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Incidence of and Risk Assessment for Adverse Cardiovascular Outcomes Following Liver Transplantation: A Systematic Review

Monica A Konerman, MD MSc¹, Danielle Fritze, MD², Richard L Weinberg, MD³, Christopher J Sonnenday, MD MHS², and Pratima Sharma, MD MS¹

¹Division of Gastroenterology and Hepatology, University of Michigan Health System, Ann Arbor, Michigan, USA

²Department of Surgery, University of Michigan Health System, Ann Arbor, Michigan, USA

³Division of Cardiology, University of Michigan Health System, Ann Arbor, Michigan, USA

Abstract

Background—Cardiovascular events represent a major source of morbidity and mortality following liver transplantation and will likely increase given the aging population and nonalcoholic fatty liver disease as a leading indication for transplant. The optimal cardiovascular risk stratification approach in this evolving patient population remains unclear. The aims of this systematic review are to: 1) refine the definition 2) characterize the incidence, and 3) identify risk factors for cardiovascular events post liver transplantation. Additionally, we evaluated performance characteristics of different cardiac testing modalities.

Methods—MEDLINE via PubMed, EMBASE, Web of Science and Scopus were searched for studies published between 2002–2016 (MELD era). Two authors independently reviewed articles to select eligible studies and performed data abstraction. **Results:** 29 studies representing 57,493 patients from 26 unique cohorts were included. Definitions of cardiovascular outcomes were highly inconsistent. Incidence rates were widely variable: 1–41% for outcomes ≤ 6 months and 0–31% for outcomes >6 months. Multivariate analyses demonstrated that older age and history of cardiac disease were the most consistent predictors of cardiovascular events posttransplant (significant in 8/23 and 7/22, studies respectively). Predictive capacity of various cardiac imaging modalities was also discrepant.

Conclusions—The true incidence of cardiovascular outcomes post liver transplant remains unknown in large part due to lack of consensus regarding outcome definition. Overall, poor data quality and gaps in knowledge limit the ability to clearly identify predictors of outcomes, but

Correspondence: Monica A. Konerman, MD MSc; University of Michigan Health System, Division of Gastroenterology and Hepatology; 3912 Taubman Center, 1500 East Medical Center Drive, SPC 5362; Ann Arbor, Michigan, 48109, USA.; konerman@med.umich.edu.

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existing data supports a more aggressive risk stratification protocol for patients of advanced age and/or with preexisting cardiac disease.

Introduction

Adverse cardiovascular (CV) events represent a major cause of morbidity and mortality following liver transplantation (LT).^{1,2} The clinical profile of LT candidates is evolving and it is anticipated that the incidence of adverse CV events is likely to continue to increase in this setting. The differences include an overall aging patient population, nonalcoholic fatty liver disease (NAFLD) becoming a leading indication for LT, higher burden of chronic kidney disease going into transplant, and increasing utilization of dual liver-kidney transplantation.^{3,4} Although there are existing guidelines from hepatology, transplant surgery, and cardiology professional societies regarding CV risk stratification prior to LT, it remains unclear if the performance characteristics of these approaches remain satisfactory in this evolving patient population.^{5–7} Specifically, it would be of interest to identify subgroups of LT candidates who are at highest risk for adverse CV outcomes post-LT such that a CV risk stratification approach could then be tailored appropriately. This approach would help balance the risks, benefits and costs of varying cardiac testing modalities and ideally also optimize posttransplant outcomes.

Multiple studies have evaluated risk factors for CV events post-LT and varying approaches to cardiac risk stratification in LT candidates. Data from these studies have been conflicting however with varying incidence rates reported for CV outcomes post-LT and differing risk factors identified as being associated with CV events post-LT. In addition, the performance characteristics of different modalities of cardiac testing in LT candidates have also been contradictory. In general, dobutamine stress echocardiography (DSE) remains a mainstay of first line cardiac testing in LT candidates, though the accuracy of this tool in appropriately identifying high risk patients is in doubt.^{8,9} To date, there has not been a systematic summary of the existing literature on this topic. As such, it has been difficult for clinicians to understand the true scope of the burden of CV events post-LT, to identify which patients are at highest risk for these outcomes, and to then apply a high yield cardiac risk stratification approach to their individual patients. Therefore, we performed a systematic review of the literature to: 1) refine the definition 2) characterize the incidence, and 3) identify risk factors for CV events post-LT. Secondary aims of this study were to assess existing predictive models for risk of CV events post-LT, and to evaluate performance characteristics of different modalities of cardiac testing in LT candidates.

Materials and Methods

Data Sources and Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations in conducting this systematic review.¹⁰ With the assistance of a medical research librarian, we performed serial literature searches for articles of interest. MEDLINE (via PubMed), EMBASE, Web of Science and Scopus were searched using the following keywords: “liver transplantation”, “cardiovascular diseases” or “cardiac imaging” or “cardiac imaging techniques”. Boolean operators and medical subject heading terms as

well as other controlled vocabulary were used to enhance electronic searches. An example of specific search strategy details is shown in Supplement Table 1.

All human subject studies published in full-text or abstract were eligible for inclusion. Additional studies of interest were identified by hand searches of bibliographies, cited reference tracking, and consultation with clinical experts on the topic. The search time frame was selected to begin in 2002 as this represents the initiation of the MELD era. The initial search was performed in December 2015 and the search was last updated on December 1, 2016.

Study Eligibility and Selection Criteria

Two study authors sequentially determined study eligibility. Studies were initially screened by the first author; decisions about study inclusion were made independently by 2 authors (M.A.K. and P.S. or D.F.). Differences in opinion regarding study inclusion were resolved through consensus. Adult (≥ 18 years) human subject studies that systematically evaluated either (1) risk factors or predictors of CV events following LT; or (2) performance characteristics of different modalities of cardiac imaging in LT candidates to risk stratify for CV events post-LT, were included.

