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High early cardiovascular mortality following liver transplantation

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Abstract

Cardiovascular disease (CVD) contributes to excess long-term mortality after liver transplantation (LT), however little is known about early post-operative CVD mortality in the current era. In addition, there is no model to predict early post-operative CVD mortality across centers. We analyzed adult recipients of primary LT in the Organ Procurement and Transplantation Network (OPTN) database between February 2002 and December 2012 to assess prevalence and predictors of early (30-day) CVD mortality, defined as death from arrhythmia, heart failure, myocardial infarction, cardiac arrest, thromboembolism, and/or stroke. We performed logistic regression with stepwise selection to develop a predictive model of early CVD mortality. Sex and center volume were forced into the final model, which was validated using bootstrapping techniques. Among 54,697 LT recipients, there were 1576 (2.9%) deaths within 30 days. CVD death was the leading cause of 30-day mortality (42.1%), followed by infection (27.9%) and graft failure (12.2%). In multivariate analysis, 9 (6 recipient, 2 donor, 1 operative) significant covariates were identified: age, pre-operative hospitalization, ICU and ventilator status, calculated MELD score, portal vein thrombosis, national organ sharing, donor BMI and cold ischemia time. The model showed moderate discrimination (c-statistic 0.66, 95% CI: 0.63–0.68). We provide the first multicenter prognostic model for the prediction of early post-LT CVD death, the most common cause of early post-LT mortality in the current transplant era. However, evaluation of additional CVD-related variables not collected by the OPTN are needed in order to improve model accuracy and potential clinical utility.

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DISCLOSURES

The authors of this manuscript have no conflicts of interest to disclose.

Keywords

risk assessment; MELD score; outcomes; heart disease; OPTN

INTRODUCTION

Cardiovascular disease (CVD), as defined by the American Heart Association(1) and includes ischemic heart disease, stroke, heart failure and thromboembolism, is a leading cause of *long-term* complications following liver transplantation (LT)(2). However, it is unknown what role CVD plays in *early* post-transplant mortality, or whether certain features may predict early CVD mortality. In addition, little is known regarding the range of CVD complications that may occur following LT apart from those related to ischemic heart disease. The specific cardiovascular and hemodynamic responses that occur in end-stage liver disease unrelated to traditional coronary risk factors may contribute to increased CVD complications post-transplant(3, 4). Finally, there are liver donor and surgical characteristics, such as donor age or cold ischemic time, which are known to increase the early mortality of the recipient(5). Given the limited availability of donor organs, recipient selection and appropriate monitoring for and prevention of early CVD mortality is of paramount importance(6). Historically, prevalent CVD has been considered a relative, and under certain circumstances absolute, contraindication to LT with estimated post-transplant mortality rates as high as 50%(7). Thus, this study aims to better define early CVD-related mortality and aid in recipient selection and recipient-donor matching in the most recent era of LT.

Among the instruments for clinical risk stratification are decision tools such as the Revised Cardiac Risk Index (RCRI)(8), which uses six variables (history of ischemic heart disease, heart failure, stroke, insulin-dependent diabetes, chronic kidney disease and high risk surgery) to predict cardiac complications after non-cardiac surgery. In addition, both noninvasive (dobutamine stress echocardiography) and invasive (coronary angiography) cardiac tests may be used preoperatively to assist in risk stratification. However, these risk algorithms and tests have poor discriminative ability to predict early cardiac mortality post-LT(9, 10). Current guidelines for preoperative cardiac evaluations before noncardiac surgery are based on studies of patient cohorts not undergoing liver transplantation, so the optimal preoperative cardiac evaluation for liver transplant patients remains unknown(9, 11, 12). Although many studies have reported on the increased incidence of long-term CVD complications following transplantation, few have focused on predictors of early CVD outcomes(13, 14). In addition, despite the high prevalence of cirrhotic cardiomyopathy, studies on early CVD outcomes after LT have predominantly focused on complications of ischemic heart disease(7, 14). Finally, attempts at describing LT-specific CVD risk predictors have been inconsistent in their findings, are limited by single center data with inherent variability in candidate selection, and often predate recent advances in surgical technique and anesthesia (2, 14–16).

Using a large multi-center national database, we hypothesized that there are unique characteristics in end-stage liver disease, and LT-specific risk factors that are associated

with excess early CVD mortality. In the long term, incorporation of these factors into validated risk algorithms may improve patient outcomes and organ utilization.

PATIENTS AND METHODS

Study Population

Adults (age ≥ 18 years) who were listed for LT between February 1, 2002 and December 31, 2012 and who underwent transplantation within the same time period were identified from the Organ Procurement Transplantation Network (OPTN) Standard Transplant Analysis and Research files (created on March 15, 2013, n=56,914). Those listed as status 1 and those who underwent re-transplantation or who received simultaneous heart, lung, intestine or pancreas transplants were excluded (n= 2,217). The Institutional Review Board of Northwestern University approved the study.

Definitions and Outcomes

Recipient cause of death was determined by a physician's review (L.B.V.) of primary and contributory causes of death (including all free text inputs) listed in the OPTN database. Any potential case with death due to CVD, defined as primary cause of death from arrhythmia, heart failure, myocardial infarction, primary cardiac arrest, thromboembolism, and/or stroke, was then manually reviewed by an independent panel of three physicians (2 cardiologists, 1 surgeon) in order to attempt to adjudicate CVD case mortality. The primary study outcome was early (30-day) CVD mortality. This standardized time period was chosen due to its use as a outcomes-based quality indicator(17). The time period also allows a fair assessment of transplant outcomes across centers and minimizes differences in variations in length of post-transplant stay from affecting the measurement. Since some operative factors, such as electrolyte flux, are not captured within the OPTN dataset and may have a differential effect on cardiac events, analyses were also categorized into perioperative CVD mortality, defined as CVD mortality within the first 24 hours of transplant, and early postoperative CVD mortality, defined as CVD mortality occurring between 1 and 30 days. Secondary outcomes included overall patient and graft survival. Patients were censored at time of death, date of last follow up, time of re-transplantation or at 30 days.

