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METABOLIC LIVER DISEASE

Reduced impact of renal failure on the outcome of patients with alcoholic liver disease undergoing liver transplantation

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Abstract

Background & Aims: Pretransplant renal failure is commonly reported to be a poor prognostic indicator affecting survival after liver transplantation (LT). However, whether the impact of renal failure on patient outcome varies according to the aetiology of the underlying liver disease is largely unknown. *Methods:* We investigated the association between renal failure at the time of LT and patient outcome in patients with alcoholic liver disease (ALD) (n = 6920), non-alcoholic steatohepatitis (NASH) (n = 2956) and hepatitis C (HCV) (n = 14 922) using the United Network for Organ Sharing (UNOS) database between February 2002 and December 2013. A total of 24 798 transplant recipients were included. *Results:* The presence of renal failure was more frequently seen in patients with ALD (23.95%) and NASH (23.27%) compared to patients with HCV (19.38%) ($P < 0.001$). In multivariate analysis, renal failure was an independent predictor of poor survival. Renal failure showed detrimental effect on patient survival in the overall series (HR = 1.466, $P < 0.0001$). Importantly, the impact of renal failure was less marked in patients with ALD (HR = 1.31, $P < 0.0001$) than in patients with NASH (HR = 1.73, $P < 0.0001$) or HCV (HR = 1.52, $P < 0.0001$). Despite a higher model for end-stage liver disease (MELD) score at the time of LT, ALD patients with renal failure had better long-term prognosis than non-ALD patients. *Conclusions:* Renal failure at the time of LT conferred a lower patient and graft survival post-LT. However, renal failure has less impact on the outcome of patients with ALD than that of patients with non-alcoholic liver disease after LT.

Keywords
alcoholic liver disease – liver transplantation – non-alcoholic liver disease – outcome – renal failure

Liver transplantation (LT) is the ideal therapy for patients with end-stage liver disease. Alcoholic liver disease (ALD) is one of the most common aetiologies among patients receiving LT in the USA and Europe (1, 2). Long-term survival after transplantation in patients with ALD is similar to that in patients with

Abbreviations
AKI, acute kidney injury; ALD, alcoholic liver disease; CKD, chronic kidney disease; HCV, hepatitis C virus; HR, hazard ratio; HRS, hepatorenal syndrome; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OPTN, organ procurement and transplantation network; SBP, spontaneous bacterial peritonitis; UNOS, United Network for Organ Sharing.

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Key points

- Renal failure before liver transplantation is more frequent in transplanted patients with alcoholic and non-alcoholic fatty liver diseases compared to hepatitis C patients.
- The development of renal failure before liver transplantation is an independent predictor of poor survival in all patients with liver transplantation.
- The impact of pretransplant renal failure on long-term survival is less marked in patients with alcoholic liver disease than in those with other aetiologies.
- Further studies should investigate strategies to prevent the development of renal failure in patients with non-alcoholic fatty liver and hepatitis C who will undergo liver transplantation.

non-alcoholic steatohepatitis (NASH) or patients with hepatitis C virus (HCV) infection (3, 4).

Patients with end-stage liver disease are predisposed to renal hypoperfusion, the most common aetiology of acute kidney injury (AKI) in cirrhosis (5, 6). Renal hypoperfusion can result in hepatorenal syndrome (HRS) or acute tubular necrosis (5, 7). The prevalence of renal dysfunction in liver transplant recipients ranges between 17% and 95% (8, 9). Since the introduction of the model for end-stage liver disease (MELD) scoring system for prioritization of LT recipient, a high percentage of patients receiving LT have renal impairment (10), which can be a critical factor for post-transplant survival (11).

