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Cardiovascular mortality in liver and kidney transplant recipients

A retrospective analysis from a single institution

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Abstract

Previous studies have demonstrated cardiovascular causes to be among the leading causes of death after liver (LT) and kidney transplantation (KT). Although both recipient populations have unique pre-transplant cardiovascular burdens, they share similarities in post-transplant exposure to cardiovascular risk factors. The aim of this study was to compare cardiovascular mortality after LT and KT.

We analyzed causes of death in 370 consecutive LT and 207 KT recipients from in-hospital records at a single tertiary transplant center. Cardiovascular causes of death were defined as cardiac arrest, heart failure, pulmonary embolism, or myocardial infarction.

After a median follow-up of 36.5 months, infection was the most common cause of death in both cohorts, followed by cardiovascular causes in KT recipients and graft-related causes in LT recipients in whom cardiovascular causes were the third most common. Cumulative incidence curves for cardiovascular mortality computed with death from other causes as the competing risk were not significantly different ($P = .36$). While 1-year cumulative cardiovascular mortality was similar (1.6% after LT and 1.5% after KT), the estimated 4-year probability was higher post-KT (3.8% vs. 1.6%). Significant pre-transplant risk factors for overall mortality after KT in multivariable analysis were age at transplantation, left ventricular ejection fraction <50%, and diastolic dysfunction grade 2 or greater, while significant risk factors for cardiovascular mortality were peripheral artery disease and left ventricular ejection fraction <50%. In the LT group no variables remained significant in a multivariable model for either overall or cardiovascular mortality.

The present study found no significant overall difference in cardiovascular mortality after LT and KT. While LT and KT recipients may have similar early cardiovascular mortality, long-term risk is potentially lower after LT. Differing characteristics of cardiovascular death between these two patient populations should be further investigated.

Abbreviations: BMI = body mass index, DM = diabetes mellitus, ESLD = end-stage liver disease, ESRD = end-stage renal disease, KT = kidney transplantation, LT = liver transplantation, LV = left ventricular, PAD = peripheral artery disease.

Keywords: cardiovascular mortality, cardiovascular risk factors, kidney transplantation, liver transplantation

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Liver transplantation (LT) and kidney transplantation (KT) improve outcomes and quality of life in patients with end-stage liver disease (ESLD)[1] and end-stage renal disease (ESRD).[2] As a result of improved accessibility and recipient survival, transplant candidates are becoming increasingly older, have more comorbidities, and experience more long-term complications, all of which created new challenges in post-transplantation care.

Both LT and KT candidates have complex burdens of cardiovascular disease, at least partly attributed to specific characteristics of ESLD and ESRD. The hyperdynamic circulation in ESLD that was once considered to lower cardiovascular risk can, in combination with poor functional status, mask cardiac conditions during non-invasive cardiac evaluation,[3] traditional cardiovascular risk factors are becoming increasingly prevalent in the aging population of LT candidates, and coronary artery disease is considered to be more common than previously thought.[4] ESRD patients have extremely high cardiovascular morbidity and mortality[5] stemming from a high prevalence of cardiovascular risk factors either as the primary cause of ESRD or part of its clinical manifestation and impaired kidney function in itself causing cardiac dysfunction.[6] In the post-transplant period, a multitude of factors can influence cardiovascular risk

in transplant recipients with potential amelioration from adequate graft function after KT, and aggravation in both recipient populations from new-onset dyslipidemia, hypertension, glucose intolerance, and nephrotoxicity as side effects of immunosuppressive agents.[7–10]

Cardiovascular events are recognized as prominent causes of early and late mortality in LT[11–14] and KT recipients.[15–20] To the extent of our knowledge, no previous analyses compared the risk of death from cardiovascular causes in these two patient populations. This study aimed to analyze post-transplant cardiovascular mortality in LT and KT recipients from a single institution. We additionally attempted to identify potential predictors of overall and cardiovascular mortality with cardiovascular factors collected during routine pre-transplant evaluation.

2. Patients and methods

2.1. Patient selection

We retrospectively identified consecutive cases of orthotopic LT from deceased donors and KT from live or deceased donors from a single tertiary center. Adult patients (≥ 18 years) who underwent LT between October 2014 and March 2018 and KT from December 2013 to December 2017 were included in the study. Each patient was reviewed only once. Patients who underwent both LT and KT were excluded.

The study was approved by the University Hospital Merkur ethics committee, and all participants provided informed consent.