We excluded studies that: (1) only enrolled patients with Living Donor LT (due to the fact that deceased donor transplants represent the majority of LT presently and risks for and rates of CV events post-LT in patients undergoing living donor LT may differ from those receiving deceased donor LT); (2) only evaluated specific subgroups of patients (ie, HCV alone); (3) only evaluated risk of overall mortality; (4) only evaluated risk of developing 1 specific cardiac outcome unless this 1 outcome was either myocardial infarction or cardiac death; (5) evaluated only 1 predictor (ie, effect of immunosuppressive agent); or (6) evaluated only intraoperative risk factors for CV events. These studies were excluded because we were interested in preoperative risk assessment for the comprehensive range of clinically relevant adverse CV events among the broader cohort of patients in need of LT. Lastly, studies for which no translation into English language was available were also excluded.

Data Abstraction and Validity Assessment

Data from eligible studies were abstracted by 2 authors using a standardized template adapted from the Cochrane Collaboration.¹¹ For all studies, we recorded: study design, sample size, patient population characteristics, duration of follow-up, predictor variables studied, outcomes measured, criteria used to define these outcomes, incidence of outcomes, and measures of association/prediction of risk for these outcomes. For cardiac imaging studies, we additionally evaluated performance characteristics of these techniques including sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for assessing risk of cardiac outcomes post-LT. We accepted the outcome definitions as stated by each study without independently validating or reviewing their data. Study authors were directly contacted for additional, unpublished data when necessary.

Assessment of Risk of Bias and Study Quality

Each study was assessed for risk of study bias and study quality. Given that all the included studies were nonrandomized cohort studies, the Newcastle-Ottawa Scale was used to judge study quality as recommended by the Cochrane Collaboration.¹² This scale uses a star system to assess the quality of a study based on 3 domains: selection of the study population, comparability of the study groups, and method of outcomes assessment. For our review, we excluded comparability components of the scale as the included studies lacked comparison groups. Studies which received stars in every domain were assessed as being of high quality.

Data Synthesis and Analysis

Given the substantial variation in definition of outcomes and inclusion/exclusion criteria, meta-analysis was not able to be performed. Two authors qualitatively synthesized the results of the included studies. Studies were categorized according to the outcome of interest (predictors of CV events or cardiac imaging performance characteristics for risk stratification), and the study time interval [short term CV events only (≤ 6 months) vs. those that also assessed longer term CV events (> 6 months)].

Results

Studies Included in the Systematic Review

1976 unique articles were identified by our systematic literature search (Figure 1). On the basis of abstract review, 76 were selected for full-text review. Two study authors classified 29 articles as meeting the predefined criteria for analysis. In total, these 29 studies included 57,493 unique patients from 27 separate patient cohorts.^{2,8,9,13–38} Twenty-three of these studies investigated predictors of CV events post-LT and 6 focused primarily on cardiac imaging performance characteristics for risk stratification. We contacted 2 authors to obtain additional unpublished data.

Characteristics of Studies on Overall Risk Factors for CV Events post-LT

All 23 studies were retrospective analyses. The sample size for included studies varied tremendously (range 76 to 54,697 patients), though the majority had between 100–500 patients (n=17). Five studies had overlapping cohorts.^{21,22,32,34,35} One study consisted of data collected in the OPTN database.³² These studies were included in the review despite overlapping cohorts given differences in predictors examined and outcomes evaluated. Among studies that evaluated risk for CV events ≤ 6 months, the average duration of follow-up was 2.8 months (range 1–6 months). For studies including outcomes occurring >6 months post-LT, the average duration of follow-up was 5.6 years (range 1–10 years).

The studies had varied inclusion and exclusion criteria as detailed in Table 1. 13 studies excluded patients with prior LTs and 7 excluded patients undergoing multi-organ transplant. The age of included patients was reported as both age at initial LT evaluation and age at time of LT. The average age reported was 53 years (range 42.3–57). The studies tended to have a male predominance (average 64.6%; range 45.6%–79%). MELD score was reported as both MELD at time of LT and at time of initial LT evaluation. The average MELD reported across studies was 18.2 (range 13.4–22). The indication for LT was most often categorized as viral

hepatitis (32.8%; range 6%–71%) with varying frequencies of alcoholic liver disease (average 17.6%; range 8%–40%). Notably, NAFLD/NASH or cryptogenic cirrhosis was an uncommon indication for LT in the majority of these studies (average 8.8%; range 2–19%). The average BMI was in the overweight and not obese category (27.1; range 23.9–29). The prevalence of comorbid diabetes was 21.4% (range 10%–41%).

Characteristics of Studies of Cardiac Imaging Modalities

A total of 6 studies had a primary aim of evaluating different modalities of cardiac imaging for risk stratification of LT candidates. All were retrospective analyses. Sample size was comparatively much smaller and ranged from 24–339, with the majority consisting of <100 patients (N=4). The average duration of follow-up was 2.9 years (range 9 months – 7 years). The imaging modalities assessed in these studies included DSE, coronary CTA, and SPECT.

The individual inclusion and exclusion criteria are detailed in Table 2. The average age was 53 years (range 42.7–56). These studies had a more notable male predominance (average 71.5%; range 63%–78%) compared to the clinical prediction studies. The average MELD reported (captured as MELD at time of LT evaluation) was 14.8 (range 11.8–16.5). The indication for LT was also predominantly either viral [31.1% (range 17.9–54)] or alcoholic liver disease [22.5% (range 11–31)]. The average BMI was only reported in 2 of the 6 studies. The prevalence of co-morbid diabetes was 25.4% (range 16%–45%).

