ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2020) **6**, 243–253
doi:10.1093/ehjqcco/qcaa009

ORIGINAL ARTICLE

Cardiovascular mortality following liver transplantation: predictors and temporal trends over 30 years

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Received 14 November 2019; revised 21 January 2020; editorial decision 24 January 2020; accepted 24 January 2020; online publish-ahead-of-print 26 February 2020

Aims There has been significant evolution in operative and post-transplant therapies following liver transplantation (LT). We sought to study their impact on cardiovascular (CV) mortality, particularly in the longer term.

Methods and results A retrospective cohort study was conducted of all adult LTs in Australia and New Zealand across three 11-year eras from 1985 to assess prevalence, modes, and predictors of early (≤30 days) and late (>30 days) CV mortality. A total of 4265 patients were followed-up for 37 409 person-years. Overall, 1328 patients died, and CV mortality accounted for 228 (17.2%) deaths. Both early and late CV mortality fell significantly across the eras ($P < 0.001$). However, CV aetiologies were consistently the leading cause of early mortality and accounted for ∼40% of early deaths in the contemporary era. Cardiovascular deaths occurred significantly later than non-cardiac aetiologies (8.8 vs. 5.2 years, $P < 0.001$). On multivariable Cox regression, coronary artery disease [hazard ratio (HR) 4.6, 95% confidence interval (CI) 1.2–21.6; $P = 0.04$] and era of transplantation (HR 0.44; 95% CI 0.28–0.70; $P = 0.01$) were predictors of early CV mortality, while advancing age (HR 1.05, 95% CI 1.02–1.10; $P = 0.005$) was an independent predictors of late CV mortality. Most common modes of CV death were cardiac arrest, cerebrovascular events, and myocardial infarction.

Conclusion Despite reductions in CV mortality post-LT over 30 years, they still account for a substantial proportion of early and late deaths. The late occurrence of CV deaths highlights the importance of longitudinal follow-up to study the efficacy of targeted risk-reduction strategies in this unique patient population.

Keywords Liver transplantation • Cardiovascular mortality • Long term • Cardiac death • Transplantation • Cirrhotic cardiomyopathy

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Introduction

With the advent of direct-acting anti-viral agents against hepatitis C, the demographics of patients referred for liver transplantation (LT) is changing.[1,2] Transplant candidates in the contemporary era are often older, have a higher proportion of vascular comorbidities and non-alcoholic fatty liver disease is becoming a major aetiology of liver disease in many centres.[3,4] In addition to the adverse cardiometabolic risk profile of transplant candidates, cirrhotic cardiomyopathy is also increasingly recognized in patients with end-stage liver disease.[5] As such, transplant recipients are at a substantial risk of perioperative cardiac events, particularly with the haemodynamic stress of LT.

While it is established that cardiovascular (CV) events are a leading cause of early death following LT, the precise mode of death, and true incidence of long-term CV mortality remain poorly characterized.[6–10] The few studies that have reported long-term CV mortality following LT have been limited by a retrospective, single-centre design, or a small cohort size.[3,11–13] With the escalating risk profiles of liver transplant candidates and improvements in early post-transplant survival, an accurate estimate of the burden, timing, and causes of long-term CV mortality is imperative as it may facilitate an opportunity for intervention.[14] Furthermore, it can facilitate equitable allocation of donor organs, which are increasingly scarce.[15] The objective of this study was to better characterize the incidence, modes, and predictors of CV death using a multicentre database of all liver transplants performed in Australia and New Zealand since 1985.

Methods

Study population

This study included all adult patients ≥18 years of age who underwent a primary liver transplant between 1 January 1985 and 31 December 2017 in Australia and New Zealand (*Figure 1*). Clinical data were obtained from the Australian and New Zealand Liver Transplant Registry (ANZLTR), which prospectively collates cumulative data on liver transplants patients from all six transplant centres in Australia and the one centre from New Zealand. Patients were excluded if they were undergoing retransplantation or multiorgan transplantation. Detailed information about the transplant centres, eligibility, and organ allocation criteria used in this registry have been published previously.[16]

Data variables

Information recorded at the time of transplantation includes recipient variables [age, gender, body mass index (BMI), model for end-stage liver disease (MELD) score, and functional capacity], comorbidities [diabetes mellitus, coronary artery disease (CAD), and presence of hypertension], laboratory variables (total bilirubin, international normalized ratio, albumin and serum creatinine), and operative variables [cold ischaemic time (CIT) and warm ischaemic time], and graft type. Transplanted livers included cadaveric, living donor, and split grafts. The primary indication for transplantation was classified by the treating transplant team. Transplantation for non-alcoholic steatohepatitis (NASH) was defined as a primary listing diagnosis of NASH or cryptogenic cirrhosis with at least one risk factor for metabolic syndrome. Patient functional status was recorded by the transplant physician as 'independent', 'partially independent', or 'fully dependent' at the time of listing. A poor functional status refers to a patient that was fully dependent.

Immunosuppression

Data on post-transplant immunosuppression use was not recorded as part of this registry. For reference, the standard regimen would include triple therapy with cyclosporine, azathioprine, and weaning doses of prednisolone from the commencement of the programme to 2000. Since early 2000s, this changed to triple therapy with tacrolimus, mycophenolate, and prednisolone. Sirolimus and everolimus, both mTOR inhibitors, were only used selectively for cases of refractory rejection or concerns regarding tacrolimus-induced nephrotoxicity or neurotoxicity.

Follow-up and outcome assessment

Follow-up data were maintained at each liver transplant centre with regular clinical review of patients. Each centre records the date of death and determines the cause of death by the most reliable source including death certificates, hospital records, and reports of post-mortem examination. Recipient cause of death was determined by a cardiologist review (A.N.K.) of primary causes of death including all free text inputs listed in the ANZLTR database. Cases were then adjudicated by a panel of cardiologists (O.F. and H.C.H.) and a transplant physician (P.J.G.) with any disagreements resolved by consensus. Death due to a CV cause was defined as primary cause of death from arrhythmia, heart failure, myocardial infarction, primary cardiac arrest, cerebrovascular event, or venous thromboembolism.

The primary aim of this study was to assess causes and predictors of 30-day and long-term (>30 days) CV mortality. A 30-day time period was chosen for quantifying early outcomes in accordance with current reporting of perioperative outcomes in non-cardiac surgery.[17] Secondary aims of the study were to report causes and trends in all-cause mortality. Operative mortality refers to death directly related to the transplant surgery occurring within 24 h of transplantation. Data were divided into three eras for assessing trends in clinical characteristics and outcomes (Era 1: 1985–95, Era 2: 1996–2006, and Era 3: 2007–17).

Predictors of CV mortality were specified *a priori*. These included demographic factors (age, gender) in addition to CV risk covariates including diabetes, hypertension, pre-existing CAD, BMI, NASH cirrhosis, and serum creatinine. Prior CAD was defined as any patient with a history of obstructive CAD, prior myocardial infarction, or coronary revascularization. Other transplant-specific critical illness indicators known to contribute to mortality including MELD score, CIT, and functional status were also assessed. The data utilized in this study is available from the ANZLTR registry which is subject to individual centre ethical and privacy restrictions that limits public access. The oversight committee for the ANZLTR approved the study, and waiver of consent was obtained in accordance with the National Health and Medical Research Council guidelines for use of deidentified data.

Statistical analysis

Results are expressed as mean ± standard deviation or median with interquartile range (IQR) for non-normally distributed data. Comparisons between groups were performed with the χ^2 test for categorical data. Continuous parametric data were assessed using the Student's *t*-test or analysis of variance with Bonferroni correction (multiple categories), while continuous non-parametric data were assessed using the Mann–Whitney *U* test. For assessment of CV risk based on transplant aetiology, hepatitis B/C was used as the reference variable as it was the commonest indication for LT in our population. Any variables with missing values were excluded. Survival curves were generated using Kaplan–Meier method and compared using the log-rank test. To identify independent predictors for CV death, multivariable Cox proportional hazards models were constructed with backward selection to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Univariable predictors yielding

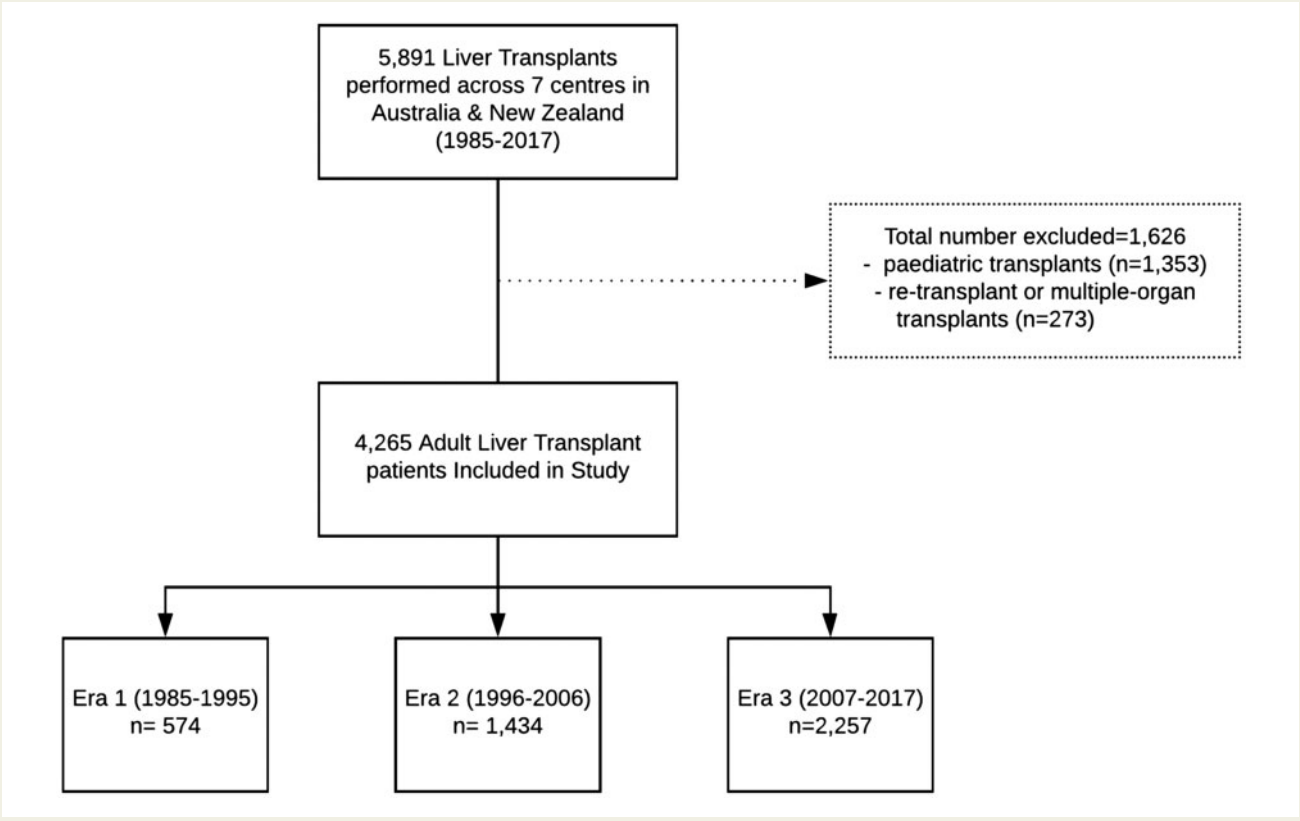

Figure 1 Study details and patient inclusion.

$P < 0.1$ were entered in the multivariable model as covariates. The proportional hazards assumption was assessed with Schoenfeld Residuals tests and no relevant violations were observed. To account for differences in follow-up length between eras on multivariate analysis, a maximal follow-up time of 10 years was used in comparing mortality trends across eras. To avoid multicollinearity between univariable predictors, a correlation coefficient of <0.7 was set. All reported *P*-values are two-tailed, with $P < 0.05$ considered significant. Statistical analysis was performed using Stata 13/MP (StataCorp, College Station, TX, USA).

Results

A total of 4265 patients were followed-up for 37 409 person-years [median 7 (IQR 3–14) years; *Figure 1*]. Mean age of the study population at transplantation was 50 ± 11 years and 66% were male. Baseline characteristics of patients transplanted across the three eras are summarized in *Table 1*. Both the recipient age and the proportion aged ≥60 years rose significantly over time (44 ± 12 vs. 52 ± 11 years; 6.5–25.1%, both $P < 0.001$; Eras 1 and 3, respectively). Hepatitis C was the most common aetiology for LT. An increasing proportion of transplants were performed for NASH and malignancy across the eras (Supplementary material online, *Table S1*). A breakdown of the number of liver transplants performed across the six centres are presented in Supplementary material online, *Table S2*.

Overall patient survival

Patient survival at 1, 5, 10, and 20 years post-transplant was 90.6%, 83.3%, 74.5%, and 50.3% (*Figure 2*). Overall, 1328 (31.1%) patients died during the study period and CV mortality accounted for 228 (17.2%) deaths. The all-cause mortality rate was 34.4 per 1000 person-years and CV mortality rate was 5.4 per 1000 person-years. Breakdown of cause-specific mortality is illustrated in *Figure 2*. Cardiovascular deaths were the second leading cause of overall mortality following malignancy. It also represented the majority of operative (<24 h) and early (≤30 days) mortality (*Table 2*). Cardiovascular deaths as a proportion of all deaths were more common in the first 30 days, compared with >30 days post-transplantation (32.3% vs. 14.7%, $P < 0.001$).

Trends across eras

Early all-cause mortality fell significantly across the three eras (Eras 1–3, respectively; 10.8%, 5.2%, 2.3%, $P < 0.001$; *Figure 3*). This was mediated by a reduction in all major modes of early post-transplant mortality, including CV mortality (Eras 1–3, respectively; 3.3%, 1.5%, 0.9%, $P < 0.001$) (*Table 3*). After adjusting for age, gender, and aetiology of cirrhosis, patients transplanted in Era 2 or 3 demonstrated a significantly lower risk of early CV mortality [adjusted HR (aHR) 0.24 95% CI 0.12–0.49; $P < 0.001$; *Figure 4*]. Of note, the difference between Era 2 and 3 was not significantly different ($P = 0.36$). All-cause and CV mortality at 10 years also improved significantly across the eras (*Table 3*) with adjusted CV mortality significantly reducing in Eras

Table 1 Baseline characteristics

Characteristics	N = 4265	Cardiovascular mortality (n = 228)	No cardiovascular mortality (n = 4037)	P-value
Age	50 ± 11	50.7 ± 11	50.1 ± 11	0.41
% male	66	139 (60.9)	2681 (66.4)	0.09
Aetiology of liver disease				
Hepatitis B	380 (8.9)	21 (9.2)	359 (8.9)	0.87
Hepatitis C	936 (21.9)	38 (16.7)	898 (22.2)	0.052
Alcohol	558 (13.2)	32 (14.4)	536 (13.0)	0.66
Malignancy	514 (12.1)	14 (6.1)	500 (12.4)	0.005
NASH	344 (8.1)	24 (10.5)	320 (7.9)	0.16
PSC	410 (9.6)	14 (6.1)	396 (9.8)	0.07
PBC	236 (5.4)	26 (11.4)	210 (5.2)	0.004
Metabolic[a]	210 (4.9)	19 (8.3)	191 (4.7)	0.01
Other[b]	677 (15.9)	40 (17.5)	637 (15.8)	0.48
BMI (kg/m^2)	27.3 ± 5	26.1 ± 4	27.5 ± 5	0.14
MELD at transplant	15 (10–23)	15 (11–26)	16 (10–23)	0.13
Creatinine at transplant	74 (55–101)	82 (64–108)	74 (53–90)	0.47
Graft type				
Whole liver (%)	92.5	95.6	92.4	0.07
Split graft (%)	7.5	4.3	7.6	0.12
Cold ischaemia time (min)	409 (313–529)	470 (378–594)	407 (312–525)	0.001
Warm ischaemia time (min)	43 (34–52)	47 (40–59)	43 (33–52)	0.15
Diabetes (%)	21.5	32.9	21.1	0.01
Hypertension (%)	10.4	18.3	10.2	0.02
Pre-existing CAD (%)	4.3	10.0	4.25	0.02
Hospitalization status				
Outpatient (%)	69.2	75	69	0.22
Inpatient not in ICU (%)	22.8	24.7	31.0	0.21
ICU (%)	8	16.8	10.2	0.058
Functional status at transplant				
Independent (%)	16.7	16.7	15.4	0.44
Partially independent (%)	54.6	52.4	54.7	0.67
Fully dependent (%)	28.7	26.2	28.4	0.66

Values are presented as mean ± standard deviation, median (interquartile range), or *n* (%) unless specified.
BMI, body mass index; ICU, intensive care unit; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
[a]Breakdown of metabolic causes of liver disease included in Supplementary material online, *Table S3*.
[b]Breakdown of other causes of liver disease included in Supplementary material online, *Table S4*.

2 and 3 compared with Era 1 (aHR 0.52, 95% CI 0.36–0.75; $P < 0.001$) (*Figure 4*).

Cause-specific breakdown of cardiovascular deaths

Operative mortality occurred in 35 (0.8%) patients. Cardiovascular causes accounted for 40% of these, which included seven cases of a primary cardiac arrest, four cases of congestive heart failure, and three pulmonary emboli (*Table 2*). The three main causes of <30-day CV deaths were cardiac arrest, cerebrovascular events, and congestive cardiac failure (*Figure 5*). Proportional causes of operative, early and late (>30 days) mortality are summarized in *Table 2*.