Potential risk factors for CVD-related mortality after LT were examined based on *a priori* clinical hypotheses. Covariates included known traditional CVD risk factors (e.g. diabetes status) as well as transplant-specific critical illness indicators known to contribute to competing mortality risk. Recipient risk factors evaluated included age at transplant, sex, race/ethnicity (Black, non-Hispanic White, Asian and Hispanic), socioeconomic status, BMI, etiology of liver disease (including diseases known to increase CVD risk, such as nonalcoholic steatohepatitis (NASH) and hepatitis C), history of comorbid CVD conditions (diabetes, angina, cerebrovascular disease, hypertension, pulmonary embolism, peripheral vascular disease, renal failure), laboratory values at time of transplant (creatinine, albumin, sodium, INR, alanine aminotransferase (ALT), bilirubin), hepatocellular carcinoma (HCC), calculated model for end-stage liver disease (MELD) score at the time of transplant, waitlist time, functional capacity prior to transplant, complications of end-stage liver disease (ascites, encephalopathy, portal vein thrombosis (PVT), etc.), hospitalization and ventilator

status at transplant. Donor risk factors included age, gender, race, BMI, cause of death, donor type (living, deceased, donation after cardiac death), donor risk index, procurement medications (inotropic support, vasopressin, antihypertensives, steroids, thyroid replacement, desmopressin), history of CVD comorbidity (diabetes, hypertension, renal disease, myocardial infarct), and health behaviors (smoking status, alcohol/cocaine/other drug use). Transplant related variables included transplant center location and volume, region, organ allocation type, cold ischemia time (CIT), steroid induction, and use of a calcineurin inhibitor.

Statistical Methods

Clinical characteristics and causes of death of primary LT recipients from the 2002–2012 OPTN dataset were described using frequency counts and percentages for categorical variables and means ± standard deviations for continuous variables. Logistic regression models were first fitted for each variable separately to determine associations with 30-day CVD mortality following LT as the dependent variable. Odds ratios with 95% confidence intervals, as well as their corresponding p-values, are shown. Twenty-two candidate variables that were significant in univariate analysis were entered into a multivariable logistic regression model. Stepwise regression was performed with entry and exit criteria set to p=0.05. Nine covariates were selected for the final model based on significance and additive contribution to the model. Further covariates did not improve model fit. It was determined a priori that center and recipient sex should be forced into the final model. The performance of the logistic regression model was then internally validated using 1000 bootstrap resamples. Bootstrapping is a nonparametric method for assigning measures of accuracy to sample estimates. Bootstrapping essentially resamples (multiple times) from the study population to approximate how precise statistical estimates (e.g. C statistic, confidence intervals) are related to the true population of interest. Kaplan-Meier analysis with log-rank test assessed time to CVD mortality, and all-cause graft and patient survival. All analysis was performed using SAS 9.3 (SAS institute, Cary, NC).

RESULTS

Patient Characteristics

The baseline characteristics of 54,697 orthotopic liver transplant recipients who were included in the final analysis are shown in Table 1. Mean age of the study sample was 54.0 ± 9.5 years, 31% were female, and 73% were non-Hispanic White. All-cause early mortality was 2.9% (n=1576). CVD accounted for 42.1% of all deaths within 30 days, followed by infection (27.9%) and graft failure (12.2%, Figure 1). Mean time to early CVD death was 6.2 ± 8.2 days, with a median of 2.0 days (range 0–30 days). The leading underlying cause of early CVD mortality was cardiac arrest (47.8%), followed by stroke (12.5%), heart failure (12.3%) and pulmonary embolism (9.1%). The prevalence of cardiac arrest as an underlying cause of CVD mortality did not differ significantly between those deaths that occurred perioperatively compared to those that occurred in the early postoperative period (46 vs. 54%, p=0.08). Since a significant proportion of events were coded as cardiac arrest, we also examined secondary causes of death listed in OPTN, which may have significantly contributed to the cardiac arrest (Table 2). There were no significant differences in the

secondary causes of death in those recipients with cardiac arrest versus other causes of early CVD mortality in the 25% of recipients who had a secondary cause of death listed.

Predictors of Early Cardiovascular Disease Mortality

Univariate predictors of early CVD mortality are shown in Table 3. Recipients who died from CVD within 30-days of LT were slightly older (55.3 ± 9.7 vs. 54.0 ± 9.5 years), with higher calculated MELD scores (22.8 vs. 19.0) and a higher prevalence of medical comorbidity (e.g. renal and pulmonary disease) than those without early CVD mortality ($p<0.05$ for all). There were no statistically significant differences in recipient race, ethnicity, sex, or pre-transplant cerebrovascular disease between those with either perioperative or early postoperative CVD mortality and those recipients without early CVD mortality. However, older age, presence of NASH (vs. hepatitis C), and pre-transplant recipient diabetes, hypertension, or chronic obstructive pulmonary disease (COPD) were all more prevalent in recipients with perioperative CVD mortality compared to those without early CVD mortality ($p<0.05$ for all). Donor factors related to early perioperative CVD mortality included higher BMI and greater likelihood of deceased donor donation (versus living donor) and donation after cardiac death ($p<0.05$ for all). These recipient and donor factors did not appear to affect early postoperative outcomes (Table 3). Operative factors included increased cold ischemia time (CIT) where the odds of overall early CVD mortality was 1.04 (95% CI 1.02–1.06) higher for every 1-hour increase in CIT ($p<0.001$). We also examined univariate predictors of cardiac arrest compared to other causes of early CVD mortality (Supplemental Table). Older age and a higher prevalence of pre-transplant diabetes and COPD were seen in recipients with cardiac arrest compared to those without early CVD mortality ($p<0.05$ for all). These factors did not predict non-cardiac arrest early CVD mortality (Supplemental Table). No other significant univariate differences were seen.