Definition of Cardiovascular Events

In all studies, outcomes were identified by retrospective chart review. Methods to confirm outcomes varied from sole use of ICD-9 coding to manual chart review. Definitions for individual cardiac events varied dramatically (Table 3 and 4). Four studies did not provide any details regarding the definition of CV outcomes.^{17,29,30,36} The majority of studies examined a composite outcome including coronary artery disease with an episode of myocardial ischemia, heart failure, and arrhythmias (N=20). 3 studies only evaluated CV-related mortality.^{23,32,35}

Incidence of Cardiovascular Events

The incidence rates for CV events post-LT for each study are detailed in Table 3 and 4. The incidence rate of outcomes within 30 days of LT was 12.8% (range 1.1–23.2%).^{17,21,22,24,28,32,33} The average outcome incidence rate for events 6 months post-LT was 22.6% (range 1.1%–50%).^{2,17,21–24,28,31–33,38} For events >6 months post-LT, incidence rate was 11.8% (range 0–31.4%).^{9,13–16,18,19,21,22,25,26,32,34–36}

Predictors of Cardiovascular Events

A detailed list of the predictors evaluated and the results of univariate analysis is provided in Supplement Table 3. For each study, the predictor variables were categorized as follows: 1) clinical characteristics including demographics and relevant comorbidities; 2) intra/postoperative factors including donor characteristics; or 3) pre-LT cardiac testing. Multivariable analysis was performed in all 23 studies. The results of these analyses are detailed in Table 3. Among the variables assessed, older age (most often analyzed as a continuous variable per year) was the most consistent independent predictor of clinical

outcomes (significant on multivariate analysis in 8 of 23 studies; effect size range per year increase 1.02–1.17 and 2.2 per decade increase). This was followed by history of cardiac disease, MELD score, and pre-LT TTE data (each significant in 7, 5, and 5 studies respectively) (Figure 2). For patients with a history of cardiac disease, the effect size ranged from 1.8–7.7. Of note, indication for liver transplant, BMI and diabetes were not identified as being consistent independent predictors of CV outcomes post-LT (significant in multivariable analysis in 4, 4, and 1 studies respectively).

Performance Characteristics of Cardiac Imaging Modalities

The reported performance characteristics of differing cardiac imaging modalities to risk stratify patients for CV outcomes post-LT are shown in Supplement Table 4.^{8,9,28,30,37} The sensitivity, specificity, NPV and PPV of DSE in LT candidates across these studies were discordant.^{8,9,28,30} Sensitivity of DSE for CV events post-LT ranged from 0%–80% with PPV of 11%–40%. The reported specificity and NPV of DSE for CV events post-LT was also strikingly variable with ranges of 47%–100% and 48%–93% respectively. Studies analyzing SPECT testing reported high NPV (91%–99%).^{9,37}

Prediction Models

Five studies provided prediction models, though none had been externally validated (Supplement Table 5).^{19,21,22,31–33} Overall, the majority of the components of the prediction models included a combination of demographic information, laboratory data, prior cardiac disease history and cardiac testing results. The area under the receiver operating characteristic curve (AUROC) for these models were modest (range 0.66–0.75) with the exception of the models by Guckelberger et al, that reported an AUROC of 0.78 and 0.80.¹⁹

Quality Assessment and Risk of Bias

Studies evaluating predictors of CV outcomes post-LT were in general assessed as being high quality (Supplement Table 2). Five studies had patient cohorts with limited representativeness compared to the overall patient population of interest and 1 study only provided limited data regarding the patient cohort.^{14,19,24,33–35} Among the cardiac imaging studies, 2 studies were assessed as having limited representativeness given the inclusion and exclusion criteria.^{20,30}

Discussion

In the setting of the aging baby boomer population, the increasing indication of NAFLD for LT, and the uptick in number of patients needing dual liver-kidney transplants, the incidence of CV events post-LT is likely to increase. Although CV events represent a major source of morbidity and mortality post-LT, our review highlights the critical gaps in knowledge on this topic including quantifying the true scope of the problem, identifying patients at highest risk for these outcomes, and defining the optimal risk stratification approach to try and minimize the frequency of these adverse events. Herein we highlight the inconsistency in outcome definitions and detail the stark variability in ranges of reported outcome incidence stemming from these variations (1–41% for outcomes ≤ 6 months and 0–31% for outcomes > 6 months post-LT). In addition, we identified the variables that despite study heterogeneity, were

consistently associated with a higher risk of CV events post-LT, namely older age and a prior history of cardiac disease. Moreover, we demonstrate the conflicting data regarding the performance characteristics of various cardiac imaging techniques including those commonly used in clinical practice.

In this context, our review details several areas in need of attention from the liver transplant community. First, there is a clear need to identify a consensus definition for clinically relevant CV events post-LT. Until such time that the specific outcomes of interest are selected and then subsequently uniformly and prospectively assessed for, the transplant community will be unable to accurately quantify the burden of CV outcomes post-LT. Based on the existing data and on current clinical practice, endpoints to be considered in the consensus definition likely include acute coronary syndrome (STEMI, NSTEMI and unstable angina), clinically significant arrhythmias (ventricular tachycardia and fibrillation, atrial fibrillation and flutter, and symptomatic heart block), heart failure, stroke, and cardiac arrest or primary cardiac death stemming from 1 of these processes. Future studies should consider grading of cardiovascular events following transplantation, using the Clavien-Dindo classification, to allow identification of events associated with significant morbidity and mortality, as opposed to transient events without sequelae.³⁹ Only with prospective surveillance for these specific outcomes and their severity, instead of the retrospective analyses with variable endpoints, can the true incidence and optimal risk assessment for CV events be ascertained.