In the setting of cirrhosis, AKI can be caused by either chronic structural kidney disease or functional renal failure, depending on the type of liver disease. For example, non-alcoholic fatty liver disease and metabolic syndrome are associated with chronic kidney disease (CKD) (12), while type II cryoglobulinemia is frequently seen in chronic HCV infection and can lead to membranoproliferative glomerulonephritis (13). In contrast, HRS is more common in ALD according to a pooled analysis that found alcohol-related cirrhosis as the underlying aetiology in 57% of cases (5). In a recent study from our group, the main causes of AKI in patients with advanced ALD were HRS and renal failure associated with infection (14). Moreover, IgA1-containing circulating immune complexes can cause secondary IgA nephropathy in patients with ALD (15). The high possibility of renal non-recovery in CKD after LT leads to the assumption that renal dysfunction in patients with NASH or HCV is more likely to be irreversible. HRS involves functional deterioration in renal function, which is more likely to be reversible after LT (16, 17).

Scoring systems to predict the prognosis of renal dysfunction in patients undergoing LT are used sparingly. Furthermore, the precise indications of combined liver–kidney transplantations remain unclear. Northup *et al.* (16) found the renal non-recovery to be as high as 32% among LT recipients who were on pre-LT renal replacement therapy and received LT alone. There is a clear need to identify the factors affecting the outcome of patients with renal failure before LT. We hypothesized that the aetiology of underlying liver disease plays a role, which is particularly evident in the fact that renal failure has less impact on survival after LT in ALD patients despite a higher prevalence of renal failure in this cohort than in other liver diseases. This study was undertaken to test this hypothesis.

Patients and methods

Patient data collection

We used the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) database and included any adult patients who received a liver transplant in the USA from February 27, 2002 through December 2012. As for the aetiologies of chronic liver disease among LT recipients, we included only those subjects with a diagnosis code of 4204, 4215 or 4216, which correspond to ALD (n = 6920), HCV (n = 14 922), and NASH (n = 2956) respectively. We excluded patients with combined ALD and HCV (n = 3076). We included only subjects aged 18 years or older, who had no missing data on their status (died, still alive, lost to follow-up, re-transplanted), with a total of 24 798 adult patients. The Institutional Review Board at the University of North Carolina at Chapel Hill approved this study.

Definitions and parameter selection

We extracted data from the UNOS database including anthropometric (e.g. body mass index), socioeconomic (e.g. race), baseline characteristics (e.g. age, gender, presence of diabetes or cardiac disease, MELD score, ascites, encephalopathy, portal vein thrombosis etc.), surgery related parameters (e.g. living or cadaver donor, combined liver/kidney transplant, ABO mismatch, cold ischaemic time etc.) and early or late complications (e.g. cardiovascular complications, rejection etc.). A detailed description of the parameters included in this study is depicted in Table S1. The UNOS database has limited information on long-term complications (e.g. cardiovascular events, development of malignancy, accurate cause of death), resulting in a significant proportion of missing data. Outcome parameters were patient survival and graft survival.

As reported elsewhere, renal failure was considered in patients with serum creatinine ≥2.5 mg/dl or treated with dialysis at the time of listing for LT (18, 19). Renal recovery was defined as serum creatinine <1.5 mg/dl at 6 months after LT.

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Statistical analysis

Univariate and multivariate Cox proportional hazards models were used to identify predictors for patient survival and graft survival. To test whether hazard ratios for a particular variable differed between aetiologies, an interaction term for the variable of interest and the aetiologies was used. Multivariate analysis included variables that were biologically relevant and/or associated significantly in the univariate analysis ($P < 0.05$).

To find significant disease-specific parameters in patients with renal failure, all the available parameters were compared by aetiology of liver disease (alcoholic vs. non-alcoholic). Pairwise comparisons via Chi-square tests were used to test for two-way associations between categorical variables. Kaplan–Meier curves were generated along with log-rank *P*-values to compare curves, and proportional hazards models were run to generate hazard ratios. *P*-values <0.05 were considered statistically significant. Analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA).

Results

Prevalence of renal failure/dialysis in patients with ALD, NASH and hepatitis C undergoing LT

We first analysed the prevalence of renal failure and dialysis before LT according to the underlying liver disease. Renal failure was present in 23.95%, 23.27% and 19.38% of patients with ALD, NASH and HCV respectively. Pairwise comparison of each group demonstrated that ALD ($P < 0.001$) and NASH ($P < 0.001$) have higher prevalence of renal failure than patients with HCV (Table 1).

Patients requiring dialysis at the time of LT were 14.99%, 13.27% and 11.27% of patients with ALD, NASH and HCV respectively. Similar to results in renal failure, pairwise comparisons indicated that the patients with ALD ($P < 0.001$) and NASH ($P = 0.0019$) were more likely to require dialysis than those with HCV. The difference between ALD and NASH was minimal and probably clinically irrelevant, despite a statistical significance due to the large sample size (Table 1).

Multivariate analysis of parameters predicting patient survival after LT

We next investigated the parameters predicting patient survival after LT. Overall, patient mortality and graft failure were observed in 6915 and 8252 cases, respectively, of 24 798 cases. Outcomes in each aetiology have been depicted in Table 2. Multivariate Cox proportional hazards models were used to identify independent parameters of patient survival. This multivariate analysis showed renal failure to be an independent prognostic factor for patient survival after adjustment for other clinical and laboratory features that have conventionally been accepted as having prognostic value in patients receiving LT (HR = 2.648, $P = 0.0067$). Other independent parameters for patient survival include: female gender, black race, donor age, body mass index, renal recovery, MELD score, anti-hepatitis B core antibody, ventilator support and previous liver transplant (Table 3). Since renal impairment may affect MELD score, we analysed the impact of renal failure across three MELD classes (MELD score <20, 20–30 and >30) (20) in terms of graft and patient survival. This analysis showed that renal failure before transplant has higher impact in terms of patient survival in patients with a MELD score between 20 and 30. Absence of renal recovery impacts patient survival across all MELD classes. Pretransplant renal impairment does not impact graft survival, however, a lack of renal recovery after transplantation does impact graft survival across all three MELD classes. Detailed multivariate results are depicted in Table S2 and S3.

Role of the aetiologies of liver disease on the impact of renal failure on patient and graft survival

We next explored the impact of renal failure on survival and the effect of underlying cause of liver disease on this

Table 2. Whole cohort outcomes according to aetiology of liver disease

	Died	Graft failure
ALD	1693	2007
NASH	628	736
Hepatitis C	4594	5509

ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis.

Table 1. Prevalence of renal failure and dialysis at the time of liver transplantation (LT). Data shown as pairwise comparison between groups

Renal failure before LT		*P*-value	Dialysis before LT		*P*-value
ALD (23.95%)	Hepatitis C (19.38%)	<0.0001	ALD (14.99%)	Hepatitis C (11.27%)	<0.0001
ALD (23.95%)	NASH (23.27%)	0.4734	ALD (14.99%)	NASH (13.27%)	0.0264
NASH (23.27%)	Hepatitis C (19.38%)	<0.0001	NASH (13.27%)	Hepatitis C (11.27%)	0.0019

ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; LT, liver transplantation.

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outcome. We excluded patients with previous LT from this analysis, since these patients are on immunosuppressive drugs, which is independently associated with renal impairment and may serve as a confounding factor. As expected, patients with renal failure at the time of LT showed poorer graft survival (Fig. 1).

We also assessed survival in each type of liver disease according to the presence or absence of renal failure. To

Table 3. Multivariate analysis of parameters predicting patient survival after liver transplantation in the whole series (n = 24 798)

