



The impact of cirrhosis in patients undergoing cardiac surgery: a retrospective observational cohort study

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Abstract

Purpose Patients with cirrhosis and concomitant coronary/valvular heart disease present a clinical dilemma. The therapeutic outcome of major cardiac surgery is significantly poorer in patients with cirrhosis compared with patients without cirrhosis. To address this, we aimed to identify associations between the severity of cirrhosis and post-cardiac surgical outcomes.

Methods A historical cohort analysis of patients undergoing cardiac surgery at the University of Alberta Hospital from January 2004 to December 2014 was used to identify and propensity score-match 60 patients with cirrhosis to 310 patients without cirrhosis. The

relationships between cirrhosis and i) mortality, ii) postoperative complications, and iii) requirement of healthcare resources were evaluated.

Results Ten-year mortality was significantly higher in cirrhotic patients compared with propensity score-matched non-cirrhotic patients (40% vs 20%; relative risk [RR], 2.0; 95% confidence interval [CI], 1.3 to 2.9; $P = 0.001$). Cirrhotic patients had more complications (63% vs 48%; RR, 1.3; 95% CI, 1.05 to 1.7; $P = 0.02$), longer median [interquartile range (IQR)] intensive care unit stays (5 [3–11] vs 2 [1–4] days; $P < 0.001$), time on mechanical ventilation (median [IQR] 2 [1–5] vs 1 [0.5–1.2] days; $P < 0.001$) and more frequently required renal replacement therapy (15% vs 6%; RR, 2.5; 95% CI, 1.2 to 5.2; $P = 0.02$) postoperatively. After adjusting for other covariates, presence of cirrhosis (adjusted odds ratio, 2.2; 95% CI, 1.1

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to 4.1) and intraoperative transfusion (adjusted odds ratio, 3.2; 95% CI, 1.6 to 6.3) were independently associated with increased mortality.

Conclusion Despite having low median model for end-stage liver disease scores, this small series of cirrhotic patients undergoing cardiac surgery had significantly higher mortality rates and required more organ support postoperatively than propensity score-matched non-cirrhotic patients. *Impact de la cirrhose chez les patients subissant une chirurgie cardiaque : une étude de cohorte observationnelle et rétrospective*

Résumé

Objectif Les patients atteints de cirrhose et de coronaropathie et/ou valvulopathie concomitante posent un dilemme clinique. Le pronostic thérapeutique d'une chirurgie cardiaque majeure est significativement moins bon chez les patients atteints de cirrhose comparativement aux patients ne souffrant pas de cette condition. Nous avons par conséquent tenté d'identifier les associations entre la sévérité de la cirrhose et l'évolution post-chirurgie cardiaque.

Méthode Une analyse de cohorte historique des patients ayant subi une chirurgie cardiaque à l'Hôpital de l'Université de l'Alberta entre janvier 2004 et décembre 2014 a été utilisée afin d'identifier et d'apparier par score de propension 60 patients atteints de cirrhose à 310 patients ne souffrant pas de cirrhose. Les liens entre la cirrhose et i) la mortalité, ii) les complications postopératoires, et iii) les besoins en ressources de soins de santé ont été évalués.

Résultats La mortalité à dix ans était significativement plus élevée chez les patients cirrhotiques comparativement aux patients non cirrhotiques appariés par score de propension (40 % vs 20 %; risque relatif [RR], 2,0; intervalle de confiance [IC] 95 %, 1,3 à 2,9; $P = 0,001$). Les patients cirrhotiques ont subi davantage de complications (63 % vs 48 %; RR, 1,3; IC 95 %, 1,05 à 1,7; $P = 0,02$), des séjours médians [écart interquartile (ÉIQ)] plus longs à l'unité de soins intensifs (5 [3–11] vs 2 [1–4] jours; $P < 0,001$), un temps médian sous ventilation mécanique plus long ([ÉIQ] 2 [1–5] vs 1 [0,5–1,2] jours; $P < 0,001$) et ont nécessité un traitement substitutif de l'insuffisance rénale plus fréquemment (15 % vs 6 %; RR, 2,5; IC 95 %, 1,2 à 5,2; $P = 0,02$) en période postopératoire. Après avoir ajusté les résultats pour tenir compte des autres covariables, la présence de cirrhose (rapport de cotes ajusté, 2,2; IC 95%, 1,1 à 4,1) et de transfusion peropératoire (rapport de cotes ajusté, 3,2; IC 95 %, 1,6 à 6,3) était indépendamment associée à une mortalité accrue.