A second focus area for the transplant community relates to the need to more accurately identify patients who require intensive cardiac risk stratification. Results of the multivariate analyses in the included studies demonstrated that incremental increase in age (effect size 1.02–1.17 per year) and background cardiac disease (effect size 1.8–7.7) were consistently associated with higher risk of CV events post-LT. Though these findings are unsurprising and relatively nonspecific, our study is the first to systematically assess and compare the specific risk factors from among the many potential contributing variables that portend worse prognosis in terms of risk of a CV event post-LT. These 2 specific risk factors are highly relevant from a clinical practice standpoint as the overall liver transplant candidate pool continues to age and present with increasing numbers of co-morbid conditions. Similarly, notable is the lack of data to support the role of other variables that are often thought to convey increased risk for cardiac outcomes. For example, diabetes, obesity and NAFLD did not appear to consistently be associated with higher risk of CV events post-LT. The reasons for this lack of independent association for these variables that have biologic plausibility for driving CV risk is unclear, but is likely in part due to differences in study design and characteristics of patients enrolled in these studies (likely driven by substantial center-level variability in recipient selection and relative tolerance of specific comorbidities).

A third key area of focus is the need to better characterize the specific performance characteristics of the various cardiac testing modalities in this patient population. Our data emphasizes the conflicting predictive accuracy of the most commonly employed cardiac imaging testing, DSE. Presently, there are multiple alternative cardiac imaging modalities, but existing data is unable to direct clinicians to the optimal testing tool. The studies querying imaging modalities were often quite small, and specific methodology and expertise

may vary across centers, limiting the generalizability of these findings to real world clinical practice.

Until such time that the above limitations can be addressed prospectively in future studies, our data would support a tailored cardiac risk stratification approach based on these risk factors. Although we were not able to concretely identify a threshold age at which CV events drastically increase, given that enrolled patients consisted primarily of middle-aged adults, the additional accrued risk above age 60, which appears to confer a relative risk of at least 1.5 times higher than younger patients, is likely to be of clinical significance. This age parameter along with cardiac disease history could potentially represent prompts for more detailed CV testing. Given potential limitations of DSE, our center has recently implemented a new tailored risk-based protocol that incorporates our findings. LT candidates with 2 of the following risk factors now undergo additional cardiac imaging testing after DSE: age 60, BMI >35, diabetes, arrhythmia requiring treatment, or prior history of coronary artery revascularization or stroke. We have selected PET/CT, a nuclear medicine imaging modality that is gaining favor due to its ability to calculate myocardial blood flow and flow reserves that have been shown to be independently prognostic of cardiac events, as our additional imaging modality.^{40,41} The performance characteristics of PET/CT in LT candidates needs to be studied in further detail however.

In conclusion, this study is the first systematic review and analysis of the large body of literature on the topic of cardiovascular events following liver transplantation. Through this review we have outlined the patient characteristics of older age and previous history of cardiac disease as being consistently associated with increased risk for adverse cardiac outcomes post-LT. We have also highlighted the areas in which the transplant community can make significant strides in order to mitigate these outcomes in the post-LT setting, including refining the evaluation of patients at highest risk for adverse cardiac outcomes and ongoing assessment of the optimal cardiac imaging modalities. From a health policy standpoint, if specific patient risk profiles, and refined screening methods, were able to be more definitively characterized, a more directed approach to cardiac risk stratification could be implemented and in turn could help balance the risks, benefits and cost effectiveness of different testing processes with the ultimate goal of reducing the rates of CV events in the posttransplant setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CV	cardiovascular
DSE	dobutamine stress echocardiography
ECG	electrocardiogram
TTE	transthoracic echocardiography
LT	liver transplant
MELD	model of end stage liver disease
HCV	hepatitis C virus
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NPV	negative predictive value
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Figure 1.
Flow diagram of studies included in the systematic review

Figure 2.

List of variables identified to have significant predictive value for CV outcomes post-LT

*Cardiac Disease includes: CAD/CHF/HTN/CVA

^Includes Standard TTE data and data from DSE

#2 studies indicated higher risk in males; 1 study higher risk in females

†Higher risk in NAFLD/Crypto in 3 studies; PBC/PSC had lower risk in 1 study and higher in another study

‡Includes pretransplant ICU status, ventilator status, pressor requirement and operative time

Table 1
General Characteristics of Included Studies: Predictors of Cardiovascular Events Post Liver Transplant

Study and Country	N	Age (mean)	% Male	Race	Indication for LT (%)	Other Patient Characteristics	Study Population	
							Inclusion Criteria	Exclusion criteria
Short Term CV Outcomes Only (<6 months)								
Konerman ²³ 2016 USA	76	54.5* (IQR 51–63)	58	82.5% White	HCV: 40.7 ETOH: 10 NASH/crypto: 14.5	MELD (median): 20.5 BMI (median): 27.3 DM: 25% Tobacco Use: 57.5%	Case control study. Patients s/p LT at their center 2000–2011.	Age <18 Prior LT No TTE for review
Kong ²⁴ 2015 South Korea	443	52.4 (SD 7.7)	79	NR	HBV: 71 ETOH: 15 HCV 6	MELD (mean): 15 BMI (mean): 23.9 DM: 24% Tobacco Use: 33%	Patients s/p LT at their center 2010–2012	<20 years old No pre-LT coronary CT History of “significant cardiac event” or coronary angioplasty No troponin I assay postoperative period
Raevens ³⁹ 2014 Belgium	173	57 (SD 11)	64	NR	ETOH: 40 HCV: 13 NASH: 7	MELD (mean): 17 BMI (mean): 26	Patients s/p LT at their center 2005–2010	Age <18 Prior LT Lack of “adequate preoperative evaluation”
Dare ¹⁷ 2014 New Zealand	202	51 (range 19–69)	67	63% White	HCV: 39 HBV: 19 AIH: 14 NASH: 7	MELD (mean): 15 BMI (mean): 28.9 DM: 23.8% CAD 5%	Consecutive patients s/p LT at their center 2000–2010	Age <18 Prior LT Acute Liver Failure Multi-organ Transplant
VanWagner ³³ 2014 USA	54, 697	54 (SD 9.5)	68.6	72.7% White 8.8% Black	HCV: 28.4 ETOH: 20.5 NASH: 5.6	MELD (mean): 19 BMI (mean): 28.2 DM: 25.4%	Patients s/p LT in OPTN database 2002–2012	Age <18 Prior LT Acute Liver Failure/Status 1 listing Multi-organ Transplant
Safadi ²⁹ 2009 USA	403	51.5 (SD 9.4)	67	90% White	NR	DM: 26.4% BM (mean)I: 27.8 Tobacco Use: 43%	Patients s/p LT at their centers 2001–2005	Missing follow-up data
Foad ² 2009 Canada	197	56* (40–75)	69	NR	HCV: 45.5 ETOH: 22	NR	Patients s/p LT at their centers 2002–2007	Age <40
Umphrey ³² 2008 USA	157	55 (SD 7.5)	71	94% White	HCV: 48 ETOH 10 Crypto: 10	MELD (mean): 21 DM: 10% Tobacco Use: 58%	Patients s/p LT at their centers 1999–2005	Lack of pre-LT DSE
Includes Long Term CV Outcomes (>6 months)								
Bushyhead ¹⁴ 2016 USA	397	56* (IQR 51–61)	73.3	73.8% White 19.1% Black	HCV 26.4 ETOH: 16.1 ETOH/HCV: 28.7 NASH/Crypto: 11.6	MELD (median): 21 DM: 18.4% CAD: 2.8 Tobacco Use: 59.7%	Patients s/p LT at their center 2005–2014	Age <18 Prior LT Acute Liver Failure Multi-organ Transplant