2.2. Data collection and follow-up

All recipients underwent preoperative evaluation which excluded patients who fulfilled the criteria for moderate to severe pulmonary hypertension on right heart catheterisation[21] and those with unmanageable active cardiovascular disease. Pre-transplant patient data were acquired from in-hospital electronic records and included demographics, smoking status, relevant comorbid conditions, and time on dialysis. Patients were considered active smokers if they had smoked in the last six months before transplantation. Hypertension was defined as systolic pressure >140 mmHg or diastolic pressure >80 mmHg recorded on more than one out-patient visit or use of antihypertensive medication. Hyperlipidemia was defined as fulfillment of laboratory criteria from a fasting lipid profile with the following cutoff values: triglycerides >1.7 mmol/L (150 mg/dL), total cholesterol >5 mmol/L (193 mg/dL) or low-density lipoproteins >3 mmol/L (116 mg/dL), or use of lipid-lowering agents. Diabetes mellitus (DM) was defined as hemoglobin A1c >6.5%, fasting blood glucose >11mmol/L (126 mg/dL) recorded on more than one occasion, a clinical note of any previous history of DM, or use of oral antihyperglycemic agents or insulin.

Echocardiographic parameters were obtained from 2-D Doppler transthoracic echocardiograms at a single time-point closest to transplantation (no later than 12 months prior), recorded as part of a routine pre-transplant evaluation. 2-D-guided M-mode and biplane Simpson's method were used to assess left ventricular (LV) ejection fraction. LV diastolic function was assessed with mitral inflow velocities and E/A ratio and tissue Doppler imaging of mitral annular motion (the mean value of septal and lateral early diastolic mitral annular velocity e' and the average E/e' ratio). Valvular abnormalities were evaluated with color flow Doppler and graded as none/mild/moderate/severe as per guideline recommendations.[22,23] Right ventricular systolic pressure was estimated from tricuspid regurgitation jet velocity with the modified Bernoulli equation and right atrial pressure approximated at 10 mm Hg.

Transplant recipients were followed through out-patient records, in-hospital progress notes, and final discharge summaries from the date of transplantation until the date of death, last follow-up, or June 2019. The primary endpoint was death from cardiovascular causes (cardiac arrest, heart failure, pulmonary embolism, or myocardial infarction); the secondary endpoint was death from any cause.

2.3. Statistical analysis

Collected data were summarized with descriptive statistics (count and frequency for categorical variables, the median and interquartile range for continuous variables). Inter-group comparisons were performed with the χ^2 test, Fisher exact test or Mann-Whitney *U* test. Survival probabilities were estimated with the Kaplan-Meier method and compared with the log-rank test. Cumulative incidence curves were computed to illustrate the risk of death from cardiovascular causes after LT and KT with death from other causes as the competing risk. Gray's modified χ^2 test was used to test the equality of cumulative incidence curves between groups.[24]

Additional explorative analyses of potential pre-transplant predictors of overall and cardiovascular mortality after LT and KT were performed with Cox proportional hazards regression. Potential univariable predictors were age at transplantation (continuous), age >60 years, sex, body mass index (BMI) ≥ 30 kg/m^2, smoking status, presence of diabetes mellitus, hypertension, hyperlipidemia or peripheral artery disease (PAD), previous cardiovascular incident (myocardial infarction, stroke or transitory ischemic attack), >1 year of dialysis, LV ejection fraction <50%, right ventricular systolic pressure >35 mm Hg, LV diastolic dysfunction grade ≥ 2, aortic stenosis (≥ mild), mitral regurgitation (≥ moderate) and tricuspid regurgitation (≥ moderate). The proportional hazards assumption for each variable was examined graphically with Schoenfeld residuals. Variables with $P < .1$ at univariable analysis were considered for inclusion in multivariable models. The final model selection was made with backward elimination. Retrospective data collection resulted in some missing data points, which were omitted from the analysis. Statistical significance was established at an α level of .05 throughout the analysis. All *P* values are based on two-sided tests. The analysis was performed with RStudio for OS X version 1.2.1335 (RStudio Inc.).

3. Results

During the enrolment period, 591 patients underwent either LT or KT. We excluded 14 patients for receiving both LT and KT. Of the 577 patients included in the final analysis, 370 underwent LT and 207 underwent KT. Fifty-one patients (8.8%) were lost to follow-up, 39 in the LT group (10.5%) and 12 in the KT group (5.8%). Thirty-five LT and 2 KT recipients underwent retransplantation during the study period. Participants were predominantly male in both cohorts. Although KT candidates were significantly younger, they had a higher prevalence of hypertension, hyperlipidemia, and PAD. Other pre-transplant patient characteristics are summarized in Table 1 and the underlying causes of ESLD and ESRD in Table 2.

