468	.468	.388	.419	.487	.494	.158	.096
	priority3	.355	.355	.462	.365	.499	.482	-.223	-.020
	priority4	.081	.081	.096	.135	.295	.343	-.058	-.200
	srg_type2	.032	.032	.073	.029	.261	.168	-.231	.018
	srg_type3	.161	.161	.105	.110	.306	.313	.152	.139
	srg_type4	.226	.226	.156	.261	.363	.440	.165	-.084
	srg_type5	.081	.081	.064	.058	.244	.234	.062	.082
	srg_type8	.048	.048	.061	.045	.240	.208	-.060	.015
	srg_type9	.048	.048	.024	.045	.153	.208	.113	.015
	srg_type10	.016	.016	.002	.029	.041	.168	.113	-.102
	srg_type11	.065	.065	.016	.068	.125	.252	.196	-.013
	srg_type13	.048	.048	.032	.052	.176	.222	.076	-.015
	srg_type14	.000	.000	.003	.000	.053	.000	.	.
	srg_type15	.000	.000	.012	.000	.108	.000	.	.
	srg_type26	.016	.016	.001	.029	.032	.168	.119	-.102
	srg_type27	.000	.000	.003	.000	.059	.000	.	.
	srg_type29	.000	.000	.011	.000	.104	.000	.	.
	incidence2	.177	.177	.077	.187	.267	.391	.260	-.025
	incidence3	.016	.016	.021	.035	.142	.185	-.035	-.152

		Means Treated		Means Control		SD Control		Std. Mean Diff.	
Subsamples	Covariates	Before	After	Before	After	Before	After	Before	After
	hypertension1	.581	.581	.747	.568	.434	.496	-.335	.026
	hyperlipidemia1	.645	.645	.859	.600	.348	.491	-.444	.094
	diabetes_type_11	.000	.000	.010	.000	.102	.000	.	.
	diabetes_type_21	.290	.290	.282	.252	.450	.435	.017	.085
	smoking5	.258	.258	.258	.281	.438	.450	.000	-.051
	smoking6	.419	.419	.241	.410	.428	.493	.359	.019
	smoking7	.274	.274	.425	.248	.494	.433	-.334	.057
	prior_infarction1	.371	.371	.412	.339	.492	.474	-.085	.066
	prior_pci1	.065	.065	.139	.071	.346	.257	-.301	-.026
	prior_cabg1	.048	.048	.034	.032	.180	.177	.068	.075
	heart_failure1	.258	.258	.156	.216	.363	.412	.231	.095
	peripheral_vascular1	.113	.113	.063	.077	.243	.268	.157	.111
	cerebrovascular1	.113	.113	.119	.090	.324	.287	-.020	.071
	dialysis1	.048	.048	.015	.042	.123	.201	.152	.030
	pulmonary1	.484	.484	.328	.461	.469	.499	.310	.045
	malignancy1	.032	.032	.035	.039	.183	.193	-.014	-.036
	liver_disease1	.371	.371	.010	.319	.097	.467	.742	.106
	gi_disease1	.355	.355	.225	.319	.417	.467	.270	.074
	age_at_surgery	54.430	54.430	63.589	52.473	13.721	17.079	-.683	.146