Study and Country	N	Age (mean)	% Male	Race	Indication for LT (%)	Other Patient Characteristics	Study Population	
							Inclusion Criteria	Exclusion criteria
Weick³⁷ 2015 USA	803	54	66	66.5% White	ETOH: 35 HCV: 43 HCC 25 NASH: 5	MELD (mean): 20 BMI (mean): 29 DM: 23% CAD: 4%	Patients s/p LT at their center 2000–2011	Prior LT Dual Liver Kidney Transplant Survival < 3 months post-OLT F/u < 3 months On everolimus
Nicolau-Raducu²⁷ 2015 USA	389	55* (IQR 50–60)	65	62% White 15% Black	Viral: 44 NASH/cypto: 19 ETOH: 16	MELD (median): 22 BMI (median): 29 DM: 31% CAD: 6% Tobacco Use: 35%	Consecutive patients s/p LT at their center 2008–2011	None
DiMaira¹⁸ 2015 Spain	250	56* (range 18–68)	69.6		Viral: 40 ETOH: 28.8 NASH: 1.6	MELD (median): 13.4 BMI 30: 8.8% DM: 21% Tobacco Use: 53%	Patients s/p LT at their center 2006–2008	Age < 18 Prior LT Multi-organ Transplant HIV Endocrine Disorders Metastatic Malignancy Cystic Fibrosis
Joseffsson²² 2014 Sweden	234	52 (SD 10.5)	69	NR	ETOH: 36 Viral: 23.5 Cholestatic: 18 Crypto/NASH: 8.5	MELD (mean): 16.5 DM: 12% CAD: 8% Tobacco Use: 43%	Patients s/p LT at their center 1999–2007	Age < 18 Prior LT Acute Liver Failure Multi-organ Transplant
Joseffsson²¹ 2014 Sweden	202	52 (SD 11)	69	NR	ETOH: 36.5 Viral: 26 Cholestatic: 19.5 Crypto/NASH: 9	MELD (mean): 16.5 DM: 20% CAD: 6.5% Tobacco Use: 51.5%	Patients s/p LT at their center 1999–2007	Age < 18 Prior LT Acute Liver Failure Multi-organ Transplant Lack of baseline GFR
Watt³⁵ 2014 USA	154	55 (SD 9.2)	64.9	NR	Cholestatic: 30.8 ETOH: 16.8 HCV: 14.4 Cryptogenic: 11.9	MELD (mean): 19.3 BMI (mean): 25.6 DM: 20.8% Tobacco Use: 50%	Nested case control study. Patients s/p LT at three centers 1990–1994	Age < 18 Prior LT CV event prior < 4 months post-OLT
VanWagner³⁴ 2014 USA	1024	56.3 (9.7)	65.9	71.6% White	NR	NR	Patients s/p LT at their center 2002–2012	Age < 18 Prior LT
Albeldawi¹² 2012 USA	775	53.3* (IQR 46–59)	66	84% White	HCV: 33.2 ETOH: 14.5 Crypto/NASH: 16	BMI 1yr post-OLT (median): 28 DM (1yr post-OLT (median): 41%	Patients s/p LT at their center 1996–2008	Age < 18
Coss¹⁶ 2011 USA	230	50.7 (SD 10.2)	57	NR	Viral: 31.5 NASH: 18.1	BMI (mean): 26.3 DM: 22.6% CAD: 16.1% Tobacco Use: 59.1%	Patients s/p LT at their center 1998–2001	Age < 18 Familial amyloidosis
Laish²⁵ 2011 Israel	252	54.5 (SD 12.8)	57.9	NR	HCV: 35 HBV: 22.2 Crypto: 11.1	BMI (mean): 24.5 DM: 14%	Consecutive patients s/p LT at their center 1991–2007	< 6 months follow-up