Derivation and validation of a liver transplant-specific risk model to predict early CVD mortality

Since both age and sex are known strong predictors of CVD we initially examined the incidence of early CVD-mortality for both males and females using age-adjusted univariate analysis. There was no significant difference in early CVD mortality by sex (data not shown), thus a combined age- and sex-adjusted model is shown. Nine (6 recipient, 2 donor, 1 operative) significant predictors of early CVD mortality were identified: age, hospitalization status, ICU status, respiratory failure on a ventilator, MELD score, history of PVT, national organ sharing (versus local/regional), donor BMI and CIT. Sex and transplant center volume were forced into the final model (Table 4). The model showed moderate discrimination (c-statistic 0.66, 95% CI: 0.63–0.68, after bootstrapping, Table 4). There was no significant interaction between transplant region and predicted risk in our model ($p=0.56$) with regard to CVD mortality, and no significant variation in early CVD events across regions (Table 5). In separate sensitivity analyses, we excluded cardiac arrest, thromboembolism, pulmonary hypertension, stroke or heart failure sequentially from the definition of CVD mortality. The covariates selected for inclusion and fit of the models for prediction of CVD mortality were similar to the main analyses presented above (c-statistic=0.66, 95% CI: 0.64–0.67 for cardiac arrest versus c-statistic=0.65, 95% CI: 0.63–0.68 for non-cardiac arrest CVD mortality). There were also no significant differences noted

in the frequency of the underlying cause of CVD mortality or in the covariates selected for inclusion into the prediction models when further separated into perioperative and early postoperative deaths (Table 3). However, model fit was slightly better for perioperative deaths (c-statistic 0.69, 95% CI: 0.66–0.70) than for early postoperative deaths (c-statistic 0.63, 95% CI: 0.62–0.66).

DISCUSSION

This study provides the first liver transplant-specific prognostic model for the prediction of early postoperative CVD mortality, with moderate model accuracy. We identified 9 (6 recipient, 2 donor, and 1 operative) significant predictors of early (30-day) postoperative CVD mortality independent of transplant center. We also observed that in the current era of liver transplantation CVD is now the leading cause of early mortality accounting for over 40% of early deaths, most of which are related to non-coronary CVD events. This highlights the fact that while we are likely appropriately excluding those at high risk of coronary complications prior to transplant, there remains a large proportion of critically ill patients with limited cardiovascular reserve who enter liver transplantation with resultant poor early outcomes.

Early cardiovascular mortality in the current era of transplantation

A preoperative CVD evaluation is undertaken in all potential LT candidates prior to transplant listing, mainly to screen for significant obstructive coronary artery disease, severe heart failure and/or severe pulmonary hypertension which are considered absolute contraindications to liver transplantation(9). Despite exclusion of these high-risk patients from transplantation, we observed a substantial early post-OLT CVD mortality rate of 1.2%. For comparison, early CVD mortality after other types of intraabdominal surgery ranges from 0.2% (laparoscopic cholecystectomy)(18) to 0.3% (Whipple)(19), and is estimated to be as high as 1.7% after coronary artery bypass grafting following acute MI(20). Small single-center studies in the initial era of LT estimated early post-LT CVD mortality anywhere from 0% to 2.7%(21–24). To our knowledge we are the first to provide a multicenter estimate that may provide more accurate and precise data on the true incidence of CVD-related death in the current era of transplantation.

As a result of the increasing average age at which patients are now being transplanted, prevalent CVD comorbidity at the time of transplantation is expected to rise(25), with adverse effects on post-transplant outcomes(26, 27) Age remained a significant predictor in our multivariate model again highlighting concerns about increased cardiac risk associated with the aging transplant recipient population.

Historically, early mortality after LT has been reported to be primarily due to infection or allograft failure and continues to remain a prevalent cause of early death globally(28, 29). However, we observed that in the present transplant era in the United States, CVD has surpassed infection and graft failure as the leading cause of death following LT. We hypothesize that this is a reflection of both improved anti-infective regimens and surgical techniques over time, and also the increasing critical illness burden, with higher median MELD scores among recipients and the high proportion of ventilator-dependent patients at

the time of transplantation(30). Such patients likely have a high prevalence of subclinical cardiac disease, and a blunted cardiovascular response to the hemodynamic stress of liver transplantation. As an example, using our study population, if a LT recipient had pretransplant respiratory failure (e.g. on a ventilator) the early CVD death rate was 4% compared with 1% in those without respiratory failure. Thus, our results imply that we may need to reevaluate transplantation practices in high MELD, poor functional status, and intensive care unit-bound potential organ recipients in order to maximize the utilization and longevity of scarce donor organs.