Table 1

Pre-transplant patient characteristics.

	All patients (N = 577)	LT candidates (n = 370)	KT candidates (n = 207)	*P* value
Demographic characteristics				
Age at transplantation, median (IQR)	57.6 (48.5-63.5)	59.3 (52.6-64.4)	51.7 (40.3-60.9)	<.001
Age >60 yr	238/577 (41.2)	176/370 (47.6)	62/207 (30.0)	<.001
Male sex, No. (%)	402/577 (69.7)	259/370 (70.0)	143/207 (69.1)	.89
Clinical characteristics				
BMI, median (IQR)	25.7 (22.8-29.1)	26.0 (23.1-29.3)	25.4 (22.4-28.8)	<.001
BMI ≥ 30 kg/m^2, No. (%)	111/564 (19.7)	70/361 (19.4)	41/203 (20.2)	.90
Current smoker, No. (%)	144/544 (26.5)	97/352 (27.6)	47/192 (24.5)	.50
Diabetes mellitus, No. (%)	174/574 (30.3)	108/368 (29.3)	66/206 (32.0)	.56
Hypertension, No. (%)	358/572 (62.6)	161/366 (44.0)	197/206 (95.6)	<.001
Hyperlipidemia, No. (%)	288/555 (51.9)	148/357 (41.5)	140/198 (70.7)	<.001
>1 year of dialysis, No. (%)	170/573 (29.7)	0	170/203 (83.7)	
PAD, No. (%)	58/575 (10.1)	15/368 (4.1)	43/207 (20.8)	<.001
Previous MI, No. (%)	25/577 (4.3)	12/370 (3.2)	13/207 (6.3)	.13
Previous CVI or TIA, No. (%)	21/577 (3.6)	13/370 (3.5)	8/207 (3.9)	>.99
Echocardiographic characteristics				
LV ejection fraction <50%, No. (%)	8/561 (1.4)	4/360 (1.1)	4/201 (2.0)	.47
RVSP >35 mmHg, No. (%)	96/560 (17.1)	64/359 (17.8)	32/201 (15.9)	>.99
LV diastolic dysfunction, grade ≥ 2., No. (%)	99/559 (17.7)	68/357 (19.0)	31/202 (15.3)	.32
Aortic stenosis, ≥ mild, No. (%)	37/561 (6.6)	29/360 (8.1)	8/201 (4.0)	.09
Mitral regurgitation, ≥ moderate, No. (%)	59/561 (10.5)	39/360 (10.8)	20/201 (10.0)	.85
Tricuspid regurgitation, ≥ moderate, No. (%)	82/561 (14.6)	58/360 (16.1)	24/201 (11.9)	.22

BMI = body mass index, CVI = cerebrovascular incident, IQR = interquartile range, KT = kidney transplant, LT = liver transplant, LV = left ventricular, MI = myocardial infarction, PAD = peripheral arterial disease, RVSP = right ventricular systolic pressure, TIA = transitory ischemic attack.

Table 2

Indications for liver and kidney transplantation.

Indication	No. (%)
Liver transplantation[*,†], n	370
Alcoholic liver disease	160 (43.2)
Cryptogenic cirrhosis	42 (11.4)
HCV	56 (15.1)
HBV	19 (5.1)
Biliary cirrhosis	47 (12.7)
HCC	128 (34.6)
Cholangiocarcinoma	13 (3.5)
NASH	3 (0.8)
AIH	5 (1.4)
NET	6 (1.6)
Acute liver failure	6 (1.6)
Other[‡]	12 (3.2)
Kidney transplantation, n	207
Diabetes mellitus	52 (25.1)
Hypertension	15 (7.2)
PKD	30 (14.5)
Glomerulonephritis	54 (26.1)
Pyelonephritis	3 (1.4)
Unknown	49 (23.7)
Other[§]	7 (3.4)

AIH = autoimmune hepatitis, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HBV = hepatitis B virus, NASH = non-alcoholic steatohepatitis, NET = neuroendocrine tumor, PKD = adult polycystic kidney disease.

[*] More than one indication was documented in some cases.

[†] One missing datum.

[‡] Including Wilson's disease, epithelioid hemangioma, α1 antitrypsin deficiency, Budd-Chiari syndrome, adenoma, Caroli disease.

[§] Including amyloidosis, Balkan endemic nephropathy, multiple myeloma, nephrolithiasis, reflux nephropathy, granulomatosis with polyangiitis.

After a median follow-up of 35.5 months (range 0.4–64.5 months), KT recipients had significantly better post-transplant survival ($P = .008$) with 1-month, 1-year and 4-year overall survival estimates of 99% (95% CI, 97.7–100%), 95.6% (95% CI, 92.8–98.5%) and 87.7% (95% CI 82.4–93.3%) respectively, while 1-month, 1-year and 4-year estimates for LT recipients were 93.2% (95% CI, 90.7–95.8%), 87% (95% CI, 83.6 - 90.6%), and 83% (95% CI, 79.1–87.1%). We recorded 80 (13.9%) deaths during follow-up, 60 (16.2%) among LT and 20 (9.7%) among KT recipients. Infection was the most common cause of death in both groups in the first post-transplant year and beyond (Tables 3 and 4), followed by graft-related causes and cardiovascular events in LT recipients, while cardiovascular

Table 3

Causes of death after liver transplantation.

Cause of death	All patients (n = 370)	<1 yr	≥ 1 yr
Total[*]	60	47	13
Cardiovascular[†]	6 (10.0%)	6 (12.7%)	0
Cardiac arrest	4 (6.7%)	4 (8.5%)	0
Pulmonary embolism	2 (3.3%)	2 (4.3%)	0
Graft dysfunction	9 (15.0%)	5 (10.6%)	4 (30.8%)
Sepsis	33 (55.0%)	24 (51.1%)	9 (69.2%)
DIC	2 (3.3%)	1 (2.1%)	1 (7.7%)
Hemorrhage	8 (13.3%)	7 (14.9%)	1 (7.7%)
Malignancy	4 (6.7%)	4 (8.5%)	0
Unknown	4 (6.7%)	3 (6.4%)	1 (7.7%)

DIC = disseminated intravascular coagulation.

[*] Primary causes of death were classified as either cardiovascular or non-cardiovascular, however more than one non-cardiovascular cause of death was documented in some cases.

[†] Defined as cardiac arrest, heart failure, pulmonary embolism, myocardial infarction.

Table 4

Causes of death after kidney transplantation.

Cause of death	All patients (n=207)	<1 yr	≥ 1 yr
Total	20	9	11
Cardiovascular*	6 (30.0%)	3 (33.3%)	3 (27.3%)
Cardiac arrest	2 (10.0%)	1 (11.1%)	1 (9.1%)
Heart failure	1 (5.0%)	0	1 (9.1%)
Pulmonary embolism	2 (10.0%)	1 (11.1%)	1 (9.1%)
Myocardial infarction	1 (5.0%)	1 (11.1%)	0
Sepsis	9 (45.0%)	5 (55.5%)	4 (36.4%)
Pneumonia	1 (5.0%)	0	1 (9.1%)
Malignancy	2 (10.0%)	0	2 (18.2%)
Unknown	2 (10.0%)	1 (11.1%)	1 (9.1%)

* Defined as cardiac arrest, heart failure, pulmonary embolism, myocardial infarction.

Table 5

Pre-transplant variables associated with overall mortality after kidney transplantation.

	Univariable		Multivariable	
Variable	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Age (continuous)	1.1 [1.0–1.1]	.003	1.1. [1.0–1.1]	.004
Age >60 years	2.7 [1.1–6.6]	.03		
PAD	2.8 [1.1.–6.8]	.03		
LV ejection fraction <50%	10.0 [2.3–44.0]	.002	7.6 [1.6–35.5]	.01
LV diastolic dysfunction, grade ≥ 2	4.6 [1.8–11.0]	.001	3.9 [1.5–10.0]	.004
Mitral regurgitation, ≥ moderate	3.7 [1.3–10.0]	.01		

LV = left ventricular, PAD = peripheral artery disease.

events were the second most common cause of death in KT recipients.