Conclusion Malgré le fait qu'elle ne résultait qu'en un modèle médian bas pour les scores d'insuffisance hépatique

terminale, cette petite série de patients cirrhotiques subissant une chirurgie cardiaque a démontré des taux de mortalité significativement plus élevés et un besoin accru de support des fonctions physiologiques en période postopératoire par rapport aux patients non cirrhotiques appariés par score de propension.

Cardiac surgery in patients with end-stage liver disease (cirrhosis) presents a significant challenge.¹ Previous uncontrolled studies have shown that cirrhotic patients have high rates of postoperative morbidity and mortality.^{2–4} Nutritional compromise, immune system dysfunction, coagulopathy, acute kidney injury, and cirrhotic cardiomyopathy have been postulated to explain this.^{1,2,5} Surgeons traditionally have been hesitant to perform elective cardiac surgery in patients with advanced liver disease that may preclude future liver transplantation eligibility and long-term survival.^{6,7}

It has been empirically agreed that cardiac surgery is contraindicated in patients with end-stage liver disease because of high mortality after cardiac surgery. Post-cardiac surgical outcomes in cirrhotic patients have been shown to be poorer in patients with high Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores. In existing practice, CTP class B/C and MELD score > 12 –14 were associated with high early and late mortality following cardiac surgery using cardiopulmonary bypass in patients with cirrhosis.^{8–14} Identification and careful evaluation of risk factors that predict the outcomes following cardiac surgery may reduce serious postsurgical complications.

Accordingly, in this study we aimed to describe (i) survival following cardiac surgery, (ii) pre/perioperative factors that were independently associated with increased mortality, and (iii) the association between severity of liver disease and post-cardiac surgical outcomes.

Methods

Study setting and population

Our cohort included 370 patients who were greater than 17 yr of age who were admitted to the adult cardiovascular surgical intensive care unit (CVICU) following cardiac surgery with cardiopulmonary bypass (CPB) from January 2004 to December 2014 at the Mazankowski Alberta Heart Institute, University of Alberta. Patients undergoing heart transplantation and pediatric patients were excluded (Figure).

Data sources and collection

Data were collected from the 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.^{15,16} It provides detailed patient information which includes demographics, medical, surgical, and postoperative clinical parameters. Preoperative and intraoperative variables were reviewed, and postoperative variables and complications were extracted using the Society of Thoracic Surgeons database definitions. Mortality information was obtained via quarterly data linkage with the Alberta Bureau of Vital Statistics.¹⁷

Patients were defined as having cirrhosis by radiological evidence (cirrhotic nodular liver on ultrasound, reversal of flow), pathological evidence (scarring/fibrosis on liver biopsy), or evidence of complications of cirrhosis such as ascites, esophageal/gastric varices, hepatic encephalopathy, or spontaneous bacterial peritonitis in the patient record. Coding of the cirrhosis diagnosis was in agreement with the International Classification of Diseases-9-clinical modification. Data on etiology and complications of cirrhosis, MELD, comorbidities before surgery, and relevant clinical laboratory parameters during, before, and after surgery for 60 cirrhotic patients were abstracted from medical charts. The MELD score was calculated according to the 2016 United Network for Organ Sharing/Organ Procurement and Transplantation Network policy.^{18,19} This study was approved by the University of Alberta Health Research Ethics Board (Pro00038965).

Outcomes

The primary outcomes of interest for our study were one-year, five-year, and ten-year mortalities. Our secondary outcomes of interest included in-hospital mortality, a composite of major postoperative complications, individual complications including cardiac tamponade, atrial fibrillation, prolonged mechanical ventilation (> 24 hr), pleural effusion, acute kidney injury, nosocomial infection, gastrointestinal hemorrhage or ischemia, delirium, resuscitated cardiac arrest, and reoperation. Other secondary outcomes included *health resource utilization*, which included chest tube insertion, CVICU length of stay, and renal replacement therapy.