Study and Country	N	Age (mean)	% Male	Race	Indication for LT (%)	Other Patient Characteristics	Study Population	
							Inclusion Criteria	Exclusion criteria
Wat³⁶ 2010 USA	798	49.4 (range 18–77)	55.5	80% White	Cholestatic: 29 HCV: 24 ETOH: 12.8 Crypto: 10.7	DM: 15%	Patients s/p LT at three centers 1990–1994	Age <18 Prior LT
Laryea²⁶ 2007 Canada	118	54	59	NR	ETOH: 20 Crypto: 17 HCV 16	BMI (mean): 29	Patients s/p LT at their centers 1998–2005	Died < 3 months post-LT
Borg¹³ 2007 Netherlands	311	42.3 (range 17–66)	45.6	NR	Cholestatic: 34 Viral: 12 Cryptogenic: 12	DM: 20.9%	Patients s/p LT at their centers 1979–2001	Age <18 Prior LT Died <1yr after LT History of MI, angina, CHF, PAD, CVA prior to LT
Guckelberger¹⁹ 2006 Germany	303	48 [*]	57.8	NR	NR	NR	Patients s/p LT at their centers 1988–1994	Died before census data obtained Required repeat LT Lost to follow-up Infant at LT

AIH, autoimmune hepatitis; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Crypto, cryptogenic; CVA, cerebrovascular; DM, diabetes mellitus; DSE, dobutamine stress ECHO; TTE, transthoracic echocardiogram; ETOH, alcohol; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; IQR, interquartile range; LT, liver transplant; MELD, model for end stage liver disease; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; NR, not reported; PAD, peripheral arterial disease; SD, standard deviation; s/p, status-post;

^{*} Median

Table 2

General Characteristics of Included Studies: Cardiac Imaging Modalities

Study and Country	N	Age (mean)	% Male	Race	Indication for LT (%)	Other Patient Characteristics	Study Population	
							Inclusion Criteria	Exclusion criteria
Includes Long Term CV Outcomes (>6 months)								
Snipelisky ³¹ 2014 USA	66	59	68	NR	HCV: 29 NASH/crypto: 27 ETOH: 20	MELD (mean): 16.5 BMI(mean):30 DM: 45% Tobacco Use:30%	Patients s/p LT at their center with coronary angiography within 1 year of DSE.	<3 yr follow-up
Cassagneau ¹⁵ 2012 France	79	52.9 (SD 10)	76	NR	ETOH: 24.1 HCV: 21 Crypto: 3.8	MELD (mean): 15 DM: 25.3% Tobacco Use: 45.6%	Patients s/p LT at their center between 2005–2008.	< 18 years old Lack of preoperative CTA or DSE <1 yr follow-up
Jodocy ²⁰ 2012 Austria	54	56 (SD 6.4)	78	NR	ETOH: 31 HCV: 20 NASH/crypto: 15	MELD (mean): 15.9 BMI (mean): 26.6 DM: 19% Tobacco Use: 39%	Patients s/p LT at their center between 2005–2006.	Lack of preoperative CTA
Opree-Lager ²⁸ 2011 Netherlands	156	49.7 (SD 10.9)	69.2	NR	ETOH 23.7 HCV 17.9 Crypto: 3.2	MELD (mean): 11.8 DM: 17.9% Tobacco Use: 30.1%	Patients s/p LT at their center between 1998–2009.	NR
Senzolo ³⁰ 2008 Italy	24	49.5 (SD 8.8)	75	NR	Viral:54 ETOH: 25	Obese: 12% DM: 29%	Consecutive patients listed for LT at their center.	NR
Zoghbi ³⁸ 2003 USA	339 87 with SPECT	51 (SD 11)	63	84% White 10% Black	Viral:45 ETOH: 11	DM: 16% Tobacco Use: 12% CAD: 9%	Patients s/p LT at their center between 1998–2001.	< 18 years old

BMI, body mass index; CAD, coronary artery disease; Crypto, cryptogenic; CTA, computed tomography angiography; CV, cardiovascular; ; DM, diabetes mellitus; DSE, dobutamine stress ECHO; TTE, transthoracic echocardiogram; ETOH, alcohol; HCV, hepatitis C virus; LT, liver transplant; MELD, model for end stage liver disease; NASH, nonalcoholic steatohepatitis; NR, not reported; ; SD, standard deviation; s/p, status-post;

Table 3
Outcomes and Predictors Evaluated and Summary of Results: Predictors of Cardiovascular Events Post Liver Transplant

Study	Definition of Outcome	Outcome Timeframe	% with Outcome	Follow-up	Predictors Significant on Multivariate Analysis	Effect Size (95% CI)
Short Term CV Outcomes Only (<6 months)						
Konerman ²³ 2016	Cardiopulmonary Death: primary cardiac arrest, cardiogenic shock, CHF, MI, arrhythmia, massive PE, respiratory failure	< 6 months post-LT	50	6 months	Incomplete Assessment of Right Ventricular Systolic Function	HR 6.57 (2.50–17.25)
Kong ²⁴ 2015	-Nonfatal MI :records, ECG, troponin >0.2ng/mL ⁻¹ -Arrhythmia: Vtach, Vfib, HB -Cardiac death: fatal MI, CHF	1 month	8.6	1 month	Gender (Female) Coronary calcium score >400	OR 2.76 (1.37–5.57) OR 4.62 (1.14–18.72)
Raevens ³⁹ 2014	-CAD -CHF -Arrhythmia -Persistent hypertension -Pulmonary hypertension -Asystole	1. 3 months 2.>3 months	1.5 2.2	NR	Moderate/severe TR	NR
Dare ¹⁷ 2014	CV events: “ie, arrhythmia, MI” [*]	30 days	NR	30 days	Prolonged Operative Time BMI (obese vs. nonobese) %Body Fat (obese vs. nonobese) Obese with DM Obese with HTN or CAD	CR 1.01 (1.00–1.01) CR 1.11 (1.06–1.16) CR 1.05 (1.03–1.08) CR 4.04 (1.75–9.31) CR 4.78 (1.37–16.76)
VanWagner ³³ 2014	Cardiac Death: cardiac arrest, MI, CHF, arrhythmia, CVA, thromboembolism	30 days	1.1	30 days	Age (years) ICU status Ventilator status MELD PVT National Organ Allocation Cold Ischemia Time	OR 1.02 (1.01–1.03) OR 1.86 (1.34–2.60) OR 2.05 (1.46–2.89) OR 1.02 (1.01–2.14) OR 1.49 (1.14–1.95) OR 1.52 (1.08–2.14) OR 1.03 (1.01–1.05)
Safadi ²⁹ 2009	Nonfatal MI: troponin I > 0.2	<30 days post-LT	9.4	30 days	Prior CVA Diuretic Use DSE	OR 7.45 (1.–32.68) OR 0.43 (0.19–0.98) NR
Fouad ² 2009	-MI -Arrhythmia: Afib, Vtach, bradycardia, PVC, sinus tach, SVT -Pulmonary edema -Cardiac death -Pulmonary HTN -Pericardial effusion -RA thrombus	< 6 months post-LT	41.6	6 months	i-MELD Intraoperative cardiac event	OR 1.08 (1.02–1.14) OR 5.89 (1.82–19.14)
Umphrey ³² 2008	-MI -CHF -Cardiac death -Asystole or Symptomatic Vtach	< 4 months post-LT	10	4 months	MELD Max predicted heart rate on DSE Max peak rate pressure product on DSE	NR