Cumulative incidence curves for cardiovascular mortality computed with death from other causes as the competing risk were not significantly different between groups ($P=.36$) (Fig. 1). However, the estimated 4-year cumulative cardiovascular mortality probability was higher in KT recipients (3.8% vs. 1.6%). Although cardiovascular mortality in the first 30 days and the first year post-transplant was similar in LT and KT recipients (1.4% vs. 1%; 1.6% vs. 1.5%), no late events (≥ 1 year) were recorded in the LT group as opposed to KT recipients in whom we registered three cardiovascular deaths beyond the first post-transplant year. This difference was more pronounced in a subgroup of older recipients (> 60 years) with 1-year probability 1.7% after LT vs. 3.2% after KT and 4-year probability 2.3% after LT vs. 10.3% after KT ($P=.16$). No cardiovascular deaths were recorded in younger KT recipients (≤ 60 years) at 1 year vs. 1.0% in LT recipients, and the 4-year probability was similar in both populations with no significant overall difference (1.0% vs. 1.4%, $P=.78$).

In univariable Cox proportional hazards analysis, age (continuous), age >60 years, PAD, LV ejection fraction <50%, diastolic dysfunction grade ≥ 2, and ≥ moderate mitral regurgitation were significant risk factors for overall mortality after KT. In a multivariable model age, LV ejection fraction <50% and LV diastolic dysfunction grade ≥ 2 remained significant (Table 5). Of note, the majority (87%) had the pseudonormal pattern (grade 2). In the LT recipient group significant univariable predictors for overall mortality were age >60 years and ≥ moderate tricuspid regurgitation). In an attempt at multivariate modelling both were merely marginally significant (Table 6).

Univariable predictors for cardiovascular mortality following kidney transplantation were similar to those for overall mortality: age (continuous), age >60 years, BMI (continuous), PAD and LV ejection fraction <50%. In a multivariable model PAD and LV ejection fraction <50% remained statistically significant (Table 7). At univariate analysis for cardiovascular mortality in LT recipients, only BMI >30 kg/m^2 met the inclusion criteria for a multivariable model, but was not statistically significant (HR 4.1, 95% CI 0.8–20.1, $P=.09$).

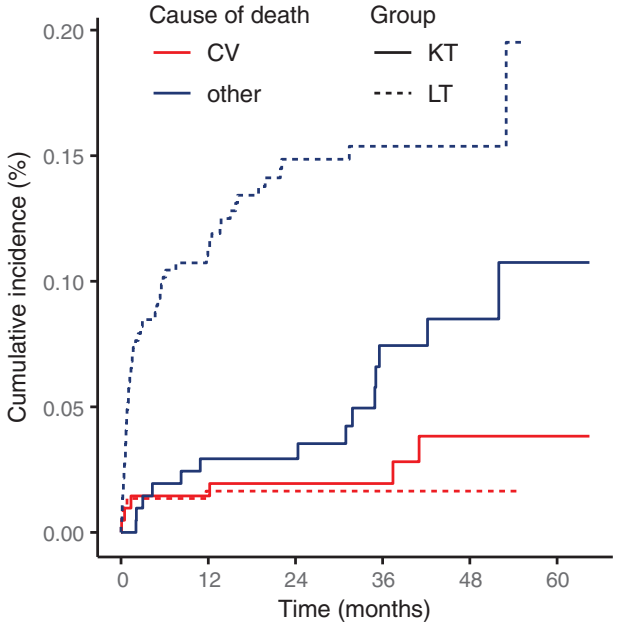

Figure 1. Cumulative incidence curves for cardiovascular mortality after liver and kidney transplantation with death from other causes as the competing risk. CV = cardiovascular, KT = kidney transplantation, LT = liver transplantation.

4. Discussion

The present study showed clear difference with respect to cardiovascular mortality between LT and KT recipients. Although the overall difference in risk of cardiovascular mortality was not significant, most cardiovascular deaths after LT occurred in the immediate perioperative period and were of non-coronary etiology, while both early and late events were captured during follow-up of KT recipients, and all defined causes of cardiovascular mortality were represented. Based on these patterns, one could speculate that continuous and

Table 6

Pre-transplant variables associated with overall mortality after liver transplantation.

	Univariable		Multivariable	
Variable	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Age >60 years	1.8 [1.1–3.1]	.02	1.6 [0.95–2.7]	.08
Tricuspid regurgitation, ≥ moderate	1.9 [1.0–3.4]	.045	1.7 [0.95–3.2]	.07

Table 7

Pre-transplant variables associated with cardiovascular mortality after kidney transplantation.