Statistical analyses

Statistical analysis was carried out using Stata version 13.0 for Windows (StataCorp LP, College Station, TX, USA). Continuous variables were described as median

[interquartile range (IQR)] and mean (standard deviation) depending on the results of normality testing. Univariate analyses for categorical variables were analyzed with conditional logistic regression. Continuous variables were tested with the Wilcoxon sign rank test for non-normally distributed variables and the paired t test for normally distributed variables. We performed a propensity score-matched analysis of cirrhotic and non-cirrhotic patients to obtain a comparable distribution of demographics, comorbidities, preoperative, operative, and postoperative clinical variables using the Rosenbaum and Rubin propensity score-matching method.²⁰ The propensity score was calculated as the probability of having cirrhosis on the observed baseline characteristics. This method allows for a high number of confounding variables and hence was used to create strata of subjects who were propensity matched, meaning exposure (i.e., cirrhosis) would be conditionally independent of measured baseline covariates. The propensity score was calculated using logistic regression.

Age, sex, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, gastrointestinal disease, renal disease, diabetes mellitus, dialysis, hypertension, hyperlipidemia, malignancy, peripheral vascular disease, present/previous smoker, previous myocardial infarction, previous coronary artery bypass surgery, previous percutaneous coronary intervention, priority of surgery, incidence of surgery, and type of cardiac surgery were the variables included in the model. These variables were selected based on known clinical or statistical differences between the unmatched cohorts. Charlson comorbidity index (CCI) was not included in the propensity matching (refer to eAppendix 1 as Electronic Supplementary Material [ESM]). Greedy matching techniques were applied to select the patients in the non-cirrhotic group to cirrhotic by matching the patients with the nearest propensity score (i.e., within three decimal places of the propensity score) for each case. Overlap of propensity scores between patients in both cohorts were evaluated using histograms, χ^2 values, and probability values. Differences in baseline factors between groups were calculated before and after propensity score-matching adjustment to assess balance.²¹ No covariate exhibited a large imbalance (standardized difference > 0.25). After the match, conditional logistic regression and Wilcoxon sign rank tests were used to determine if the intraoperative variables that were not accounted for in the propensity score matching were statistically significant between cirrhotic and non-cirrhotic patients that underwent cardiac surgery.

To adjust for other covariates not accounted for in propensity matching, multivariable conditional logistic regression analysis was used to determine the association

between cirrhosis and mortality. Covariates were included based on a P value < 0.10 from univariable analysis. After exclusion of collinear, non-significant, and non-clinically important variables, the final model was built using a purposeful selection method. Results were reported as unadjusted and adjusted odds ratio (aOR) with 95% confidence interval (CI) and P value < 0.05 . The final model performance was estimated using the area under the receiver operator curve (AUROC). Kaplan–Meier survival analysis was used to evaluate long-term survival time stratified between cirrhotic and non-cirrhotic patients (log rank test).

Results

In our final study population, a total of 60 cirrhotic patients were propensity score-matched, in a ratio of approximately 1:5, to 310 non-cirrhotic patients undergoing cardiac surgery. The cirrhotic and non-cirrhotic patient cohorts were well balanced for age, sex, body mass index, and clinical and preoperative variables (Table 1). Operative variables shown in Table 2 were also balanced between the two patient cohorts in terms of surgical priority, procedures, and incidence. Cirrhotic patients had significantly longer median [IQR] CPB time (128 [99–200] vs 116 [83–161] min; $P = 0.02$) and were more likely to receive two or more units of blood (57% vs 38%; relative risk [RR], 1.5; 95% CI, 1.2 to 1.9; $P = 0.03$) or median [IQR] transfusions (58% vs 43%; RR, 1.4; 95% CI, 1.05 to 1.73; $P = 0.03$) during surgery (red blood cell, 1 [0–3] vs 0 [0–1]; $P < 0.001$; fresh frozen plasma, 0 [0–2] vs 0 [0–0]; $P = 0.003$; and platelets, 0 [0–1] vs 0 [0–1]; $P = 0.02$).