Variables	Univariate *P*-value	Hazard Ratio	Multivariate *P*-value	Hazard Ratio
Female gender	<0.0001	1.123	<0.0001	1.190
Recipient age	<0.0001	1.016	0.1530	1.003
Black race	<0.0001	1.512	<0.0001	1.360
Donor age	<0.0001	1.012	<0.0001	1.013
Body mass index	<0.0001	0.990	<0.0001	0.984
Creatinine at transplant	<0.0001	1.084	0.2413	0.979
Dialysis treatment	<0.0001	1.449	0.1198	1.114
Renal failure	<0.0001	1.466	0.0067	1.200
Renal recovery	<0.0001	2.829	<0.0001	2.648
Combined liver–kidney transplant	<0.0001	1.221	0.9235	1.007
Diabetes	<0.0001	1.298	0.2405	1.054
Ascites at transplant	<0.0001	1.143	0.2448	1.042
SBP at registration	0.0354	1.091	0.2891	1.063
Encephalopathy at transplant	<0.0001	1.315	0.0538	1.104
Total bilirubin at transplant	<0.0001	1.007	0.6753	1.001
MELD score	<0.0001	1.008	0.0007	0.991
Anti-hepatitis B core antibody	<0.0001	1.154	0.0003	1.142
Ventilator support	<0.0001	1.968	0.0090	1.245
Portal vein thrombosis	0.0003	0.846	0.3354	0.936
Previous liver transplant	<0.0001	1.923	<0.0001	1.562
Donor type (cadaver)	<0.0001	1.336	0.6468	1.090
Whole liver transplant	<0.0001	1.315	0.7808	1.045
Cold ischaemic time	<0.0001	1.014	0.0989	1.007

MELD, model for end-stage liver disease; SBP, Spontaneous Bacterial Peritonitis.

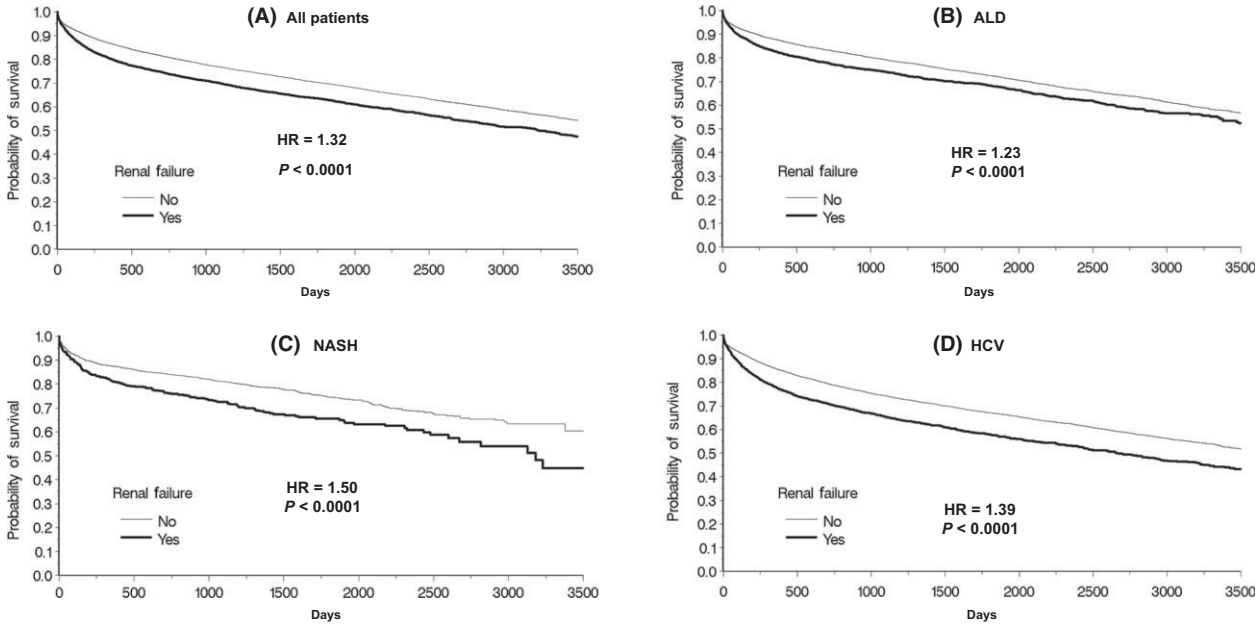

Fig. 1. Impact of renal failure on graft survival according to the aetiology of the underlying liver disease. (A) Overall series, (B) Alcoholic liver disease (ALD), (C) Non-alcoholic steatohepatitis (NASH), and (D) Hepatitis C virus (HCV).