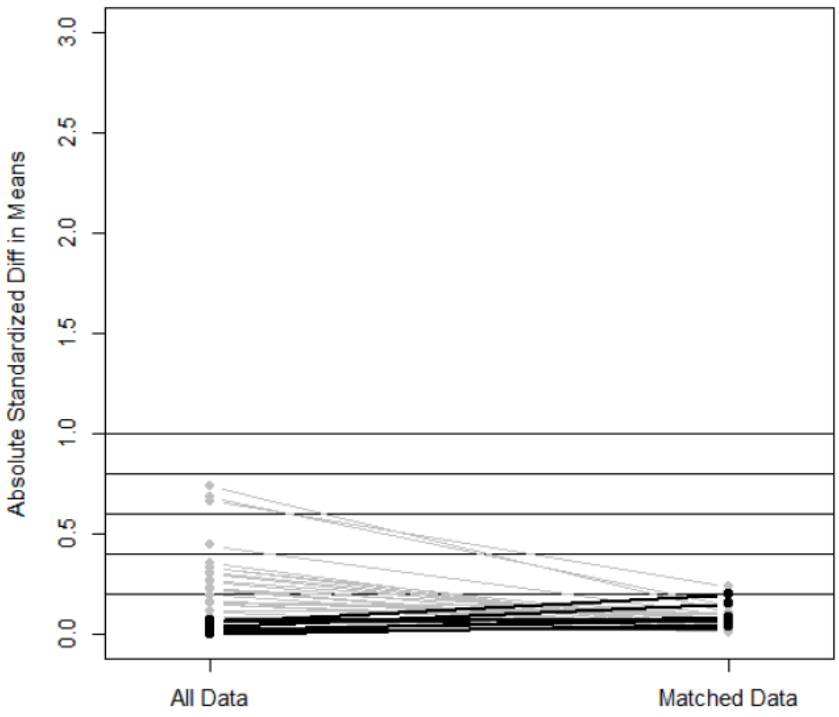
Diagnostic plots of covariates balance:

The following plots were produced and are displayed to show the covariates balance. The covariate balance was massively improved in the matched sample.

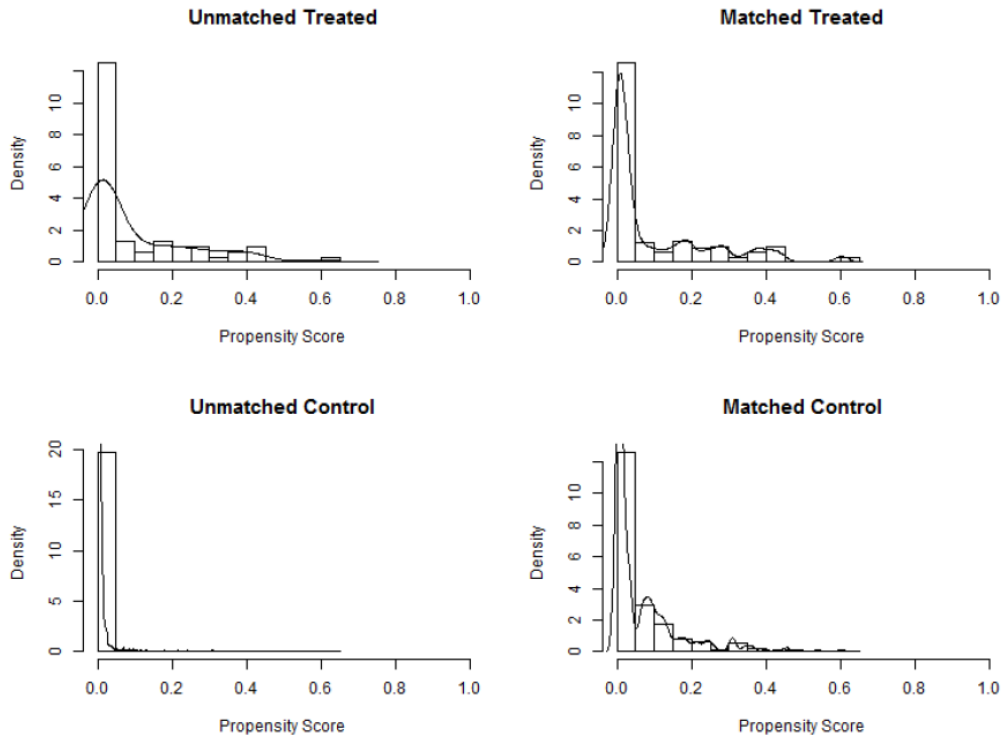
1. Dot plot of distribution of propensity scores before and after matching in both cohorts: Matches had chosen using 5:1 nearest neighbor matching on propensity score. Black dots indicate matched individuals; grey unmatched individuals. This figure explains adequate overlap of the propensity scores, with a good control match for each treated individual.



2. Line plot of standardised differences in means of covariates before and after matching: The standardized differences of means give us a quick overview of whether balance has improved for individual covariates. This figure shows the standardized difference of means of each covariate has decreased after matching.



3. Actual propensity score distributions of both groups before and after matching overlaid with a kernel density estimate :



4. Histograms with density estimates of standardized differences before and after matching: