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Association of Pre-Transplant Renal Function with Liver Graft and Patient Survival after Liver Transplantation in Patients with Nonalcoholic Steatohepatitis

Running Title: Kidney Function and Outcomes in Liver Transplant Recipients with NASH

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Background: Nonalcoholic Steatohepatitis(NASH) is one of the top three indications for liver transplantation in western countries. It is unknown whether renal dysfunction at the time of liver transplantation has any effect on post-liver transplantation outcomes in recipients with NASH.

Methods: From the United Network for Organ Sharing-Standard Transplant Analysis and Research(UNOS-STAR) dataset, we identified 4,088 NASH recipients who received deceased donor liver transplant. We divided our recipients *a priori* into three categories: Group I with estimated glomerular filtration rate (eGFR)<30 ml/min/1.73m^2 at the time of LT and/or received dialysis within 2 weeks preceding LT(n=937); Group II included recipients who had eGFR≥30 ml/min/1.73m^2 and did not receive renal replacement therapy prior to LT(n=2,812); and Group III included recipients who underwent SLK transplantation(n=339). We examined the association of pre-transplant renal dysfunction with death with functioning graft, all-cause mortality, and graft loss using competing risk regression and Cox proportional hazards models.

Results: The mean±SD age of the cohort at baseline was 58±8 years, 55% were male, 80% were Caucasian, and average exception MELD score was 24±9. The median follow-up period was 5 years (median=1,816 days, interquartile range (IQR):1,090-2,723 days). Compared to Group I recipients , Group II recipients had 19% reduced trend for risk for death with functioning graft[Sub-Hazard Ratio(SHR)(95% CI):0.81(0.64-1.02)] and similar risk for graft loss [SHR(95% CI):1.25(0.59-2.62)] while Group III recipients had similar risk for death with functioning graft[SHR(95% CI):1.23(0.96-1.57)] and graft loss [SHR(95% CI):0.18(0.02-1.37)] using adjusted competing risk regression model.

Conclusions: Recipients with preserved renal function before liver transplantation showed trend toward lower risk of death with functioning graft compared to SLK recipients and those with pre-transplant severe renal dysfunction in patients with NASH.

Key Words: Nonalcoholic steatohepatitis, liver transplantation, graft loss, mortality, renal function

Introduction

It is estimated that one in four liver transplant recipients has an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m^2 at the time of liver transplantation (LT).(1) Renal dysfunction, both pre- or post-LT, is an important comorbidity associated with an increased risk of death, morbidity and cost.(2) Serum creatinine, a major component of the Model for End-stage Liver Disease (MELD) score, has driven the increased incidence of renal dysfunction among patients undergoing LT since the introduction of MELD in 2002.(3) Moreover, end-stage liver failure patients with preserved renal function and unremarkable urinalysis may be noted to have histologic abnormalities on kidney biopsy.(4) More than 50% of the patients with end-stage liver disease and preserved renal function have morphological renal abnormalities, mainly IgA nephropathy and diabetic changes, evident on the renal biopsy.(4) As a result, the frequency of simultaneous liver kidney (SLK) transplantation compared to LT alone has increased.(3)

Pre-existing renal dysfunction before LT is associated with an increased risk of development of end-stage renal disease (ESRD), as well as death after transplantation.(1, 5) The more perplexing clinical question is being able to determine which recipients with renal dysfunction will have recovery of their kidney function versus those recipients who continue to experience a worsening renal dysfunction after LT. Most of these liver transplant recipients will continue to worsen due to calcineurin inhibitor toxicity and lack of recovery from hepato-renal syndrome (HRS)(6) necessitating renal replacement therapy. Several guidelines have attempted to address this question; and all of them utilize the pre-existing renal dysfunction before LT,(7-10) for allocation of SLK transplantation.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease with a prevalence ranging between 20-30% in the western society.(11, 12) Nonalcoholic Steatohepatitis (NASH) is the subset of NAFLD with progressive histologic damage that can

lead to end-stage liver failure.(13) Patients with NASH are at higher risk for developing renal dysfunction as result of obesity, diabetes mellitus, and hypertension-related chronic kidney disease (CKD).(11, 14) Patients in a large observational study showed strong association between the presence of NAFLD and the development of incident CKD.(15) Consequently, the prevalence of CKD in patients with end-stage liver failure secondary to NASH is even higher compared to patients with other etiologies of end-stage liver failure, and NASH is associated with higher risk of kidney graft loss even after SLK transplantation.(16) However, it is unknown whether the renal dysfunction at the time of LT has any effect on post-liver transplant survival or graft loss in recipients with NASH.

To address this knowledge gap, we aimed to investigate the association of pre-transplant renal dysfunction with post-transplant death with functioning graft, all-cause mortality, and graft loss using a large nationally representative cohort of patients with liver failure secondary to NASH in the United States (US). We hypothesized that the recipients with preserved renal function versus renal dysfunction had significantly lower risk of death with functioning graft, all-cause mortality risk after LT, similar risk for graft loss and longer kidney transplantation free survival after LT. We also hypothesized that recipients with SLK transplantation had significantly higher risk for death with functioning graft and all-cause mortality, but similar risk for graft loss after LT compared to recipients with severe renal dysfunction.