Timing of cardiovascular death

For deaths at ≤30 days, CV deaths occurred earlier than non-cardiac deaths [2 (0–9) vs. 8 (2–17) days, $P < 0.001$]. However, CV deaths beyond 30 days occurred significantly later than non-cardiac deaths [8.8 (4–14) years vs. 5.2 (2–11) years; $P < 0.001$]. When comparing specific modes of CV death in the early and late periods, we found higher rates of myocardial infarction in the late period (3.3% vs. 18.0%, $P = 0.005$), lower rates of CV aetiology in the late period (44.3% vs. 27.5%, $P = 0.02$), and comparable rates of cardiac arrest (27.9% vs. 33.5%, $P = 0.42$).

Predictors of cardiovascular mortality

Univariable predictors of early (<30 days) CV mortality are shown in *Table 4*. Recipients who died early from a CV cause were younger,

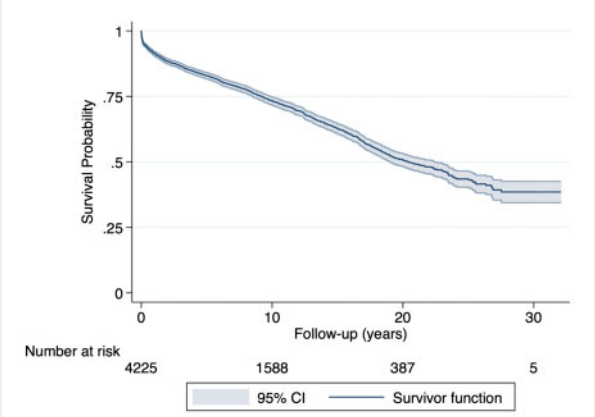

Figure 2 Kaplan–Meier survival estimate for whole cohort (1985–2017).

Table 2 Modes of cardiovascular death following liver transplantation

Cause of death	*n*	%
All cardiovascular deaths (*n* = 228)		
Cardiac arrest	73	32.0
Myocardial infarction	32	14.0
Pulmonary embolism	11	4.8
Congestive cardiac failure	31	13.6
Cerebrovascular	73	32.0
Cardiovascular other	8	3.6
Operative death (*n* = 35)		
Cardiovascular	14	40.0
Cardiac arrest[a]	7	
Congestive cardiac failure	4	
Pulmonary embolism	3	
Operative complication	10	28.6
Unknown	11	31.4
≤30-day cardiovascular death (*n* = 61)		
Cardiac arrest	17	27.9
Congestive cardiac failure	7	11.5
Myocardial infarction	2	3.3
Pulmonary embolism	5	8.2
Cerebrovascular	27	44.2
Cardiovascular other	3	4.9
>30-day cardiovascular mortality (*n* = 167)		
Cardiac arrest	56	33.5
Myocardial infarction	30	18.0
Congestive cardiac failure	24	14.4
Cerebrovascular events	46	27.5
Pulmonary embolism	6	3.6
Other cardiac causes	5	3.0

[a]Operative cardiac arrest arrhythmia available for three patients which included two cases of ventricular arrhythmias, one asystolic arrest.

more likely to have pre-existing CAD and poor functional status at transplantation. There were no significant differences in BMI, MELD score, transplant aetiology, or the frequency of diabetes or hypertension. On multivariate Cox regression analysis (*Table 5*), only a history of CAD (HR 4.8, 95% CI 1.2–22.8; $P = 0.03$) and era of transplantation (Era 2/3 vs. Era 1: HR 0.44; 95% CI 0.28–0.70; $P = 0.01$) significantly increased risk of early CV mortality.

Significant clinical univariate predictors of late CV mortality included age, diabetes, NASH, hypertension, transplant era, and functional status. However, on multivariable analysis, only age was found to be a significant predictor with an HR of 1.05 (95% CI 1.02–1.10, $P = 0.005$).

No differences in early or late CV mortality was noted on comparison of transplant aetiologies (Supplementary material online, *Table S5*). To assess differences in centre volume and outcomes, we compared three low-volume centres (Adelaide, Perth, Auckland) which had performed 30% of transplants to three high-volume centres (Brisbane, Sydney, Melbourne). No significant differences in overall death (HR 0.93, 95% CI 0.82–1.06; $P = 0.28$), early (HR 0.54, 95% CI 0.24–1.23; $P = 0.15$), or late (HR 0.87, 95% CI 0.61–1.26; $P = 0.48$) CV mortality was noted.

Discussion

To our knowledge, this is the largest study reporting long-term temporal trends and modes of CV death following LT. Analysis of this multicentre registry of all LTs performed across Australia and New Zealand has generated several important observations. First, we observed a significant reduction in early and late CV mortality over a 30-year period. Improved CV outcomes occurred despite performing transplants in an older, higher-risk patient cohort. Second, although overall CV mortality was lower in the contemporary era, about 40% of early deaths were still attributable to a primary cardiac cause. Third, a significant increase in myocardial infarction and a consistent hazard for cardiac arrest both early and late, suggests that LT recipients remain at a substantial CV risk after the immediate post-transplant period.

Assessment of trends across the three eras provides a unique perspective of the evolution in LT outcomes. All-cause and CV mortality were significantly lower in Eras 2 and 3 compared with Era 1. The overall reduction in rates of CV mortality reflect similar improvements in Australia over the same time period. For instance, age-standardized rates of CV mortality in the general population fell between 40% and 50% from 1985 to 2010, which was comparable to that observed in the liver transplant population.[18] Although the rate of change was comparable, this importantly reflects a translation of improvements in cardiac care to this unique patient population. Proposed reasons for these observed changes include, but are not limited to, improvements in preoperative cardiac assessment and patient selection, medical therapy, revascularization, operative techniques, and post-operative care in the contemporary eras.[8,17] Of interest, early CV mortality was not significantly different across Eras 2 and 3. Improvements in all-cause mortality likely reflect cumulative experience in both operative techniques and perioperative management of these patients.[14,19] The consistent hazard for CV mortality in