	Univariable		Multivariable	
Variable	**HR [95% CI]**	***P* value**	**HR [95% CI]**	***P* value**
Age (continuous)	1.1 [1.0–1.2]	.04		
Age >60 years	5.2 [0.95–28.6]	.06		
BMI (continuous)	1.1 [1.0–1.3]	.06		
PAD	6.2 [1.5–44.8]	.02	7.5 [1.3–42.0]	.02
LV ejection fraction <50%	18.0 [1.9–159.0]	.01	10.5 [1.1–97.3]	.04

BMI = body mass index, LV = left ventricular, PAD = peripheral arterial disease.

prolonged exposure to numerous traditional and ESRD-specific cardiovascular risk factors affects cardiovascular mortality in KT recipients at all time points as opposed to LT recipients in whom hemodynamic stress of LT mediates early post-transplant cardiovascular risk. On the other hand, long-term cardiovascular risk may be lower in LT patients.

Thirty-day cardiovascular mortality of 1.4% mainly of non-coronary causes in our cohort of LT recipients is in concordance with findings of previous multicentric analyses.[11,12] LT is a high-risk procedure[25] with major volume shifts during clamping of the hepatic vein and graft reperfusion, performed in patients with already altered hemodynamics due to ESLD. Some retrospective studies reported an association of pre-existing coronary artery disease and 30-day cardiovascular mortality,[12] or pre-transplant cardiovascular disease (defined as previous myocardial infarction, PAD, or cerebrovascular disease) and 90-day all-cause mortality.[26] In contrast, others found ESLD- and procedure-related variables to be significantly associated with the risk of perioperative cardiovascular death[11] or a composite outcome of major adverse cardiovascular events.[27,28] Patients with ESLD and very severe cardiovascular comorbidities may be generally discouraged from undergoing LT, but even subclinical disease can be significant in the setting of perioperative stress. Eligibility criteria during preoperative cardiovascular evaluation are still loosely defined and vary between centers and on a case-to-case basis.

Reversibility of ESLD-specific hemodynamic abnormalities or cardiac manifestations such as cirrhotic cardiomyopathy[29] and transitory postoperative disturbances seem to be in line with the pattern of events presented here. We recorded no cardiovascular deaths in LT recipients who survived the first post-transplant year. However, cardiovascular events are consistently among the top five causes of late mortality in LT recipients.[12–14,30] They were also found to be at higher risk for cardiovascular death in the late post-transplant period compared to the age-matched peers without LT.[31] A possible explanation is that long-term atherogenic and diabetogenic adverse effects of calcineurin and mTOR inhibitors[7–9] cumulatively raise cardiovascular risk over time, and the relatively short follow-up of this study may have been too short to capture late cardiovascular mortality. In a retrospective study by Borg et al[32] and a recent study by Koshy et al[12] the time until late death from cardiovascular events was significantly longer compared to that from non-cardiovascular causes. It should also be noted that in our study most LT recipients were on long-term immunosuppression regimens that consisted of a combination of either tacrolimus or cyclosporine with mycophenolate mofetil, which resulted in steroid-sparing. To which such sparing use of corticosteroids, may have potentially produced a more favorable post-transplant cardiovascular risk profile is a matter of speculation.

ESRD patients on dialysis are at a 10 to 20 times higher risk of cardiovascular mortality than the age-, sex-, race- and DM-matched general population.[5] Classic algorithms such as the Framingham risk score still underestimate the risk of ischemic heart disease in KT recipients, indicating excess cardiovascular risk not attributable to traditional risk factors even after successful KT.[33,34] Cardiovascular events are regarded as the most common cause of death at all time points after KT, supported by several population-based studies.[15,16,18] In our cohort, the most frequent cause of death of KT recipients were infective complications both in the first post-transplant year and beyond. Direct comparison of our results with registry data is difficult given the small sample size and single-center setting. However, limitations to these large-scale studies should be noted as well. The analysis from the United States Renal Data System included more than a third of early deaths from unknown or unrecorded causes and even more missing data points over a longer follow-up time.[18] In another US retrospective study with data from an integrated health system different data sources resulted in varying proportions of primary causes of death due to different coding systems.[17] We also enrolled recently transplanted patients. Temporal trends of leading causes of death in KT recipients demonstrate significant risk reduction for cardiovascular mortality and diverging reports regarding mortality from infection.[16,18,19] Improved cardiovascular care and newer immunosuppressive regimens (esp. steroid-sparing protocols) probably have contributed to the decrease in cardiovascular mortality.