Performance of the current risk model in the context of existing risk scores

Commonly used risk indices can be divided into liver-specific (Childs-Turcott-Pugh (CTP) (31) and MELD(32)), general (Simplified Acute Physiology Score (SAPS) II(33) and Acute Physiology and Chronic Health Evaluation (APACHE)(34)) or organ failure (Sequential Organ Failure Assessment (SOFA)(35)) scores, none of which was specifically developed to assess CVD mortality. In addition, the c-statistics range from 0.5–0.6 for pre-transplant calculation of each of the aforementioned indices to predict early post-LT outcomes, and therefore they have overall poor discriminative ability as useful tools in the pre-transplant setting (36–38). The current risk model performs somewhat more robustly (c-statistic=0.66) in a liver transplant population. However, our model is still not optimal for discrimination, and thus is more appropriate for use as a base model for the development of additional CVD-specific risk models with more refined variables than are available within the OPTN database. We note that in our model, several of the variables are related to either donor or operative factors and therefore would not be available in the pre-transplant setting to use as post-transplant predictors. However, knowledge that these factors—donor BMI, national organ sharing, CIT—collectively affect early CVD mortality may serve as a basis for future modeling aimed at maximizing donor-recipient matching in order to impact patient-centered outcomes.

Although we examined strong cardiac risk factors (e.g., diabetes mellitus, hypertension) for inclusion in the model, none of these were significantly associated with 30-day CVD mortality. Our findings are consistent with prior single-center studies that have also failed to demonstrate that traditional clinical CVD risk factors are associated with early mortality among liver transplant recipients (13, 14). However, we did find several unique predictors of CVD-mortality including history of portal vein thrombosis (PVT), higher donor BMI and higher CIT, all of which have been associated with lower overall survival post LT, though not specifically with CVD mortality (39–41). It is plausible that prior PVT may suggest an underlying hypercoagulable state or endothelial dysfunction, which have been associated with acute coronary syndrome(42). Although hemorrhage has traditionally been regarded as the most significant hemostatic complication of liver disease, there is increasing recognition that hypercoagulability is a prominent aspect of cirrhosis(43, 44). Thus, a pathophysiologic mechanism apart from traditional plaque rupture may be an underlying cause of acute coronary syndrome in a liver transplant population, possibly via de novo thrombotic occlusion(45).

Limitations

Our study has several limitations. First, the current analysis may be limited due to the lack of precise measurement of pre-operative CVD risk variables on individual recipients, such as preoperative cardiovascular testing, laboratory values, medication use, and family history of CVD, not currently available within the OPTN database. Second, transplant centers are not provided with defined criteria for recording a CVD death or comorbid cardiac condition and the OPTN database may be skewed due to reporting bias. A predominant proportion of reported CVD-related death within OPTN was coded as "cardiac arrest." We acknowledge that there are multiple potential underlying mechanisms of cardiac arrest. However, even when cardiac arrest was removed from the definition of CVD mortality, we observed similar results in the prediction of early CVD mortality with similar model accuracy. These limitations may have led to misclassification of cause of death, which, if non-systematic, could lead to poorer model discrimination than would be found in other settings.

Identifying LT-specific CVD risk factors has important policy implications for both Medicare reimbursement and for organ allocation(46). The SRTR risk prediction models are used by the Centers for Medicare & Medicaid Service (CMS) to certify transplant centers for reimbursement. Transplant centers are required to achieve or exceed 1-year expected graft and patient survival as determined by these risk-adjusted models (47). Therefore, centers may be motivated to restrict access to higher risk patients, who might still benefit from transplantation. Despite the limitations of the OPTN database, the current study has rigorously evaluated the available national data. We provide a novel risk model to serve as a comparator for future more in-depth studies focused on determining which, if in fact any, additional CVD variables should be collected by OPTN and therefore included in the risk-adjusted Scientific Registry of Transplant Recipients (SRTR) performance measures.

Conclusions

CVD mortality is the leading cause of early post-operative deaths in the current era of liver transplantation, reflecting an aging and increasingly sicker transplant population. Future studies using large, multicenter databases are needed to validate and expand on our proposed base model in order to improve patient outcomes and maximize the benefit of scarce organ donors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations (alphabetical)

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
AUROC	Area under the receiver operating curve
BMI	Body mass index
CVD	Cardiovascular disease
CIT	Cold ischemic time
COPD	Chronic Obstructive Pulmonary Disease
CTP	Childs-Turcott-Pugh
DDLT	Deceased donor liver transplant
HCV	Hepatitis C virus
ICU	Intensive care unit
LDLT	Living donor liver transplant
LT	Liver transplantation
MELD	Model for end-stage liver disease
NASH	Nonalcoholic steatohepatitis
OPTN	Organ Procurement and Transplant Network
PVT	Portal Vein Thrombosis
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment

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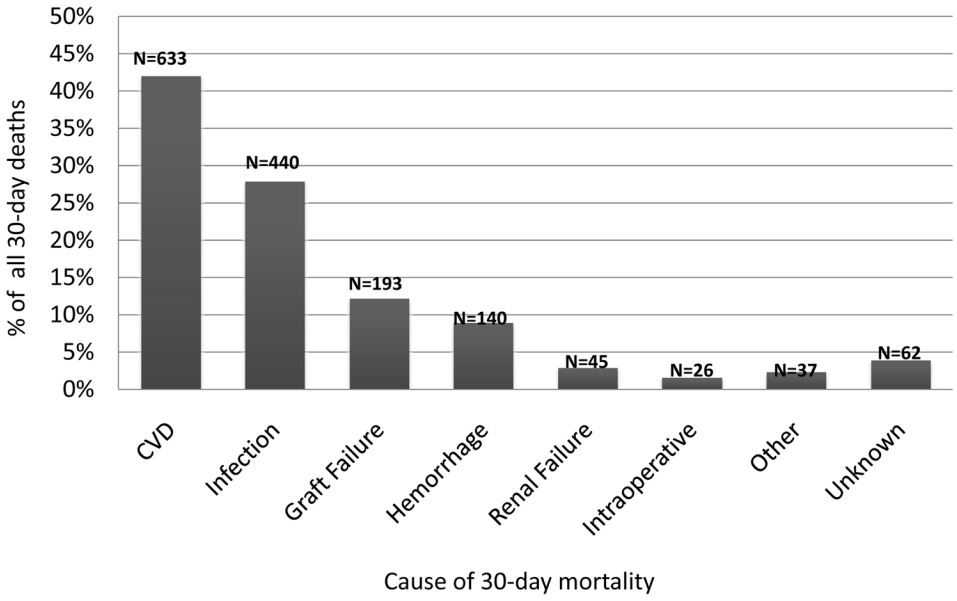

Figure 1.

Distribution of cause of death for 1,576 adult first liver transplant recipients who died within 30 days of liver transplantation (OPTN data 2002–2012). CVD=cardiovascular disease

Table 1

Clinical characteristics of first orthotopic liver transplant recipients in the Organ Procurement and Transplantation Network Database (OPTN) 2002–2012

Characteristic	N = 54,697
Age, mean ± SD, years	54.0 ± 9.5
Sex (women), No (%)	17,198 (31.4)
Race & ethnicity, No (%)	
Non-Hispanic White	39,747 (72.7)
Black	4820 (8.8)
Hispanic	7165 (13.1)
Asian	2435 (4.5)
Other	530 (0.97)
Socioeconomic Status, No (%)	
Less than high school education	2405 (4.4)
Working for income at time of transplant	11,463 (21.0)
Etiology of Liver Disease, No (%)	
Hepatitis C	15,529 (33.5)
Alcohol	11,220 (24.2)
NASH	3085 (6.7)
Other	16,545 (30.2)
Calculated MELD score at transplant, mean ± SD	19.0 ± 10.4
Waitlist time, mean ± SD, days	273.6 ± 493.5
Hepatocellular Carcinoma, No (%)	12,694 (23.2)
Simultaneous liver-kidney transplant, No (%)	3206 (5.9)
BMI (kg/m^2) at transplant, mean ± SD	28.2 ± 5.6
Pretransplant Comorbid CVD Conditions, No (%)	
Angina	790 (3.4)
Cerebrovascular Disease	137 (0.6)
Diabetes	13902 (25.4)
Hypertension	4399 (19.6)
Functional status at transplant, No (%)	
Independent	24411 (49.7)
Partially dependent	12229 (24.9)
Totally dependent	12528 (25.5)
Hospitalization status at transplant, No (%)	
Not hospitalized	41090 (75.2)
Hospitalized not in ICU	9032 (16.5)
In ICU	4489 (8.2)
Revised Cardiac Risk Index (RCRI), mean	1.79 ± 1.21

Abbreviations: SD, standard deviation; NASH, nonalcoholic steatohepatitis; MELD, model for end-stage liver disease; BMI, body mass index; ESLD, end-stage liver disease; CVD, cardiovascular disease; RRT, renal replacement therapy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt

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Table 2

Secondary causes of death in those patients who died of cardiac arrest within 30 days of liver transplantation

Secondary cause of CVD-related mortality	All early CVD deaths N=633	All cardiac arrests N=303	Perioperative cardiac arrest N=140 (46%)	Postoperative cardiac arrest N=163 (54%)
Infectious/Sepsis	46 (7.3)	20 (6.6)	3 (2.1)	17 (10.4)
Graft Failure	30 (4.7)	16 (5.3)	4 (2.9)	12 (7.4)
Hemorrhage	32 (5.1)	19 (6.3)	9 (6.4)	10 (6.1)
Operative	14 (2.2)	7 (2.3)	5 (3.6)	2 (1.2)
Renal Failure	18 (2.8)	11 (3.6)	3 (2.1)	8 (4.9)
Unknown/None	475 (75.0)	225 (74.3)	113 (80.7)	112 (68.7)
Other*	18 (2.8)	5 (1.7)	3 (2.1)	2 (1.2)

Other for Cardiac Arrest Deaths = malignancy (1), suicide/trauma (0), drug/toxin (0), other (4)

Other for CVD Deaths = malignancy (1), suicide/trauma (1), drug/toxin (0), other (16)

Table 3

Univariate predictors of perioperative (within 24 hours) and early postoperative (1–30 days) mortality following orthotopic liver transplantation

Characteristic	No CVD Mortality (N = 54,064)	Any early CVD mortality (N=633)	Perioperative CVD mortality (N=235)			Early postoperative CVD mortality (N=398)		
				OR (95% CI)*	P value		OR (95% CI)*	P value
Recipient Age, mean ± SD, years	54.0 ± 9.5	55.3 ± 9.7	56.2 ± 9.7	1.03 (1.01, 1.04)	<0.001	54.7 ± 9.7	1.01 (0.99, 1.02)	0.134
Recipient Sex (women), No (%)	16977 (31.4)	221 (34.9)	87 (37.0)	1.28 (0.99, 1.68)	0.065	134 (33.7)	1.11 (0.90, 1.37)	0.332
Recipient Race & ethnicity, No (%)								
Non-Hispanic White	39292 (72.7)	455 (71.9)	174 (74.0)	Reference	Reference	281 (70.6)	Reference	Reference
Black	4767 (8.8)	53 (8.4)	21 (8.9)	0.99 (0.63, 1.57)	0.982	32 (8.0)	0.94 (0.65, 1.36)	0.735
Hispanic	7079 (13.1)	86 (13.6)	28 (11.9)	0.89 (0.60, 1.33)	0.580	58 (14.6)	1.15 (0.86, 1.52)	0.348
Asian	2401 (4.4)	34 (5.4)	12 (5.1)	1.13 (0.63, 2.03)	0.686	22 (5.5)	1.28 (0.83, 1.98)	0.264
Other	525 (1.0)	5 (0.8)	0 (0.0)	n/a	n/a	5 (1.3)	1.33 (0.55, 3.24)	0.526
Recipient Socioeconomic Status, No (%)								
Less than high school education	2369 (5.4)	36 (7.0)	9 (3.8)	0.87 (0.45, 1.69)	0.680	27 (6.8)	1.59 (1.07, 2.35)	0.021
Working for income	11391 (26.1)	72 (13.7)	28 (14.5)	0.48 (0.32,0.72)	<0.001	44 (13.3)	0.43 (0.32, 0.60)	<0.001
Etiology of Liver Disease, No (%)								
Hepatitis C	15375 (33.6)	154 (27.8)	47 (23.3)	Reference	Reference	107 (30.4)	Reference	Reference
Alcohol	11092 (24.2)	128 (23.1)	42 (20.8)	1.24 (0.82, 1.88)	0.314	86 (24.4)	1.14 (0.84, 1.48)	0.457
NASH	3046 (6.7)	39 (7.0)	20 (9.9)	2.15 (1.27, 3.63)	0.004	19 (5.4)	0.90 (0.55, 1.46)	0.662
Others	16312 (35.6)	233 (42.1)	93 (46.0)	1.87 (1.31, 2.65)	<0.001	140 (39.8)	1.23 (0.96, 1.59)	0.104
Calculated MELD score at transplant, mean	19.0 ± 10.4	22.8 ± 11.5	22.3 ± 11.9	1.03 (1.02, 1.04)	<0.001	23.1 ± 11.2	1.04 (1.03, 1.04)	<0.001
Waitlist time, mean, days	273.4 ± 492.8	288.5 ± 548.8	342.7 ± 637.8	1.00 (1.00, 1.00)	0.032	256.6 ± 486.7	1.00 (1.00, 1.00)	0.498
Organ Allocation Type, No (%)								
Local	41223 (76.3)	456 (72.0)	157 (66.8)	Reference	Reference	299 (75.1)	Reference	Reference
Regional	10001 (18.5)	127 (20.1)	54 (23.0)	1.42 (1.04, 1.93)	0.027	73 (18.3)	1.02 (0.78, 1.30)	0.962

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Characteristic	No CVD Mortality (N = 54,064)	Any early CVD mortality (N=633)	Perioperative CVD mortality (N=235)			Early postoperative CVD mortality (N=398)		
				OR (95% CI)*	P value		OR (95% CI)*	P value
National	2840 (5.3)	50 (7.9)	24 (10.2)	2.20 (1.44, 3.42)	<0.001	26 (6.5)	1.26 (0.84, 1.89)	0.256
Hepatocellular Carcinoma, No (%)	12584 (23.3)	110 (17.4)	48 (20.4)	0.85 (0.62, 1.16)	0.303	62 (15.6)	0.61 (0.46, 0.80)	<0.001
Simultaneous liver-kidney transplant, No (%)	3180 (5.9)	26 (4.1)	0 (0.0)	n/a	n/a	26 (6.5)	1.12 (0.75, 1.67)	0.583
Recipient BMI (kg/m^2) at transplant, mean	28.2 ± 5.6	28.5 ± 5.8	28.9 ± 5.8	1.02 (0.99, 1.04)	0.081	28.4 ± 5.7	1.00 (0.99, 1.02)	0.665
Laboratory Values at transplant, mean ± SD								
Creatinine (mg/dL)	1.51 ± 1.33	1.87 ± 1.49	1.90 ± 1.44	1.15 (1.08, 1.23)	<0.001	1.85 ±1.51	1.14 (1.08, 1.20)	<0.001
Sodium (mEq/L)	135.9 ± 5.1	136.3 ± 5.8	136.0 ± 5.8	1.00 (0.98, 1.03)	0.784	136.6 ± 5.8	1.03 (1.00, 1.05)	0.022
Recipient Complications of ESLD, No (%)								
Ascites at transplant	42289 (79.1)	530 (84.4)	197 (84.2)	1.40 (0.99, 2.00)	0.059	333 (84.5)	1.44 (1.10, 1.89)	0.009
Spontaneous Bacterial Peritonitis	1779 (8.0)	34 (11.6)	15 (13.8)	1.84 (1.07, 3.18)	0.029	19 (10.4)	1.34 (0.83, 2.16)	0.233
Encephalopathy	36219 (67.5)	485 (77.0)	177 (75.6)	1.49 (1.11, 2.01)	0.009	308 (77.8)	1.68 (1.33, 2.14)	<0.001
Portal Vein Thrombosis	4117 (7.7)	78 (12.5)	34 (14.8)	2.08 (1.44, 2.99)	<0.001	44 (11.2)	1.50 (1.10, 2.06)	0.011
TIPS	5576 (10.5)	87 (14.0)	36 (15.7)	1.60 (1.12, 2.28)	0.010	51 (12.9)	1.27 (0.95, 1.71)	0.108
Variceal Bleed	1300 (5.9)	32 (10.9)	11 (9.8)	1.73 (0.93, 3.24)	0.085	21 (11.6)	2.09 (1.32, 3.30)	0.002
Recipient Comorbid CVD Conditions, No (%)								
Angina	768 (3.3)	22 (7.1)	10 (8.3)	2.62 (1.37, 5.03)	0.004	12 (6.3)	1.95 (1.08, 3.52)	0.026
Cerebrovascular Disease	135 (0.6)	2 (0.7)	1 (0.9)	1.47 (0.20, 10.62)	0.701	1 (0.5)	0.88 (0.12, 6.33)	0.899
Diabetes	13727 (25.4)	175 (27.7)	75 (31.9)	1.38 (1.05, 1.81)	0.022	100 (25.1)	0.99 (0.79, 1.24)	0.902
Hypertension	4339 (19.6)	60 (20.3)	32 (28.3)	1.63 (1.08, 2.45)	0.021	28 (15.3)	0.74 (0.50,1.13)	0.150
Other Recipient Comorbid Conditions								
Chronic Obstructive Pulmonary Disease	329 (1.5)	11 (3.7)	5 (4.5)	3.14 (1.27, 7.75)	0.013	6 (3.2)	2.22 (0.98, 5.04)	0.057
Respiratory Failure on ventilator	2152 (4.0)	90 (14.2)	24 (10.2)	2.74 (1.80, 4.20)	<0.001	66 (16.6)	4.80 (3.67, 6.27)	<0.001
Renal failure requiring RRT	5530 (10.2)	126 (19.9)	40 (17.0)	1.80 (1.28, 2.53)	<0.001	86 (21.6)	2.42 (1.90, 3.08)	<0.001
Functional status at transplant, No (%)								