Clinical outcomes

The mortality rates for one year (22%, $n = 13$ vs 8%, $n = 24$; RR, 2.8; 95% CI, 1.5 to 5.2; $P = 0.002$), five years (37%, $n = 22$ vs 18%, $n = 55$; RR, 2.1; 95% CI, 1.4 to 3.1; $P = 0.001$) and ten years of follow-up (40%, $n = 24$ vs 20%, $n = 63$; RR, 2; 95% CI, 1.3 to 2.9; $P = 0.001$) in patients undergoing cardiac surgery were significantly higher in cirrhotic patients compared with propensity score-matched non-cirrhotic controls (see Table 3). Stated otherwise, patients with cirrhosis had 41 deaths per 1,000 patient-years compared with 28 deaths per 1,000 patient-years of follow-up in non-cirrhotics. In-hospital mortality was also higher in cirrhotic patients compared with controls (15% vs 5% in controls, RR, 3.1; 95% CI, 1.4 to 6.8; $P = 0.05$). Nevertheless, there was no significant difference between cirrhotic patients and non-cirrhotic patients in terms of 30-day mortality. A composite of major postoperative complications (eAppendix 2 as ESM) occurred more

commonly in patients with liver cirrhosis vs controls (63% vs 48%, RR, 1.3; 95% CI, 1.05 to 1.7; $P = 0.02$). Cirrhotic patients were significantly more likely to develop cardiac arrest (8.3% vs 1.3%; RR, 6.5; 95% CI, 1.8 to 23.4; $P = 0.006$), pneumonia (23.3% vs 9.7%; RR, 2.4; 95% CI, 1.4 to 4.3; $P = 0.004$), pleural effusion (15% vs 5%; RR, 2.9; 95% CI, 1.4 to 6.3; $P = 0.009$), and acute kidney injury (21.7% vs 7.7%; RR, 2.8; 95% CI, 1.5 to 5.2; $P = 0.001$). They were also more likely to require chest tube insertion (10% vs 3%; RR, 3.1; 95% CI, 1.2 to 8.2; $P = 0.02$), prolonged (more than 24 hr) mechanical ventilation (33% vs 22%; RR, 1.5; 95% CI, 1.01 to 2.3; $P = 0.05$), and renal replacement therapy (15% vs 6%; RR, 2.5; 95% CI, 1.2 to 5.2; $P = 0.02$) postoperatively. Cirrhotic patients remained in the intensive care unit (ICU) postoperatively for significantly longer median [IQR] days than non-cirrhotic controls (5 [3–11] vs 2 [1–4] days; $P < 0.001$). Cumulative survival amongst cirrhotic patients at one, five, and 10 years was significantly lower than controls (log rank, 0.01)

Multivariable conditional logistic regression was performed to adjust for potential confounders in the final model. The results of this analysis are provided in Table 4. After adjusting other covariates in the model, cirrhosis (aOR, 2.2; 95% CI, 1.1 to 4.1), and any intraoperative transfusions (aOR, 3.2; 95% CI, 1.6 to 6.3) were independently associated with increased overall mortality. The final model performance was estimated by AUROC and was 0.71.

Predictors of survival in cirrhotic patients undergoing cardiac surgery

Univariable analysis was performed on 60 patients with cirrhosis to compare the results between survivors and non-survivors (eAppendix 2 as ESM). Overall, the median [IQR] MELD score in these cirrhotic patients was low (11 [9–18]), indicating that cardiac surgery was performed in patients with less advanced liver disease. In comparing survivors, non-survivors were significantly older [mean (SD) years, 59.5 (12.5) vs 50.7 (13.0); $P = 0.01$] and had a higher prevalence of preoperative ascites (45.8% vs 13.9%; RR, 1.3; 95% CI, 1.05 to 1.7; $P = 0.008$), a higher median [IQR] MELD score (12.1 [8.6–20.3] vs 8.8 [4.4–15.4]; $P = 0.03$), a higher median [IQR] CCI (5 [3–7] vs 2 [1–3]; $P < 0.001$), and a higher median [IQR] creatinine (108 [83–144] vs 79 [58–93]; $P < 0.001$) preoperatively. In addition, they had significantly longer median [IQR] ICU days (10.5 [4.5–25] vs 4 [2–5]; $P < 0.001$) and in-hospital days (32 [18–51] vs 9 [6–14]; $P < 0.001$) and required more organ support, which included vasopressors (87.5% vs 61.1%; RR, 1.4; 95% CI, 1.06 to 1.9; $P = 0.03$), median [IQR] days of mechanical ventilation (5 [2–18] vs 2 [1–2]; $P = 0.004$),

Table 1 Clinical and preoperative characteristics of cirrhotic patients and non-cirrhotic controls

Variables	<i>n</i>	Cirrhosis	<i>n</i>	Non-cirrhosis	<i>P</i> value	Standardized difference
Age	60	54 (13.4)	310	52.5 (17)	0.44	0.15
Male sex	60	42 (70)	310	218 (70)	0.91	0.14
BMI	45	27.4 [24–32]	236	28.4 [25–33]	0.13	
Medical history						
Hypertension	60	35 (58.3)	310	176 (56.8)	0.82	0.03
Dyslipidemia	60	38 (63.3)	310	186 (60)	0.61	0.09
Type 2 diabetes	60	16 (26.7)	310	78 (25.2)	0.79	0.08
Prior MI	60	22 (36.7)	310	105 (33.8)	0.69	0.06
Prior PCI	60	4 (6.7)	310	22 (7.1)	0.92	– 0.03
Prior CABG	60	3 (5)	310	10 (3.2)	0.52	0.08
Heart failure	60	16 (26.7)	310	67 (21.6)	0.41	0.09
NYHA class					0.80	
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)	0.84	0.02
Preoperative renal failure	60	3 (5)	310	13 (4.2)	0.82	
CCI	60	3 [1–5]	310	2 [1–4]	0.11	
MELD	38	11 [9–18]	-	-	-	
Preoperative investigations						
Extent of coronary artery disease (> 75%)					0.53	
One or two VD	60	6 (10)	310	30 (9.7)		
Three VD	60	13 (21.7)	310	61 (19.7)		
Left main artery	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, %					0.22	
> 50%	60	9 (27.3)	310	81 (26.13)		
> 35–50%	60	8 (24.2)	310	44 (14.2)		
> 20–34%	60	2 (6.1)	310	12 (3.9)		
< 20%	60	1 (3)	310	0		
Not available	60	37 (61.7)	310	173 (55.8)		

Age is presented as mean (standard deviation). Other values are presented as median [interquartile range] and proportion (percentage). BMI = body mass index; CABG = coronary artery bypass graft; CCI = Charlson comorbidity index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MELD = model for end-stage liver disease; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; VD = vessel disease.

and renal replacement therapy (45.8% vs 2.8%; RR, 16.5; 95% CI, 2.3 to 119.6; $P < 0.001$) compared with survivors. Causes of death for the nine cirrhotic patients who died in hospital post-cardiac surgery were multiorgan failure ($n = 3$), hemorrhage/bleeding ($n = 2$), neurological failure ($n = 2$), postoperative surgical complications ($n = 1$), and intra-abdominal sepsis ($n = 1$).

Discussion

Key findings

In this propensity score-matched cohort analysis of patients undergoing cardiac surgery, the ten-year mortality was significantly higher in cirrhotic patients compared with

Table 2 Operative variables in patients with and without cirrhosis

Variables:	<i>n</i>	Cirrhosis	<i>n</i>	Non-cirrhosis	<i>P</i> value	Standardized difference
Operative variables						
Surgical priority					0.26	
Emergent	60	6 (10)	310	25 (8.1)		0.05
Urgent in hospital	60	27 (45)	310	130 (42)		0.09
Urgent out of hospital	60	22 (36.7)	310	113 (36.5)		− 0.02
Non-urgent out of hospital	60	5 (8.3)	310	42 (13.6)		0.01
Surgical incidence					0.54	
First operation	60	48 (80)	310	240 (77.7)		
Second operation	60	11 (18.3)	310	58 (18.8)		0.26
Third or greater	60	1 (1.7)	310	11 (3.6)		− 0.03
Surgery					0.46	
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	60	128 [99–200]	310	116 [83–161]	0.02	
Aortic cross-clamp time	60	82 [48–115]	310	75 [46–115]	0.14	
Any transfusion	60	35 (58)	310	134 (43)	0.03	
Number of blood products						
One	60	1 (2)	310	16 (5)		
Two or more	60	34 (57)	310	118 (38)		
No transfusion	60	25 (41)	310	176 (57)		
Intraoperative RBC	60	1 [0–3]	310	0 [0–1]	0.0001	
Intraoperative FFP	60	0 [0–2]	310	0 [0–0]	0.003	
Intraoperative cryoprecipitate	60	0 [0–0]	310	0 [0–0]	0.08	
Intraoperative platelet	60	0 [0–1]	310	0 [0–1]	0.02	

Values presented as median [interquartile range] and proportion (percentage). CABG = coronary artery bypass graft; FFP = fresh frozen plasma; RBC = red blood cell.

non-cirrhotic controls. Patients with cirrhosis suffered more postoperative complications, required significantly longer stays in the ICU and hospital, and had increased requirements for postoperative organ support. Cirrhosis was also independently associated with increased post-cardiac surgical mortality.

Comparison with previous literature

Previous observational studies have shown that cirrhotic patients undergoing cardiac surgery have increased mortality. A 2010 systematic review of nine retrospective analyses of 12–44 patients with cirrhosis undergoing a wide range of cardiac operations showed that the overall mortality was 17% with MELD scores of > 13.²² In a retrospective analysis, Vanhuysse *et al.* reported that the in-hospital mortality rate was 26% in 34 patients with a mean

MELD score of 12. Both CTP and MELD scores were associated with an increased postoperative mortality.²³ In a retrospective cohort study from 2013, Morimoto *et al.* reported that the number of deaths in hospital following cardiac surgery in 32 patients with liver disease was 15.6% with an average mean (standard deviation) MELD score of 11.5 (5.1).²⁴ A prospective study in the same year reported 12% mortality immediately after cardiac surgery in 58 cirrhotic patients with mean MELD scores of 18.²⁵ Both studies affirmed the usefulness of MELD in association with in-hospital mortality. In 2014, Lin and colleagues reported that 55 cirrhotic patients who underwent cardiac surgery over a 19-year period had an in-hospital mortality rate of 16.4% and that preoperative serum bilirubin prior to coronary artery bypass graft (CABG) was independently associated with mortality. Nevertheless, the MELD score failed to predict the overall mortality.²⁶ Despite low

Table 3 Postoperative outcomes and complications in cirrhotic and non-cirrhotic patients

Variables	<i>n</i>	Cirrhosis	<i>n</i>	Non-cirrhosis	<i>P</i> value
Primary outcome					
One-year mortality	60	13 (22)	310	24 (8)	0.002
Five-year mortality	60	22 (37)	310	55 (18)	0.001
Ten-year mortality	60	24 (40)	310	63 (20)	0.001
Secondary outcomes					
In-hospital mortality	60	9 (15)	310	15 (5)	0.05
30-day mortality	60	5 (8.3)	310	12 (3.9)	0.18
CVICU LOS, days	60	5 [3–11]	309	2 [1–4]	<0.001
Any major complications	60	38 (63)	310	148 (48)	0.02
Cardiac complications	60	22 (36.7)	310	87 (28)	0.21
Cardiac tamponade	60	2 (3.3)	310	13 (4.2)	0.80
Reoperation	60	12 (20)	310	69 (22.3)	0.67
Cardiac arrest	60	5 (8.3)	310	4 (1.3)	0.006
Atrial fibrillation	60	14 (23.3)	310	52 (16.8)	0.25
Respiratory complications	60	31 (51.7)	310	85 (27)	<0.001
Intubation days	60	2 [1–5]	310	1 [0.5–1.2]	<0.001
Prolonged ventilation (> 24 hr)	60	20 (33)	310	67 (22)	0.05
Pneumonia	60	14 (23.3)	310	30 (9.7)	0.004
Pleural effusion	60	9 (15)	310	16 (5)	0.009
Chest tube insertion	60	6 (10)	310	10 (3)	0.02
ARDS	60	4 (6.7)	310	18 (5.8)	0.76
Neurological complications	60	2 (3.3)	310	14 (5)	0.65
Delirium	60	2 (3.3)	310	14 (4.5)	0.65
Renal complications	60	14 (23.3)	310	29 (9)	0.003
Acute kidney injury	60	13 (21.7)	310	24 (7.7)	0.001
Postoperative renal replacement therapy	60	9 (15)	310	19 (6)	0.02
Gastrointestinal complications	60	5 (8.3)	310	17 (6)	0.36
Bleeding	60	5 (8.3)	310	13 (4.2)	0.15
Mesenteric ischemia	60	0	310	3 (1)	0.29
Infectious complications	60	4 (6.7)	310	27 (9)	0.80
Superficial wound infection	60	3 (5)	310	14 (4.5)	0.91
Deep sternal wound infection	60	1 (1.7)	310	5 (1.6)	1.00
Harvest site infection	60	1 (1.7)	310	10 (3.2)	0.5
UTI	60	1 (1.6)	310	3 (1)	0.65

Values presented as median [interquartile range] and proportion (percentage). ARDS = acute respiratory distress syndrome; CVICU = cardiovascular intensive care unit; LOS = length of stay; UTI = urinary tract infection.

median MELD scores, our study shows in-hospital and ten-year mortality rates in patients with liver cirrhosis undergoing cardiac surgery were significantly higher than a propensity matched non-cirrhotic control population.

In patients with cirrhosis, cardiac surgery is associated with a higher likelihood of postoperative complications. 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, and

renal and respiratory failure after cardiac surgery.⁹ Another retrospective case analysis in 2005 showed high rates of postoperative sternal wound infections, hepatic decompensation, bacteremia, and massive bleeding in cirrhotic patients.²⁷ Occurrence of pulmonary, renal, and infectious complications were also reaffirmed in two other retrospective cohort studies in 2011²⁸ and 2013.²⁹ More recently, a systematic review in 2015 showed that cirrhosis is associated with a higher incidence of acute kidney injury and sepsis following cardiac surgery.¹ Nevertheless, none

Table 4 Multivariable analysis for the independent association of factors with increased mortality in propensity matched cirrhotic and non-cirrhotic patients

	Univariate			Multivariate AUROC: 0.71		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Cirrhosis	2.7	1.48 to 5.03	0.001	2.2	1.14 to 4.12	0.02
Any transfusion	3.7	2.06 to 6.8	0.0001	3.2	1.64 to 6.3	0.001
Number of blood products	1	1.00 to 1.02	0.03	0.99	0.98 to 1.01	0.86
Cardiopulmonary bypass time	1.004	1.00 to 1.00	0.02	1.001	0.99 to 1.00	0.63

Values reported as unadjusted odds ratio (univariate) and adjusted odds ratio (multivariate) with 95% confidence interval. AUROC = area under the receiver operator curve; CI = confidence interval.

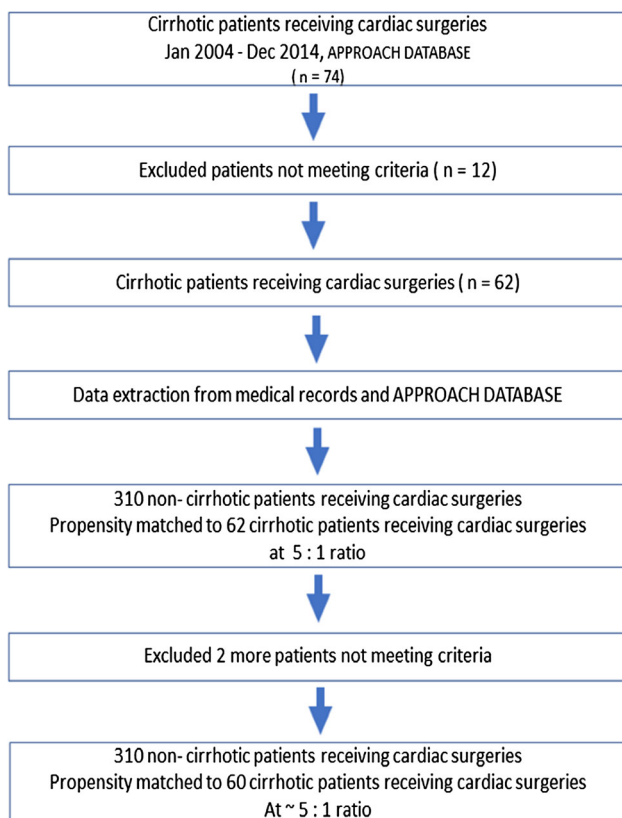


Figure Patient selection flow diagram. APPROACH: Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease.

of the above-mentioned studies included a matched control population. In our propensity score-matched analysis, we showed that cirrhosis was associated with an over two-fold increase in ten-year mortality along with increased incidence rates of postoperative complications such as cardiac arrest, pneumonia, pleural effusion, and acute kidney injury. Potentially as a consequence of increased rates of postoperative complications, existing literature consistently reports longer in-hospital and ICU stays and

greater healthcare expenditure in cirrhotic patients.^{30–32} This was reaffirmed by our study with a matched control cohort by recording significantly longer in-hospital and ICU stays, prolonged mechanical ventilation, and increased requirement for renal replacement therapy in cirrhotic patients compared with non-cirrhotic controls.

Several studies have shown that factors such as Euroscore, MELD, central venous pressure, and CABG status were independently associated with increased mortality in cirrhotic patients undergoing cardiac surgery. In 2012, Arif *et al.* showed that the Euroscore and MELD score were associated with increased overall mortality in cirrhotic patients undergoing CPB requiring cardiac surgery.³³ A year later, Lopez-Delgado *et al.* showed that central venous pressure is also independently associated with short-term mortality in cirrhotic cardiac surgery patients.²⁵ In a later report, Lin *et al.* showed that preoperative bilirubin and CABG status were independently associated with early and late mortality.²⁶ In our study, although the median MELD score for the cirrhosis cohort was low (median ~ 11), the median MELD was higher in non-survivors than in survivors.

An additional observation made in our study was that patients with cirrhosis who had an intraoperative/perioperative necessity for an increased number of blood products were at greater risk for increased ten-year-mortality. This was in agreement with a report in 2008 that showed independent association between the need for blood transfusion and increased mortality after cardiac surgery³⁴ and a large multicentre cohort study in 2014, which described that receiving one or two units of blood was independently associated with increased mortality after on-pump coronary artery bypass surgery.³⁵

Limitations

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

single-centred observational study with a limited sample size. Retrospective studies all include important sources of bias including the likelihood of residual confounding. In our institution, cardiac surgeries are performed based on the cardiac surgeon's discretion and variation in practices may have made our sample prone to selection bias. To control for operator-dependent variables, we performed post hoc analyses to determine if there were statistically significant differences between the cirrhosis/non-cirrhosis perioperative variables (surgeon, pump-time, cross-clamp time, and perioperative transfusions). While there were significant differences between the groups in pump-time and number of transfusions, adjusting for these variables (Table 4) did not significantly alter our findings. The majority of cirrhotic patients undergoing cardiac surgery had low MELD scores (only nine patients out of 60 had MELD scores > 20), which may be appropriate in the surgical setting but may also introduce selection bias. To try and limit selection bias, we performed a propensity score matching with non-cirrhotic patients.³⁶ We did not have data for international normalized ratio, bilirubin, and creatinine in patients without cirrhosis to compare the intraoperative bleeding rates in patients with cirrhosis. We did not have data on patients with cirrhosis who did not undergo cardiac surgery to provide a comparison of long-term survival in patients with cirrhosis who underwent cardiac surgery. Finally, data regarding cause of death in cirrhotic patients who died post-hospital discharge or from the APPROACH database for propensity matched non-cirrhotic controls were unavailable.

Conclusion

This propensity score-matched study shows that cirrhotic patients undergoing cardiac surgery have a 40% ten-year mortality incidence. Cirrhosis was independently associated with a two-fold increase in ten-year mortality after adjusting for covariates. Further research should focus on the identification of clinically important cut-offs of preoperative parameters, which may allow a more accurate prognosis to be presented to patients with cirrhosis who face potential cardiac surgery.

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and Sean van Diepen contributed to study design, and revised the final manuscript. Amanda Ewasiuk, Demetrios J. Kutsogiannis, Derek R. Townsend, and Jayan Negendran revised the final manuscript.

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