Study	Definition of Outcome	Outcome Timeframe	% with Outcome	Follow-up	Predictors Significant on Multivariate Analysis	Effect Size (95% CI)
Includes Long Term CV Outcomes (>6 months)						
Bushyhead ¹⁴ 2016	Inpatient hospitalizations for: -MI -CHF	Over follow-up period	3.5	NR	Pulmonary Artery Systolic Pressure (PASP; per 5mmHg) PBC (vs. EtOH/HCV) Crypto (vs. EtOH/HCV)	HR 1.79 (1.48–2.17) HR 21.9 (1.33–362.22) HR 19.4 (1.21–312.27)
Weick ²⁷ 2015	Development of CAD or CVA *	> 4 months	7.8	4.42 yr (mean)	Age at LT (per yr) DM at LT	HR 1.06 NR
Nicolau-Raducu ²⁷ 2015	-Acute Coronary Syndrome: unstable angina or MI -troponin >0.02ng/mL, CPK>6.5ng/mL, MB >5% -b/w 1 or more of following: chest pain, ECG changes c/w ischemia, new wall motion abnormalities on ECG -New onset CHF: worsening LV dysfunction -Arrhythmia: Afib, symptomatic bradycardia -Cardiac Arrest: asystole, symptomatic Vtach/Vfib -excluded sepsis or MSOF requiring cardiac resuscitation -CVA -PVD	1.Early: <1 year 2.Late: >1 year	1.15.2 2. 3.9	3.4 yr (median)	Age at LT (per year) MELD NASH/cryptogenic cirrhosis h/o CAD Acute Kidney Injury Pre-LT requirement for vasopressors	OR 0.9 (0.85–0.96) OR 1.1 (1.0–1.2) NR OR 7.7 (2.7–21) OR 7.9 (2.3–26.9) OR 7.8 (2–27)
DiMaira ¹⁸ 2015	-Coronary Death -Myocardial Infarction -Coronary Insufficiency -Angina -CVA: ischemic or hemorrhagic, TIA -PAD -CHF -Arrhythmia	Over follow-up period	14.4	5.6 (median)	Framingham Risk Score	HR 1.06 (1.02–1.10)
Joseffsson ²² 2014	-Arrhythmia: Afib, Aflutter, severe bradycardia, ventricular arrhythmia -Acute Coronary Syndrome: "attending cardiologist diagnosis" or ICD-10 code -Sudden Cardiac death/acute circulatory failure	1. Peri-transplant 2. Post-LT discharge	1.17 2.14.5	4yr (mean)	Prolonged Qtc Q wave ECG feature consistent with CAD	NR
Joseffsson ²¹ 2014	-Arrhythmia: Afib, Aflutter, severe bradycardia, Vtach, Vfib -Acute Coronary Syndrome: "attending cardiologist diagnosis" or ICD-10 code -Sudden Cardiac death/acute circulatory failure	1. Peri-transplant 2. Post-LT discharge	1.17.5 2.12	3.8 yr (mean)	Baseline Renal impairment (GFR <60) Prolonged Qtc	HR 2.19 (1.25–3.85) HR 4.75 (2.07–10.9)