Characteristic	No CVD Mortality (N = 54,064)	Any early CVD mortality (N=633)	Perioperative CVD mortality (N=235)			Early postoperative CVD mortality (N=398)		
				OR (95% CI)*	P value		OR (95% CI)*	P value
Independent	24235 (49.8)	176 (32.5)	68 (34.5)	Reference	Reference	108 (31.4)	Reference	Reference
Partially dependent	12111 (24.9)	118 (21.8)	44 (22.3)	1.30 (0.89, 1.89)	0.183	74 (21.5)	1.37 (1.02, 1.84)	0.037
Totally dependent	12281 (25.3)	247 (45.7)	85 (43.2)	2.47 (1.79, 3.40)	<0.001	162 (47.1)	2.96 (2.32, 3.78)	<0.001
Hospitalization Status at transplant, No (%)								
Not hospitalized	40726 (75.5)	364 (57.5)	140 (59.6)	Reference	Reference	224 (56.3)	Reference	Reference
Hospitalized not in ICU	8900 (16.5)	132 (20.9)	49 (20.8)	1.60 (1.16, 2.22)	0.005	83 (20.8)	1.70 (1.32, 2.18)	<0.001
In ICU	4352 (8.1)	137 (21.6)	46 (19.6)	3.08 (2.20, 4.30)	<0.001	91 (22.9)	3.80 (2.97, 4.86)	<0.001
Revised Cardiac Risk Index (RCRI), mean	1.79 ± 1.21	2.13 ± 1.38	2.21 ± 1.45	1.25 (1.15, 1.36)	<0.001	2.08 ± 1.33	1.18 (1.10, 1.26)	<0.001
Donor Factors								
Age, mean, years	41.4 ± 16.9	41.8 ± 15.8	43.5 ± 14.7	1.01 (1.00, 1.02)	0.064	40.8 ± 16.3	0.99 (0.99, 1.00)	0.479
Sex (female), No (%)	21988 (40.7)	258 (40.8)	99 (42.1)	1.06 (0.82, 1.38)	0.650	159 (40.0)	0.97 (0.79, 1.19)	0.771
Ethnicity, No (%)								
Non-Hispanic White	37091 (68.6)	442 (69.8)	189 (80.4)	Reference	Reference	253 (63.6)	Reference	Reference
Black	8449 (15.6)	71 (11.2)	19 (8.1)	0.44 (0.28, 0.71)	<0.001	52 (13.1)	0.90 (0.67, 1.22)	0.501
Hispanic	6590 (12.2)	91 (14.4)	21 (8.9)	0.63 (0.40, 0.98)	0.042	70 (17.6)	1.56 (1.19, 2.03)	0.001
Donor Risk Index, mean	1.33 ± 0.35	1.34 ± 0.34	1.38 ± 0.35	1.48 (1.00, 2.18)	0.050	1.32 ± 0.33	0.87 (0.64, 1.18)	0.365
Donor BMI (kg/m^2), mean	26.9 ± 6.1	27.6 ± 6.3	29.1 ± 6.5	1.03 (1.01, 1.04)	<0.001	26.7 ± 6.0	0.99 (0.98, 1.01)	0.491
Donation after Cardiac Death, No (%)	5422 (10.0)	72 (11.4)	37 (15.7)	1.68 (1.18, 2.38)	0.004	35 (8.8)	0.87 (0.61, 1.23)	0.414
Living Donor, No (%)	2344 (4.3)	17 (2.7)	0 (0.0)	n/a	n/a	17 (4.3)	0.99 (0.61, 1.60)	0.950
Donor Medications within 24 hours of procurement, No (%)								
Inotropic support	29361 (58.8)	325 (54.2)	121 (53.3)	0.80 (0.62, 1.04)	0.097	204 (54.7)	0.85 (0.69, 1.04)	0.113
Antihypertensives	11024 (21.4)	135 (21.9)	48 (20.4)	0.95 (0.69, 1.30)	0.730	87 (22.8)	1.09 (0.86, 1.39)	0.482
Steroids	38287 (74.9)	451 (73.9)	175 (75.1)	1.01 (0.75, 1.36)	0.948	276 (73.2)	0.92 (0.73, 1.15)	0.445
Thyroid replacement	28369 (55.5)	306 (50.0)	122 (52.1)	0.88 (0.68, 1.13)	0.309	184 (48.7)	0.76 (0.62, 0.93)	0.009
Donor Comorbidities								