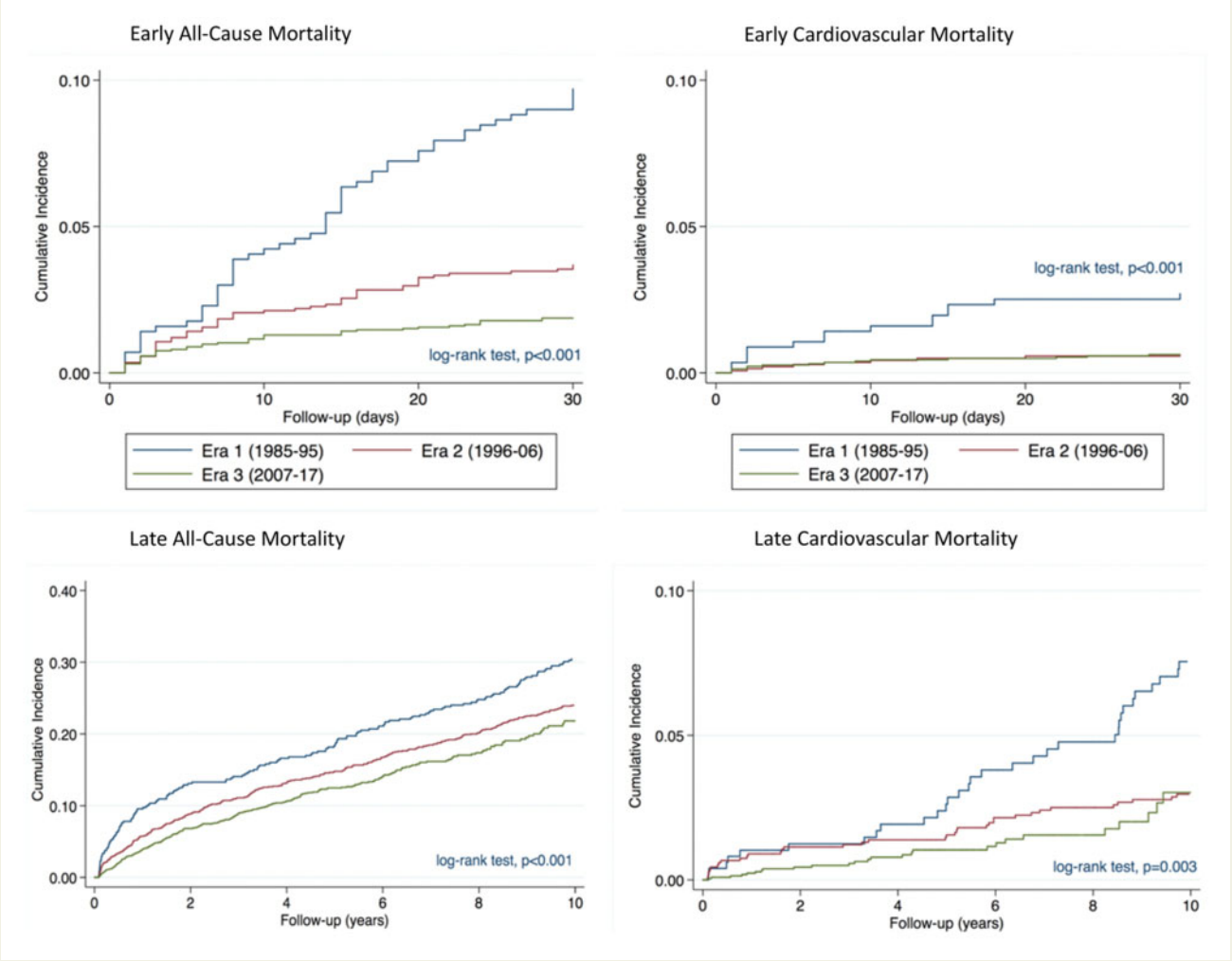

Figure 3 Trends in cumulative all-cause and cardiovascular mortality across eras.

Eras 2 and 3, may be due to the increasingly complex profile of patients who are more susceptible to perioperative cardiac complications during the haemodynamic stress of LT.[1,20]

Despite reductions in mortality across the eras, a CV aetiology was consistently the leading cause of operative and early deaths. We observed a substantial early CV mortality rate of 1.4%, which is comparable to a recent study of the UNOS cohort that estimated a CV mortality rate of 1.2%.[6] It is instructive to compare rates of early CV death with other types of non-cardiac surgery. For example, a Whipple's procedure, a relatively complex operation, carries an early CV mortality risk of 0.3%, while an oesophagectomy has risk of 0.2%.[21] Reasons for the risks conferred by LT include such factors as patient frailty and comorbidity, operative and anaesthetic complexity, profound haemodynamic alterations and coagulopathy.[8,20] Nevertheless, a four-fold increase in perioperative CV mortality compared with other complex non-cardiac surgeries warrants assessment of current risk minimization strategies in this cohort.

When assessing the modes of death, we found that non-coronary events including cardiac arrest, cerebrovascular events, and heart failure were the leading causes of early mortality. Although underrecognized, cirrhotic cardiomyopathy is estimated to be present in 40–50% of patients with end-stage liver disease.[5,22] It is conceivable that a blunted ventricular response to stress and electrophysiological abnormalities can precipitate perioperative non-coronary events including arrhythmias and heart failure.[23,24] There is a paucity of evidence surrounding the management of cirrhotic cardiomyopathy with a randomized controlled trial of beta-blockers not showing any benefit.[25] As highlighted in a recent consensus statement by the Cirrhotic Cardiomyopathy Consortium, utility of novel load-independent echocardiographic indices and sensitive biomarkers including brain natriuretic peptide (BNP)should be prospectively assessed, in order to facilitate earlier diagnosis and the potential use of targeted therapies in this high-risk cohort.[26–28]

Pre-existing CAD at transplantation was an independent risk factor for early CV death. This was the case despite only a minority of early events occurring directly as a result of myocardial infarction. The exact reasons for this discrepancy are unclear although it is conceivable that deaths classified as cardiac arrest may have occurred

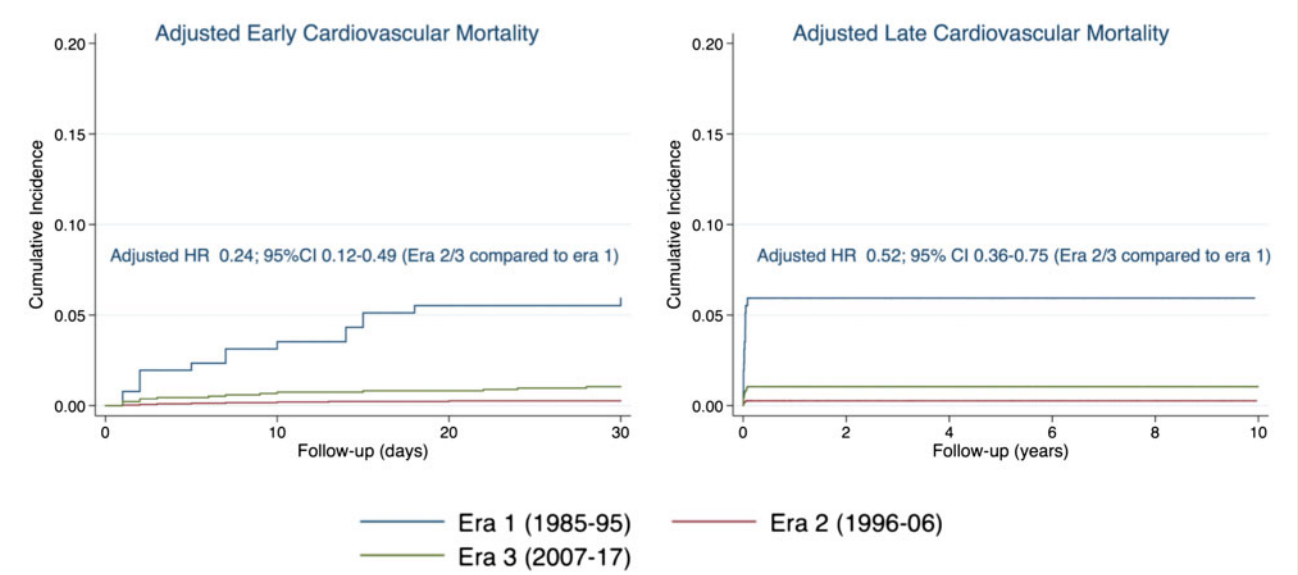

Figure 4 Adjusted rates of early and late cardiovascular mortality across eras.

following an acute coronary event complicated by a malignant arrhythmia. While other studies have assessed the hazard conferred by CAD, the predominant focus was on prediction of perioperative CV events as opposed to mortality.[7,13,29–32] This may be due to low rates of mortality in the contemporary era, particularly in single-centre studies.[7,31,33] As such, the independent association between CAD and early CV death in this large multicentre cohort is an important finding. However, the optimal strategy for preoperative non-invasive evaluation of CAD in an asymptomatic liver transplant population is unclear, with a paucity of evidence and guideline recommendations. A recent meta-analysis comparing dobutamine stress echocardiography and myocardial perfusion scintigraphy has highlighted the low sensitivity of these modalities for the detection of obstructive CAD in patients with liver cirrhosis.[34] Whether addition of an anatomic imaging strategy such as computed tomographic coronary angiography, can further improve preoperative risk stratification in this population warrants further study.[33] Of note, randomized controlled trials have previously demonstrated a lack of efficacy of preoperative revascularization in mitigating CV events prior to non-cardiac surgery.[35] Despite this, guidelines continue to consider unrevascularized CAD as a relative contraindication for LT.[14,36] Future studies are needed to assess whether preoperative coronary revascularization can mitigate risk of cardiac complications in this target population.

A finding of interest was the lack of significant association of age with early CV mortality. These findings are in contrast to previously published literature.[6,8,29] The reasons for these differences remain speculative. However, variations in regional practice as well as selection bias that favours listing of older individuals with fewer comorbidities that are not captured in this registry including sarcopenia, may offer a potential explanation.[37] Notwithstanding, our findings suggest that an appropriately vetted cohort can attain comparable early post-transplant CV outcomes, irrespective of age.

Significant univariate predictors of interest including diabetes and NASH were not independently associated with early or late CV death in this study. The lack of independent association for these risk factors that have biologic plausibility for driving CV disease progression is unclear.[32,38] One reason may be due to competing causes of death in a transplant population, whereby diabetes also increases risk of mortality due to other causes including graft failure and infection.[3,39] Furthermore, as this registry only provides a snapshot of pre-transplant comorbidities, the risk conferred by the above variables may be underestimated because as many as 40% of patients develop post-transplant metabolic syndrome.[40] Lastly, it is conceivable that the recognition of these conditions pre-transplant may have culminated in more effective management strategies that may mitigate CV risk in the longer term.

Cardiovascular deaths >30 days in our cohort occurred approximately 9 years following transplantation, which was significantly later than non-cardiac aetiologies. This highlights the importance of long-term follow-up to ascertain the true incidence of CV mortality—an area currently lacking in adequately powered, multicentre studies. Whether LT confers a hazard for long-term CV mortality remains a matter of debate.[12,13,41] The CV mortality rate of 5.4 per 1000 person-years in our study was three times that reported among Australian adults and comparable to pooled estimates in individuals with established atherosclerotic coronary disease.[42,43] Taken together, these findings suggest that long-term CV mortality may be higher in liver transplant recipients than previously recognized.

Implications

First, the preponderance of perioperative non-coronary events highlights the importance of extending CV risk-assessment beyond simply ruling-out CAD. Features of cirrhotic cardiomyopathy can be masked

Table 3 Causes of death across eras

Causes of death	Total	Era 1: 1985–95 (*n* = 574)	Era 2: 1996–2006 (*n* = 1434)	Era 3: 2007–17 (*n* = 2257)	*P*-value
All-cause death	1328	374 (65.2)	610 (42.5)	344 (15.2)	<0.001
Cardiovascular	228 (17.2)	80 (13.9)	101 (7.0)	47 (2.1)	<0.001
Malignancy	351 (26.4)	76 (13.2)	156 (10.9)	119 (5.3)	<0.001
Graft failure	210 (15.8)	67 (11.7)	96 (6.7)	47 (2.1)	<0.001
Sepsis	210 (15.8)	74 (12.9)	98 (6.9)	38 (1.7)	<0.001
Gastrointestinal	69 (5.2)	16 (2.8)	39 (2.7)	14 (0.6)	<0.001
Multiorgan failure	110 (8.3)	20 (3.5)	46 (3.2)	44 (1.9)	0.02
Other/unknown	150 (11.3)	41 (11.0)	74 (5.2)	35 (1.5)	<0.001
30-day causes of death					
All-cause death	189	62 (10.8)	74 (5.2)	53 (2.3)	<0.001
Cardiovascular	61 (32.2)	19 (3.3)	21 (1.5)	21 (0.9)	<0.001
Sepsis	44 (23.2)	20 (3.4)	16 (1.1)	8 (0.4)	<0.001
Operative complication	28 (14.8)	4 (0.7)	19 (1.3)	5 (0.2)	<0.001
Graft failure	25 (13.2)	13 (2.3)	6 (0.4)	6 (0.3)	<0.001
Other/unknown	31 (16.4)	6 (1.0)	12 (0.8)	13 (0.6)	0.82
Causes of death >30 days to 10 years[a]					
All-cause death	773	156 (30.4)	327 (24.0)	290 (13.2)	<0.001
Cardiovascular	94 (12.2)	32 (6.3)	36 (2.6)	26 (1.2)	<0.001
Malignancy	266 (34.4)	43 (8.4)	105 (7.7)	118 (5.4)	0.004
Graft failure	145 (18.7)	35 (6.8)	69 (5.1)	41 (1.9)	<0.001
Sepsis	108 (14.0)	28 (5.5)	50 (3.7)	30 (1.4)	<0.001
Multiorgan failure	55 (7.1)	1 (0.2)	17 (1.2)	37 (1.7)	0.03
Other/unknown	105 (13.6)	17 (3.3)	50 (3.7)	38 (1.7)	0.18

Values are presented as *n* (%).
[a]Proportions of causes of death >30 days to 10 years estimated with the total *n* per era minus any deaths in first 30 days; gastrointestinal cause of death refers to death primarily due to gastrointestinal haemorrhage and pancreatitis.

by a hypercontractile resting cardiac function.[22] Studies assessing whether an attenuated left ventricular contractile reserve on stress testing, for example, confers a hazard for perioperative CV complications warrant further study.[24] Second, the consistent hazard for cardiac arrest observed both early and late post-transplantation is a novel finding. Since the pathophysiology of cardiac arrest or sudden cardiac death can be variable, future studies are needed to critically evaluate the mechanisms of this mode of death in liver transplant recipients.[44] Lastly, the rates of long-term CV death in this study raise the question of whether LT itself accentuates cardiac risk. This should be assessed independent of the risk conferred by post-transplant metabolic syndrome and immunosuppression itself. Currently, a paucity of data exists on the optimal management of long-term CV risk in these patients. Randomized studies following renal transplantation have demonstrated significant reductions in CV events with statin therapy, for instance.[45] Whether employing more intensive treatment targets for blood pressure and lipid level lowering can attenuate long-term risk following LT warrants further study.

Limitations

The retrospective nature of this study is associated with certain limitations. First, we were limited by reliance on available data and were unable to supplement this with chart review as patients were deidentified as part of the national registry. Furthermore, a failure to capture the evolution in risk factors post-transplantation and medication use may lead to over or underestimation of long-term risk. Second, as individual transplant centres were not provided with defined criteria for recording cause of death, the database may be prone to reporting bias. For instance, we lacked details specifically with regards to whether cerebrovascular events were due to a primary ischaemic or haemorrhagic aetiology. Although a majority of strokes are likely to be ischaemic in nature, the coagulopathy in patients with liver cirrhosis may lead to an over-representation in episodes of intracranial bleeding that may not be captured in this registry. To account for this, cause of death was adjudicated by an interdisciplinary panel with all available Supplementary material online including cause of death comments to reduce misclassification. Third, the database lacked detail on the severity of CAD and whether preoperative revascularization was undertaken. This may have assisted in further risk stratifying patients to assess whether revascularization mitigates risk. Fourth, we also lacked information pertaining to cirrhotic cardiomyopathy, which may have also affected post-transplant CV outcomes. Lastly, the differences in duration of follow-up between the eras could have modulated the survival analyses. To minimize this potential bias, we set a 10-year limit for assessment of long-term outcomes. Sensitivity analyses of risk predictors

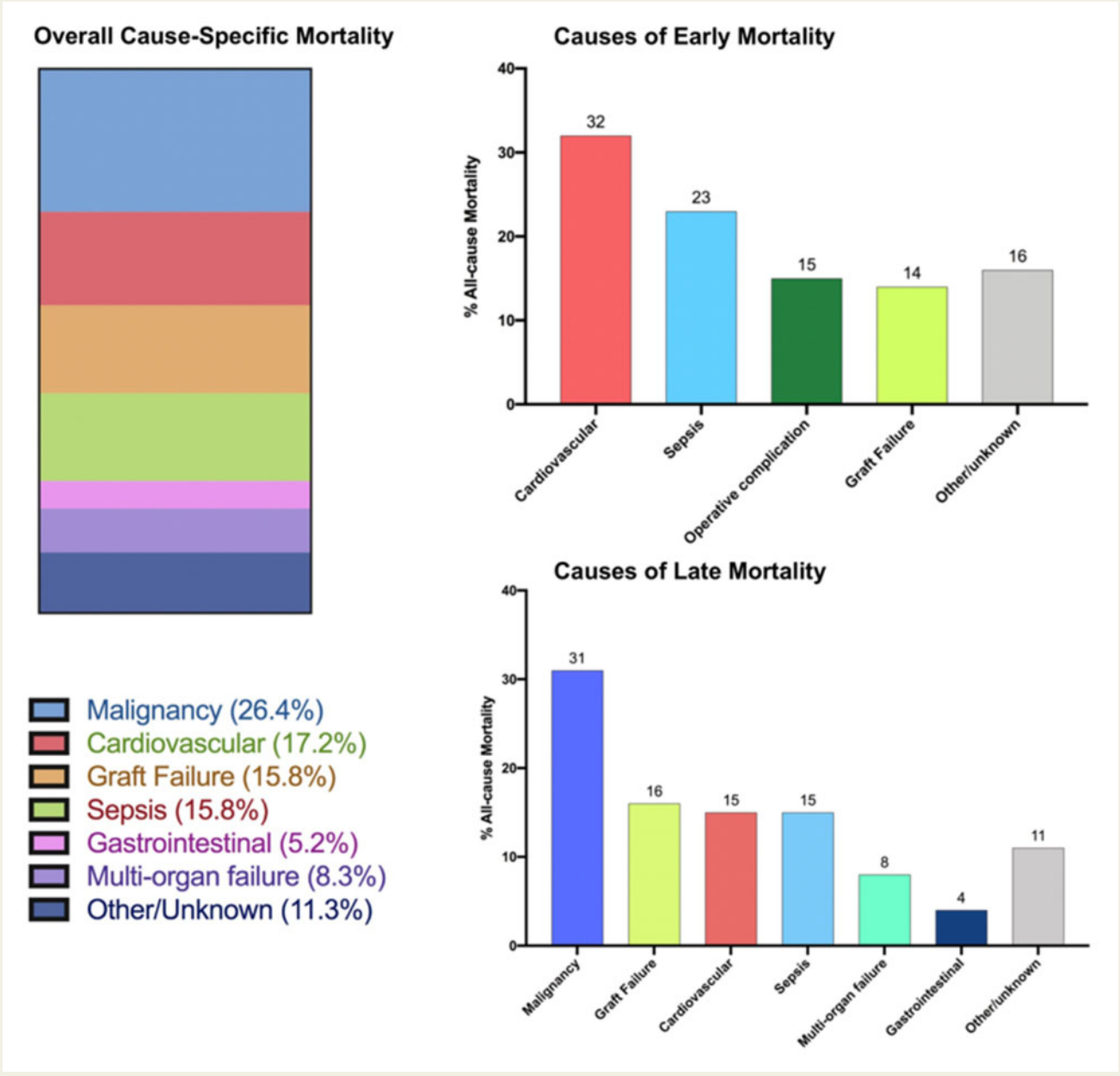

Figure 5 Cause-specific mortality following liver transplantation.

with variations in the maximal follow-up did not demonstrate significant differences.

Conclusion

In this large multicentre cohort of patients that underwent LT, we report significant improvements in early and late CV mortality over a 30-year period. Despite this, CV aetiologies were consistently the leading cause of early mortality and a significant contributor to late mortality. Given the escalating risk factor profile of transplant recipients and the limited availability of donor organs, further studies with longitudinal follow-up are needed to improve our current understanding of modifiable risk factors and to provide targets for therapeutic interventions that mitigate risk of perioperative and late CV death.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

Table 4 Predictors of early (≤30 days) cardiovascular mortality

	Early CV mortality ($n = 61$)	No CV mortality ($n = 4076$)	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age	47.1	50.2	0.98 (0.95–0.99)	0.03	0.98 (0.95–1.0)	0.07
Sex (male %)	57	42	0.98 (0.96–0.99)	0.13		
NASH cirrhosis (%)	3.3	4.2	0.77 (0.19–2.3)	0.72		
BMI	27.8	27.4	1.0 (0.91–1.1)	0.8		
Creatinine	104	84	1.1 (1.0–1.05)	0.08	1.0 (0.99–1.08)	0.71
Cold ischaemia time	423	455	1.0 (0.99–1.1)	0.31		
Diabetes	27.3	21.5	1.4 (0.5–3.5)	0.51		
Hypertension (%)	5	10.5	0.45 (0.1–3.3)	0.71		
Pre-existing CAD (%)	15	4.4	3.9 (1.1–13.4)	0.02	4.6 (1.2–21.20)	0.04
MELD score	22	16	1.1 (1.0–1.1)	0.09	0.99 (0.98–1.08)	0.90
Poor functional status (%)	46.4	27.7	2.3 (1.2–4.8)	0.03	1.8 (0.8–4.3)	0.17
Transplant era[a]	—	—	0.47 (0.31–0.7)	0.01	0.44 (0.28–0.70)	0.01

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.
[a]transplant era 1 as reference variable.

Table 5 Predictors of late (>30 days) cardiovascular mortality

	Late CV mortality ($n = 167$)	No CV mortality ($n = 2937$)	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age	52.2	50.1	1.04 (1.02–1.06)	<0.001	1.05 (1.02–1.10)	0.005
Sex (male %)	62.3	66.3	1.05 (0.77–1.44)	0.74		
NASH cirrhosis (%)	5.5	3.9	2.1 (1.1–4.1)	0.03	1.99 (0.85–4.6)	0.19
BMI	25.2	27.5	0.93 (0.84–1.1)	0.11		
Creatinine	85	84	1.01 (0.99–1.02)	0.12		
Cold ischaemia time	487	424	1.00 (0.99–1.02)	0.4		
Diabetes	27.3	21.5	2.4 (1.4–4.1)	0.002	1.14 (0.56–2.29)	0.71
Hypertension (%)	5	10.4	2.78 (1.45–5.30)	0.002	1.66 (0.82–3.40)	0.16
Pre-existing CAD (%)	8.1	4.3	2.41 (0.87–6.7)	0.09	1.45 (0.50–4.20)	0.49
MELD score	18	17	1.00 (0.98–1.01)	0.97		
Poor functional status	16.1	28.6	0.52 (0.25–1.07)	0.07	0.58 (0.26–1.31)	0.19
Transplant era[a]	—	—	0.66 (0.52–0.84)	0.01	0.77 (0.40–1.5)	0.44

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.
[a]transplant era 1 as reference variable.

Funding

A.N.K. is a recipient of the National Health and Medical Research Council of Australia/National Heart Foundation Post-Graduate Scholarship and Royal Australasian College of Physicians Blackburn Scholarship. A.W.T. is a recipient of the Early Career Fellowship from the National Health and Medical Research Council of Australia.

Conflict of interest: none declared.

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