Study	Definition of Outcome	Outcome Timeframe	% with Outcome	Follow-up	Predictors Significant on Multivariate Analysis	Effect Size (95% CI)
Watt ³⁵ 2014	-MI, -CVA, -Cardiac arrest -CHF	1. Over follow-up period 2. > 4 months post-LT	1. 18.4% 2. 9.6%	10 yr (mean)	Baseline Adiponectin	HR 0.794 (0.65–0.98)
VanWagner ³⁴ 2014	-MI -CHF -Afib -Cardiac Arrest -CVA -PE	1. 30 day 2. 1 yr	1. 23.2 2. 31.4	1 yr	30day Age MELD Race CHF CAD CVA 1yr Age MELD Race CHF CVA	OR 1.04 (1.02–1.06) OR 1.05 (1.04–1.07) OR 2.44 (1.34–4.42) OR 2.3 (1.6–3.4) OR 1.5 (1.09–2.1) OR 2.4 (1.2–4.8) HR 1.05 (1.03–1.06) HR 1.04 (1.03–1.05) HR 1.74 (1.15–2.63) HR 1.9 (1.5–2.4) HR 1.8 (1.1–2.8)
Albeldawi ¹² 2012	-Acute Coronary Syndrome: STEMI, NSTEMI, UA -CHF -Arrhythmias -Stable Angina -Ischemic CVA -PVD	Over follow-up period	10.7	3.3 yr (median)	Age at LT (years) Gender (Male) DM post-LT HTN post-LT Mycophenolate Mofetil Etiology of Liver Disease (PBC/ PSC)	OR 1.2 (1.1–1.3) OR 2.0 (1.2–3.3) OR 2.0 (1.3–3.3) OR 1.8 (1.1–3.0) OR 2.0 (1.3–3.2) HR 0.3 (0.1–0.9)
Coss ¹⁶ 2011	-CAD: stable or unstable angina, angiographic evidence of atherosclerosis >50% -MI -CHF -CVA or TIA	1. < 1 year 2. > 1 year	1. 8.6 2. 16.9	8.2 yr (median)	CAD DM Pre-LT troponin >0.07 ng/mL Tobacco use	HR 6.25 (3.43–11.38) HR 1.87 (1.03–3.40) HR 1.94 (1.05–3.56) HR 2.16 (1.13–4.11)
Laish ²⁵ 2011	-TIA -CVA -ACS -MI	>6 months	10.3	6.2 yr (mean)	PTMS	NR
Watt ³⁶ 2010	CV Death: MI, CVA, Cardiac arrest, CHF/ cardiomyopathy	>1-year post-LT	5	10 yr (median)	Age (decades) Cryptogenic cirrhosis ETOH cirrhosis	HR 2.21 (1.34–3.36) HR 5.59 (2.04–15.29) HR 4.79 (1.73–13.27)
Laryea ²⁶ 2007	-CVA/TIA -MI -ACS -Sudden Cardiac Death	Over follow-up period	21.2	4.8 yr (mean)	PTMS	NR
Borg ¹³ 2007	-Acute MI -Sudden Cardiac Death -Angina: stable and unstable -CHF -CVA or TIA -PVD	>1-year post-LT	7.7	6.2yr (median)	Age (year) Renal insufficiency (1yr post-LT) Effective Anti-hypertensive Regimen (1 yr post-LT)	HR 1.17 (1.02–1.34) HR 0.06 (0.01–0.41) NR

Study	Definition of Outcome	Outcome Timeframe	% with Outcome	Follow-up	Predictors Significant on Multivariate Analysis	Effect Size (95% CI)
Guckelberger ¹⁹ 2006	-MI: ECG or cardiac enzyme elevation -CAD: clinical symptoms confirmed with stress ECG or LHC -CVA/TIA -PAD	10yr	13.2	10 years	Age (year) Gender (male)	OR 1.06 (1.02–1.10) OR 2.85 (1.33–6.08)

Afib, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CR, count ratio; Crypto, cryptogenic; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; DSE, dobutamine stress ECHO; TTE, transthoracic echocardiogram ;ECG, electrocardiogram ;ETOH, alcohol; GFR, glomerular filtration rate; HB, heart block; HCC, hepatocellular carcinoma; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; LT, liver transplant; MELD, model for end stage liver disease; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; NR, not reported; NSTEMI, non-ST elevation MI; OR, odds ratio; PAD, peripheral arterial disease; PBC, primary biliary cirrhosis; PE, pulmonary embolism; PSC, primary sclerosing cholangitis; PTMS, posttransplant metabolic syndrome; PVD, peripheral vascular disease; PVT, portal vein thrombosis; SD, standard deviation; STEMI, ST elevation MI; TR, tricuspid regurgitation; VFib, ventricular fibrillation; Vitach, ventricular tachycardia; UA, unstable angina

* No additional detail provided for definition of outcome

Table 4

Outcomes Evaluated and Summary of Results: Cardiac Imaging Modalities

Study	Definition of Outcome	% with Outcome	Follow-up Duration	Imaging Modalities	Assessment
Snipelisky ³¹ 2014	Cardiac-related mortality [*]	7.5	3 yr	DSE	DSE has limitations as a screening test for LT. DSE has poor sensitivity, specificity, NPV, PPV and may not be an adequate screening tool for CAD in pre-LT patients
Cassagneau ¹⁵ 2012	Primary: Composite of major cardiac events including -Cardiac Death -Nonfatal MI: q-wave on ECG, CK-MB >3× ULN, with elevated troponin Ic -CAD requiring revascularization: pre or postoperative -CHF -Arrhythmia: Vtach, Vfib, symptomatic heart block Secondary: Composite of major coronary events including -Cardiac Death -Q-wave MI -CAD requiring revascularization: pre or postoperative	10 4	1.5 yr	DSE Coronary CTA	Coronary CTA has excellent negative predictive value (95%) for postoperative major cardiac events and for postoperative major coronary events in LT patients. Prognostic value comparable to DSE
Jodocy ²⁰ 2012	-MI -Angina -Arrhythmia -CHF	0	9–15 months	Coronary CTA	CTA imaging was very effective to assess peri- and postoperative CV risk.
Oprea-Lager ²⁸ 2011	-MI or myocardial ischemia -Arrhythmia -Pulmonary edema	25.6	3.35 yr	SPECT	Abnormal SPECT showed a statistically significant increase in mortality but not in cardiac complications
Senzolo ³⁰ 2008	*Cardiac events ^{*,*}	0	86.1 ± 9.5 months	SPECT/ MIBG scintigraphy	SPECT MPI has a limited role and low PPV. Abnormal myocardial perfusion SPECT may be due to alterations in the microcirculation (as evidenced by MIBG scintigraphy)
Zoghbi ³⁸ 2003	-Nonfatal MI: new chest pain with new ST-segment changes and transient elevation in CK and CK-MB or Troponin -Cardiac Death	2.3	21 ± 13 months	SPECT	Normal SPECT has high NPV.

CAD, coronary artery disease; CHF, congestive heart failure; CTA, computed tomography angiography CV, cardiovascular; DSE, dobutamine stress ECHO; TTE, transthoracic echocardiogram; ECG, electrocardiogram; LT, liver transplant; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; Vfib, ventricular fibrillation; Vtach, ventricular tachycardia; ULN, upper limit of normal;

* No additional detail provided for definition of outcome