Characteristic	No CVD Mortality (N = 54,064)	Any early CVD mortality (N=633)	Perioperative CVD mortality (N=235)			Early postoperative CVD mortality (N=398)		
				OR (95% CI)*	P value		OR (95% CI)*	P value
Diabetes	5268 (10.2)	63 (10.3)	32 (13.6)	1.38 (0.95, 2.01)	0.089	31 (8.2)	0.78 (0.54, 1.13)	0.190
Hypertension	17295 (33.7)	222 (36.2)	97 (41.5)	1.40 (1.08,1.81)	0.012	125 (33.0)	0.97 (0.78, 1.20)	0.781
Myocardial Infarct	1808 (3.9)	23 (4.2)	10 (4.8)	1.23 (0.65, 2.33)	0.524	13 (3.8)	0.97 (0.56, 1.69)	0.916
Renal Disease	22539 (44.1)	293 (47.8)	121 (51.7)	1.36 (1.05, 1.76)	0.020	172 (45.4)	1.05 (0.86, 1.29)	0.615
Donor Health Behaviors								
Smoker	15823 (30.1)	195 (31.6)	75 (32.2)	1.11 (0.84, 1.46)	0.479	120 (31.3)	1.06 (0.85, 1.31)	0.611
Alcohol dependency	1887 (19.6)	18 (14.2)	6 (13.0)	0.62 (0.26, 1.46)	0.271	12 (14.8)	0.72 (0.39, 1.32)	0.287
Cocaine	6828 (13.4)	72 (12.0)	26 (11.3)	0.82 (0.55, 1.24)	0.345	46 (12.4)	0.91 (0.67, 1.24)	0.547
Graft cold ischemia time, mean, min	7.0 ± 3.6	7.6 ± 3.4	8.3 ± 3.3	1.06 (1.03, 1.09)	<0.001	7.3 ± 3.3	1.02 (0.99, 1.04)	0.186

Abbreviations: SD, standard deviation; NASH, nonalcoholic steatohepatitis; MELD, model for end-stage liver disease; BMI, body mass index; ESLD, end-stage liver disease; CVD, cardiovascular disease; RRT, renal replacement therapy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt

*compared to no CVD mortality

Table 4

Multivariate predictors of 30-day cardiovascular mortality after orthotopic liver transplantation

Characteristic	Total Population	30-day cardiovascular mortality		
	N=54,697	Beta Coefficient	Odds Ratio(95% CI)	P-value
Age, year, mean ± SD	54.0 ± 9.5	0.017	1.02 (1.10–1.03)	0.001
Female (forced in), n (%)	17,198 (31.4)	0.184	1.20 (1.00–1.45)	0.052
Medical condition prior to transplant, n (%)				
Not hospitalized	41,090 (75.2)	Reference		
Hospitalized not in ICU	9032 (16.5)	0.208	1.23 (0.95–1.60)	0.121
In ICU	4489 (8.2)	0.623	1.86 (1.34–2.60)	<0.001
Respiratory failure, n (%)	2242 (4.1)	0.719	2.05 (1.46–2.89)	<0.001
MELD score (calculated), mean ± SD	19.0 ± 10.4	0.018	1.02 (1.01–1.03)	<0.001
National Organ Allocation (versus Local/Regional), n (%)	2890 (5.3)	0.419	1.52 (1.08–2.14)	0.016
Portal vein thrombosis, n (%)	4195 (7.8)	0.397	1.49 (1.14–1.95)	0.004
Donor BMI, mean ± SD	28.2 ± 5.6	0.013	1.01 (1.00–1.02)	0.024
Cold ischemia time, hours, mean ± SD	0.12 ± 0.6	0.032	1.03 (1.01–1.05)	0.001
Center volume (forced in)				
Tertile 1	n/a	Reference		
Tertile 2	n/a	0.176	0.84 (0.55–1.27)	0.404
Tertile 3	n/a	0.390	0.68 (0.46–1.01)	0.055

Abbreviations: SD, standard deviation, CI, confidence interval; ICU, intensive care unit; BMI, body mass index

Table 5

Comparison of prevalence of causes of early cardiovascular disease mortality across transplant regions

Region	Median MELD score	Composite CVD mortality	Cardiac Arrest	Stroke	Thromboembolism	Myocardial Infarction	Heart Failure	Arrhythmia	Other*
1	17.3	1.34%	0.40%	0.15%	0.25%	0.25%	0.25%	0.05%	0.00%
2	17.9	1.07%	0.52%	0.11%	0.11%	0.09%	0.12%	0.09%	0.03%
3	18.0	0.88%	0.37%	0.11%	0.08%	0.08%	0.09%	0.08%	0.07%
4	18.2	0.99%	0.39%	0.20%	0.14%	0.10%	0.02%	0.04%	0.10%
5	19.9	1.39%	0.77%	0.21%	0.12%	0.05%	0.21%	0.03%	0.00%
6	16.2	1.10%	0.49%	0.24%	0.12%	0.00%	0.24%	0.00%	0.00%
7	19.1	1.25%	0.45%	0.21%	0.16%	0.18%	0.12%	0.08%	0.06%
8	18.8	1.10%	0.47%	0.14%	0.08%	0.25%	0.17%	0.00%	0.00%
9	17.1	1.31%	0.88%	0.15%	0.00%	0.05%	0.20%	0.03%	0.00%
10	16.1	1.24%	0.61%	0.08%	0.16%	0.16%	0.08%	0.10%	0.04%
11	17.6	1.26%	0.68%	0.06%	0.09%	0.13%	0.23%	0.06%	0.02%

*Other = ruptured aneurysm, pulmonary hypertension, hypertensive crisis

Abbreviations: MELD, model for end-stage liver disease; CVD, cardiovascular disease