In a multivariate model, pre-transplant LV systolic and diastolic dysfunction in KT candidates were independent risk factors for all-cause mortality after transplantation. Although KT was found to improve systolic function,[35,36] functional status, and survival[35] in ESRD patients with congestive heart failure in a prospective setting, adequately powered prospective controlled trials evaluating safety of KT in patients with various degrees of systolic heart dysfunction are lacking. On the other hand, reports on changes in LV diastolic function after KT vary.[37–39] In order to reduce negative impact of impaired systolic and diastolic heart function on post-transplant outcomes, waiting time should be shortened as much as is possible (e.g. by promoting pre-emptive and living-donor transplantation). Good control of blood pressure and optimizing graft function represent additional potentially modifiable factors for reversal of cardiac dysfunction after KT,[40] thus leading to improvement of post-transplant cardiovascular risk.

Traditional cardiovascular risk factors were not significant predictors of overall mortality in either LT or KT recipients. Similarly, PAD (a marker for generalized atherosclerosis) was a significant risk factor for cardiovascular mortality after KT, but DM, hypertension or hyperlipidemia were not independent predictors in either cohort. Since the cardiovascular risk profile of transplant recipients undergoes dynamic changes after transplantation with a high incidence of post-transplant metabolic syndrome and its components,[41,42] post-transplant risk profiling could have a better predictive value for both overall and cardiovascular mortality.

This study's single-center nature introduces limitations in generalizability as patient selection and immunosuppressive regimens may vary between institutions. It is also subject to

pitfalls inherent to all retrospective and observational studies such as missing data which might have diminished the already comparably small sample size's statistical power. We attribute the loss to follow-up encountered (8.8% of the total study population) to the division of recipient care to other smaller institutions as the data source were in-hospital electronic records from a tertiary transplant center. Participants who underwent retransplantation during the study period were predominantly LT recipients, the majority of whom experienced graft failure within the first post-transplant year and did not influence the primary outcome of cardiovascular mortality as we recorded no late cardiovascular deaths that could be potentially attributed to early postoperative stress after a second transplantation. We also recognize certain limitations regarding variable selection and definition. LV mass was not in the pre-specified scope of data collection, and LV hypertrophy could be an overlooked confounding factor between diastolic dysfunction and overall mortality given the probable etiological overlapping, high prevalence in ESRD,[43] and previous association with mortality after KT.[44] Our definitions of DM, hypertension, and hyperlipidemia which encompassed patient history and treatment records as well as records of physical and laboratory measurements may have been insufficiently precise in depicting blood pressure, glycemic and lipid control.

In summary, while this study failed to demonstrate a significant difference in the overall risk of cardiovascular death in LT and KT recipients, a more nuanced interpretation can reveal distinctions in temporal and causative patterns of cardiovascular mortality in these two populations. Cardiovascular causes contribute to early mortality both in LT and KT recipients, and late cardiovascular mortality seems to be higher in KT recipients than LT recipients, the latter warranting further investigation over a longer follow-up time and in a larger study sample. These findings stress the already recognized need for an individualized approach in investigating pre-transplant risk and providing post-transplant cardiovascular care. Prospective studies in a randomized setting that would help identify high-risk groups and optimize outcomes in transplant recipients are still generally lacking and much needed.

Author contributions

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References

[1] Duffy JP, Kao K, Ko CY, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652–9.
[2] Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341: 1725–30.
[3] Garg A, Armstrong WF. Echocardiography in liver transplant candidates. JACC Cardiovasc Imaging 2013;6:105–19.
[4] Keeffe BG, Valantine H, Keeffe EB. Detection and treatment of coronary artery disease in liver transplant candidates. Liver Transplant 2001; 7:755–61.
[5] Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9(12 Suppl): S16–23.
[6] Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease effects on the cardiovascular system. Circulation 2007;116:85–97.
[7] Heisel O, Heisel R, Balshaw R, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: A systematic review and meta-analysis. Am J Transplant 2004;4:583–95.
[8] Hakeam HA, Al-Jedai AH, Raza SM, et al. Sirolimus induced dyslipidemia in tacrolimus based vs. tacrolimus free immunosuppressive regimens in renal transplant recipients. Ann Transplant 2008;13:46–53.
[9] Trotter JF, Wachs ME, Trouillot TE, et al. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. Liver Transplant 2001;7:401–8.
[10] Glover TE, Watson CJE, Gibbs P, et al. Conversion from calcineurin to mammalian target of rapamycin inhibitors in liver transplantation: a meta-analysis of randomized controlled trials. Transplantation 2016; 100:621–9.
[11] VanWagner LB, Lapin B, Levitsky J, et al. High early cardiovascular mortality after liver transplantation. Liver Transplant 2014;20:1306–16.
[12] Koshy AN, Gow PJ, Han H-C, et al. Cardiovascular mortality following liver transplantation: predictors and temporal trends over 30 years. Eur Hear J - Qual Care Clin Outcomes 2020;6:243–53.
[13] Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012;57:675–88.
[14] Watt KDS, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: Results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420–7.
[15] Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000;57:307–13.
[16] Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. Transplantation 2010;89:851–7.
[17] Kahwaji J, Bunnapradist S, Hsu J-W, Idroos ML, Dudek R. Cause of death with graft function among renal transplant recipients in an integrated healthcare system. Transplantation 2011;91:225–30.
[18] Awan AA, Niu J, Pan JS, et al. Trends in the causes of death among kidney transplant recipients in the United States (1996-2014). Am J Nephrol 2018;48:472–81.
[19] Mazuecos A, Muñoz Terol JM, García Alvárez T, et al. Increase in malignancies as cause of death in renal transplant patients. Transplant Proc 2009;41:2159–62.
[20] Weinrauch LA, D'Elia JA, Weir MR, et al. Infection and malignancy outweigh cardiovascular mortality in kidney transplant recipients: Post hoc analysis of the FAVORIT trial. Am J Med 2018;131:165–72.
[21] Rodríguez-Roisin R, Krowka MJ, Hervé P, et al. Pulmonary–hepatic vascular disorders (PHD). Eur Respir J 2004;24:861–80.
[22] Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.
[23] Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:372–92.
[24] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141–54.