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explore the impact of renal failure on survival in each aetiological group, we conducted pairwise comparison in each disease group. Importantly, the impact of renal failure was significantly less marked in patients with ALD than in patients with NASH or hepatitis C (Fig. 2) (Table 4).

Differences in baseline characteristics in patients with renal failure with ALD compared to patients with NASH and hepatitis C

We also sought to identify potential explanations for the reduced impact of renal failure in patients with ALD. As expected, ALD patients with renal failure showed better patient and graft survival than patients without ALD (i.e. NASH and hepatitis C) with renal failure (Fig. 3). In fact, the long-term survival of patients with ALD and renal failure was similar to patients without renal failure.

To identify factors contributing to the difference in impact of renal failure based on underlying liver disease, we compared clinical and laboratory parameters between ALD patients with renal failure and non-ALD patients with renal failure in the whole series. As shown in Table 5, ALD patients with renal failure had more frequent bacterial peritonitis, greater frequency of encephalopathy (higher than grade 3), higher MELD scores and received more frequent dialysis compared to non-ALD patients with renal failure. In contrast, non-ALD patients with renal failure had a higher frequency of female gender, black race, diabetes, malignancy other than hepatocellular carcinoma, positive anti-hepatitis B core antibody, older age, higher body mass index, higher serum creatinine and longer cold and warm ischaemic time compared to those of ALD patients with renal failure. There were no differences between the two groups with respect to the frequency of combined liver–kidney transplant (1655 patients in the total cohort underwent a combined transplantation), positive rate of hepatitis B surface antigen, ventilator support, portal vein thrombosis, ABO mismatching, whole liver transplant, acute rejection episode, renal recovery, renal failure as cause of death and cardiovascular cause of death. The presence of diabetes, which is associated with parenchymal

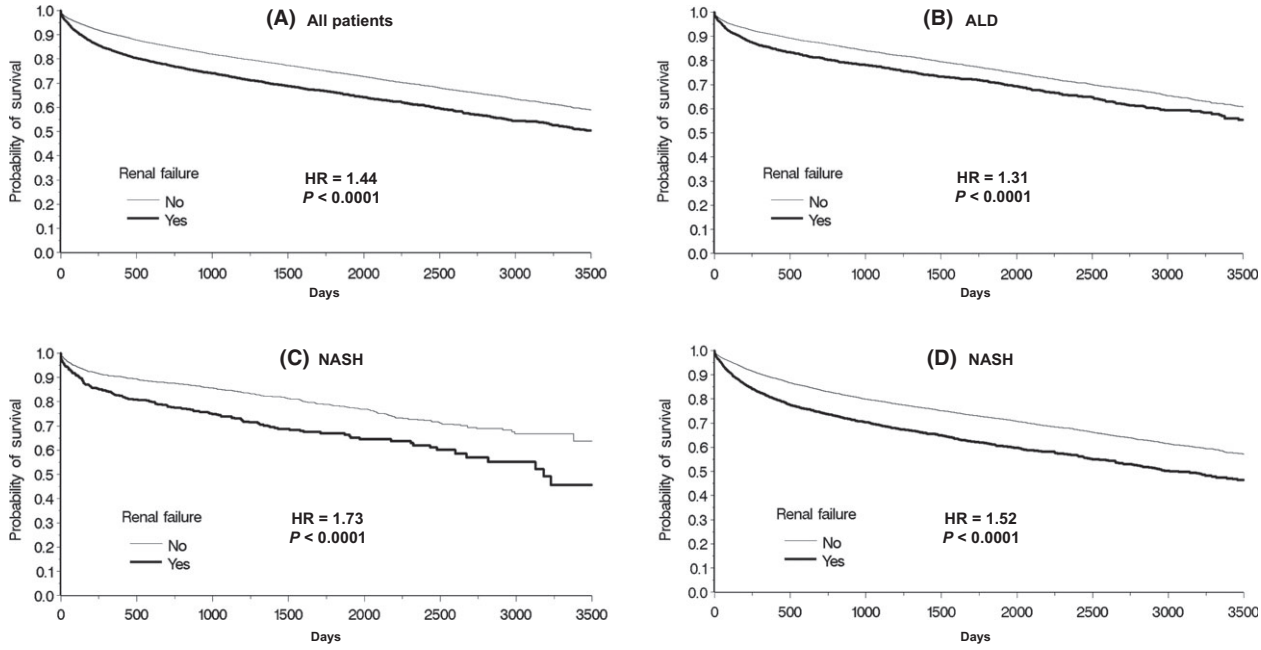

Fig. 2. Impact of renal failure on patient survival according to the aetiology of the underlying liver disease. (A) Overall series, (B) Alcoholic liver disease (ALD), (C) Non-alcoholic steatohepatitis (NASH), and (D) Hepatitis C virus (HCV).

Table 4. Impact of renal failure before liver transplant (LT) on patient survival and graft survival after LT by disease aetiology*

Comparison for patient survival (hazard ratio)	*P*-value	Comparison for graft survival (hazard ratio)	*P*-value
ALD (1.314) vs. Hepatitis C (1.521)	0.0224	ALD (1.231) vs. Hepatitis C (1.392)	0.0482
ALD (1.314) vs. NASH (1.732)	0.0067	ALD (1.231) vs. NASH (1.499)	0.0417
NASH (1.732) vs. Hepatitis C (1.521)	0.1583	NASH (1.499) vs. Hepatitis C (1.392)	0.3732

*This analysis does not include patients with previous LT.

ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis.

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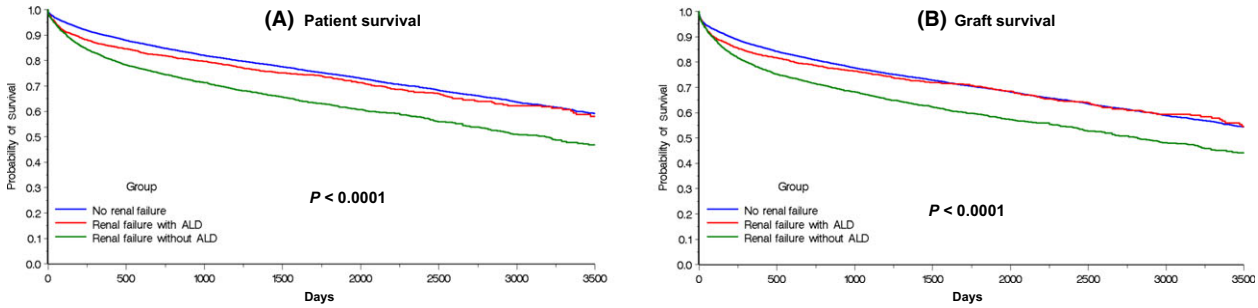

Fig. 3. Comparison of survival between renal failure patients with or without alcoholic liver disease. (A) Patient survival, (B) Graft survival.

Table 5. Prevalence of clinical and laboratory parameters in patients with either ALD or non-ALD and renal failure at the time of liver transplant

Parameters	ALD (n = 1610)	Non-ALD (n = 3203)	P-value
Female gender	22.30%	33.37%	<0.0001
Recipient Age	53.40 ± 8.97	54.84 ± 7.62	<0.0001
Black race	4.10%	13.92%	<0.0001
Body mass index	27.90 ± 5.76	29.02 ± 6.07	0.0155
Creatinine at transplant	3.43 ± 1.73	3.74 ± 2.04	<0.0001
Dialysis treatment	62.55%	58.35%	0.0051
Creatinine at discharge	1.77 ± 1.25	1.86 ± 1.32	0.1411
Creatinine at last follow-up	1.85 ± 1.44	1.91 ± 1.51	0.0594
Renal recovery	58.73%	56.30%	0.1444
Combined liver–kidney transplant	31.18%	31.47%	0.8377
Diabetes	22.73%	35.47%	<0.0001
Hypertension	20.48%	25.59%	0.0611
Ascites at transplant	57.14%	54.45%	0.0761
SBP at registration	15.59%	11.43%	<0.0001
Encephalopathy at transplant	24.20%	21.27%	0.0218
Malignancy at transplant*	0.63%	2.04%	0.0002
MELD score	29.27 ± 9.34	24.78 ± 10.01	0.0018
Hepatitis B surface antigen	1.61%	1.72%	0.8006
Anti-hepatitis B core antibody	6.79%	26.90%	<0.0001
Ventilator support	12.48%	10.74%	0.0715
Portal vein thrombosis	6.75%	8.31%	0.0598
ABO mismatching	8.45%	8.93%	0.5770
Whole liver transplant	1.24%	1.59%	0.3419
Cold ischaemic time	6.97 ± 3.09	7.06 ± 3.74	<0.0001
Warm ischaemic time	40.76 ± 23.90	41.66 ± 19.46	<0.0001
Acute rejection episode	5.61%	5.10%	0.4856
Renal failure as cause of death	3.09%	2.61%	0.6112
Cardiovascular cause of death	17.56%	15.30%	0.2587

*It refers to hepatocellular carcinoma. This analysis excluded those patients with a previous liver transplant.
ALD, alcoholic liver disease; MELD, model for end-stage liver disease; SBP, Spontaneous Bacterial Peritonitis.

renal disease, could partially explain the poor outcome of patients with renal failure of non-alcoholic aetiology.

Discussion

Development of renal failure in patients receiving LT is a critical event affecting survival. We investigated the prevalence of renal failure in patients undergoing LT and the impact of the aetiology of underlying liver disease. Patients with ALD and NASH have higher prevalence of renal failure at the time of LT than patients with hepatitis C, and the presence of renal failure was independently associated with lower survival following LT. Importantly, patient survival differed significantly with aetiology of liver disease in patients with renal failure receiving LT. Our study reinforces previous studies, suggesting that pretransplant renal failure is particularly harmful in patients with NASH (12, 21).

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We analysed data from the UNOS database from 2002 to 2013 that included approximately 25 000 adult LT recipients to evaluate the impact of renal failure on post-LT survival. The UNOS database has been used extensively in other studies (1, 3, 22). However, this database lacks specific data that would allow an assessment of duration of renal failure, dialysis and pre-existing CKD before LT. Furthermore, detailed patient level data to determine the cause of renal dysfunction, causes of death and cardiovascular complications is not readily available in the UNOS database. We should cautiously interpret the cause of death considering the follow-up period of patients after LT. Cardiovascular complications are generally late events appearing 10–15 years after LT as a relevant cause of death. Thus, a considerable proportion of LT patients lacked sufficient follow-up duration for identifying parameters as a cause of death in our study. Immunosuppressive agents, especially calcineurin inhibitors, can cause acute on chronic kidney injury, but precise information on those medications was not available in the UNOS database. These constraints limited our ability to evaluate the cause of renal non-recovery and the exact cause of mortality. Further studies using prospectively collected data should be performed.

In this study, renal failure was more common in patients with ALD and NASH than in those with hepatitis C. This higher prevalence can be due to several reasons: first, recent studies using UNOS database have shown that patients with ALD have more severe liver dysfunction and higher prevalence of bacterial peritonitis than those with hepatitis C (1, 3). The severity of liver disease has been reported to be closely associated with the development of renal failure in cirrhotic patients (23, 24), which can partially explain the high prevalence of renal failure in ALD patients undergoing LT. Second, patients with NASH are more likely to have diabetes, which is commonly associated with intrinsic renal disease and/or progressive CKD. These co-morbid conditions may explain the higher prevalence of renal failure in patients with NASH. Patients with diabetes also have worse post-LT outcomes (25). AKI is associated with high mortality in patients with advanced cirrhosis (26, 27). Not surprisingly, renal failure also has a negative impact on the survival of patients undergoing LT (9–11, 16, 28). Consistent with previous studies, our study shows that renal failure is associated with poor patient survival and graft survival in the overall series and in each liver disease group undergoing LT. Moreover, we analysed survival impact of renal failure across MELD groups; it was only a predictive factor in 20–30 MELD group. Furthermore, survival analysis across MELD groups showed that MELD <20 group were less likely to survive than those with higher MELD score (Fig. S1). Higher survival rate of patients with higher MELD score can be explained, at least in part, by the increase in number of combined liver–kidney transplants (12.44% vs. 0.97%, $P < 0.0001$) in these patients. We are conducting a separate study to address the impact of combined transplant in this cohort.

The major finding in this study is that the impact of renal failure is less marked in patients with ALD than in patients with NASH or hepatitis C. The exact mechanisms by which different aetiologies of liver disease impact survival could not be clearly determined from the available UNOS data. One potential hypothesis is that renal failure in patients with ALD is more relevant to hepatic dysfunction, and that renal recovery is more common in ALD than non-ALD patients. According to recent reports, HRS is more common in ALD (5), and a considerable portion of HRS patients experience renal recovery after LT (10, 17). Furthermore, renal failure in patients with ALD can be due to IgA nephropathy, which is known to be partially reversible after abstinence (15).

Patients with NASH commonly have parenchymal kidney disease, such as diabetic nephropathy. The presence of CKD in patients with NASH may have contributed to the higher percentage non-recovery of renal failure after LT (12). Recent reports showed that diabetes, either alone or co-morbid with obesity, is associated with significantly greater post-transplant mortality (22, 25). In this study, we found that diabetes was more common in non-ALD patients with renal failure than ALD patients with renal failure. Renal failure in combination with NASH may result in a more aggressive natural history leading to increased risk of other health outcomes including cardiovascular events and ultimately lower overall survival, (21). Future studies should prospectively evaluate the factors associated with outcome in patients with NASH and renal failure.

Patients with HCV infection can have concomitant CKD. Indeed, a recent investigation showed a higher prevalence of CKD and shorter kidney survival in patients with chronic HCV infection (29). In this study, we could not use detailed information on the cause of renal dysfunction in patients with HCV infection, however, the possibility of concomitant CKD can partially explain the poor outcome in renal failure of patients with HCV infection.

Predicting the natural course of renal dysfunction following LT can help improve the selection of patients for LT vs. combined liver–kidney transplant. AKI at the time of transplant due to HRS is expected to largely resolve whereas acute tubular necrosis, when severe, may transition directly to CKD or end-stage renal disease and necessitate a concomitant liver–kidney transplant. Previous studies suggested that the duration of pretransplant renal dysfunction has a negative impact on post-transplant renal function outcome (28, 30). Current guidelines recommend that a dialysis period longer than 8 weeks is an indication for combined liver–kidney transplantation in patients with cirrhosis and HRS (31). Based on the results of this study, renal failure has a more negative impact on patient survival in patients with NASH undergoing LT, and these patients

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could benefit more from combined liver–kidney transplantation. However, more research is required to clarify this question.

In conclusion, our study shows that renal failure is associated with poor post-LT outcome, and the impact of renal failure on patient and graft survival is less marked in patients with ALD. These results may assist in identifying patients at risk of progressive renal disease, and identifying patients amenable to specific therapies while on the transplant wait list. Biomarker development for predicting renal non-recovery would be valuable in predicting risk for progressive CKD after LT.

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