[25] Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35: 2383–431.
[26] Tovikkai C, Charman SC, Praseedom RK, et al. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. BMJ Open 2015;5: e006971.
[27] VanWagner LB, Serper M, Kang R, et al. Factors associated with major adverse cardiovascular events after liver transplantation among a national sample. Am J Transplant 2016;16:2684–94.
[28] Patel SS, Lin F, Rodriguez VA, et al. The relationship between coronary artery disease and cardiovascular events early after liver transplantation. Liver Int 2019;39:1363–71.
[29] Zardi EM, Zardi DM, Chin D, et al. Cirrhotic cardiomyopathy in the pre- and post-liver transplantation phase. J Cardiol 2016;67:125–30.
[30] Gelson W, Hoare M, Dawwas MF, et al. The pattern of late mortality in liver transplant recipients in the United Kingdom. Transplantation 2011;91:1240–4.
[31] Johnston SD, Morris JK, Cramb R, et al. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002;73:901–6.
[32] Borg MAJP, Van Der Wouden EJ, Sluiter WJ, et al. Vascular events after liver transplantation: a long-term follow-up study. Transpl Int 2008;21:74–80.
[33] Kasiske BL, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 2000;11:1735–43.
[34] Ducloux D, Kazory A, Chalopin JM. Predicting coronary heart disease in renal transplant recipients: a prospective study. Kidney Int 2004; 66:441–7.
[35] Wali RK, Wang GS, Gottlieb SS, et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. J Am Coll Cardiol 2005;45: 1051–60.
[36] Melchor JL, Espinoza R, Gracida C. Kidney transplantation in patients with ventricular ejection fraction less than 50 percent: Features and posttransplant outcome. Transplant Proc 2002;34:2539–40.
[37] Dudziak M, Dębska-Ślizień A, Rutkowski B. Cardiovascular effects of successful renal transplantation: a 30-month study on left ventricular morphology, systolic and diastolic functions. Transplant Proc 2005; 37:1039–43.
[38] Hawwa N, Shrestha K, Hammadah M, et al. Reverse remodeling and prognosis following kidney transplantation in contemporary patients with cardiac dysfunction. J Am Coll Cardiol 2015;66:1779–87.
[39] Salari A, Monfared A, Fahim SHSN, et al. The survey of diastolic function changes in end-stage renal disease patients before and 3 and 6 months after kidney transplantation. Transplant Proc 2012;44: 3007–12.
[40] Ferreira SRC, Moisés VA, Tavares A, et al. Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. Transplantation 2002;74:1580–7.
[41] Pagadala M, Dasarathy S, Eghtesad B, et al. Posttransplant metabolic syndrome: an epidemic waiting to happen. Liver Transplant 2009;15:1662–70.
[42] Goldsmith D, Pietrangeli CE. The metabolic syndrome following kidney transplantation. Kidney Int Suppl 2010;78:S8–14.
[43] Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995;47:186–92.
[44] Patel RK, Pennington C, Stevens KK, et al. Effect of left atrial and ventricular abnormalities on renal transplant recipient outcome-a single-center study. Transplant Res 2014;3:1–10.