Materials and Methods

Data Source and Cohort Definition

A total of 60,394 liver transplant recipients (January 2002 through June 2013) were identified from the United Network for Organ Sharing-Standard Transplant Analysis and Research (UNOS-STAR) dataset as the population. NASH LT recipients were determined by primary or secondary indication for liver transplantation as reported to UNOS. Only individuals who had NASH as a cause of liver failure and who had data regarding renal dysfunction or renal replacement therapy were included in the study. The algorithm for the cohort definition is shown in Figure 1. We excluded patients with a diagnosis of hepatocellular carcinoma (HCC) (n=12,068), or those who received a living donor transplant (n=2,516), or transplantation from split liver donors (n=3,212), non-heart beating donors (n=2,607), multi-organ transplants (n=688) (except SLK). Some of the excluded patients had more than one exclusion criteria. Furthermore, after exclusion of recipients with non-NASH etiology of chronic liver disease (n=36,075), 4,088 NASH-related liver transplant recipients were included in the final study cohort: 3,749 were liver-only recipients, and 339 were SLK transplant recipients. We also linked the liver transplant data to the kidney transplant data in the UNOS-STAR database using encrypted recipient identifier ID to identify those patients who received kidney transplant after their liver or SLK transplant. The Institutional Review Boards of the University of Tennessee Health Science Center and the University of Memphis approved the study, with exemption from informed consent.

Exposure Variable

Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation: GFR (mL/min/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American).(17) We divided our

recipients *a priori* into three categories according to their renal dysfunction before LT. Group I included recipients who had estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 at the time of LT and/or received dialysis within 2 weeks preceding LT (n=937) and served as reference group; Group II included recipients who had eGFR ≥ 30 ml/min/1.73m^2 and did not receive renal replacement therapy prior to LT (n=2,812); and Group III included recipients who underwent SLK transplantation (n=339).

Covariates

The UNOS-STAR database was utilized to determine baseline demographic characteristics at the time of LT, information on comorbidities, laboratory data at the time of LT, and donor related data.

Outcome Assessment

The primary outcomes of interest were death with functioning graft, all-cause mortality, and graft loss after LT. Mortality and graft loss data, censoring events, and associated dates were obtained from UNOS-STAR data source.

These outcomes were defined as follows:

1.For the death with functioning graft analysis, the start of the follow-up period was the date of transplantation, and patients were followed up until death or other events including graft loss, lost to follow-up, or end of follow-up period. For this analysis we used competing risk regression, where the primary outcome was death and the competing outcome was graft loss. Data was censored for loss to follow-up, or end of follow-up period.

2. For the all-cause death analysis, the start of the follow-up period was the date of transplantation, and patients were followed up until death or other censoring events including

lost to follow-up, or end of follow-up period. For this analysis, we used Cox proportional hazards regression.

3.For the graft loss analysis, the start of the follow-up period was the date of transplantation, and patients were followed up until graft loss or other events including death, lost to follow-up, or end of follow-up period. For this analysis we used competing risk regression, where the primary outcome was graft loss and the competing outcome was death. Data was censored for loss to follow-up, or end of follow-up period.

4, The kidney transplant free analysis, the start of the follow-up period was the date of transplantation, and patients were followed up until kidney transplantation or other events including liver graft loss, death, lost to follow-up, or end of follow-up period. For this analysis we used Kaplan-Meier method only.

Statistical analysis

Baseline recipient characteristics were summarized according to the renal dysfunction at the time of LT and presented as percentages for categorical variables and mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Continuous and categorical variables were compared using p for trend test.

The associations between different renal dysfunction categories and outcomes after LT were assessed using competing risk regression using the Fine and Gray model (18) for death with functioning graft and graft loss, and Kaplan-Meier method with log-rank test and Cox proportional hazard models for all-cause mortality.

Independent variables were included in the multivariate models based on theoretical considerations. Variance influence factors (VIF) were used to indicate collinearity between independent variables. Proportional hazards assumptions were tested using scaled Schoenfeld residuals in the Cox proportional hazard models. Models were incrementally adjusted for the

following potential confounders based on theoretical considerations and their availability in this study: model 1: unadjusted; model 2: adjusted for age, sex, race/ethnicity; model 3: additionally adjusted for comorbidities (malignancy and diabetes), exception MELD score at the time of transplantation, presence of ascites at the time of transplantation, history of transjugular intrahepatic portosystemic shunt (TIPS) placement, functional status and laboratory data (serum albumin [mg/dL], International Normalized Ratio [INR] and serum bilirubin [mg/dL]); and model 4: additionally adjusted for donor related (age, sex, race and BMI of the donor), and transplantation related (cold ischemic time and cytomegalovirus (CMV) mismatches) data and characteristics.

We conducted several sensitivity analyses to evaluate the robustness of our main findings. The association between the absence or degree of underlying renal dysfunction and outcomes after LT were examined in subgroups of patients stratified by age, sex, race, presence or absence of diabetes, and exception MELD score. Potential interactions were formally tested by inclusion of relevant interaction terms. 3,323 (81%) recipients had complete data for analysis in the final model (model 4). Missing values were not imputed in primary analyses, but were substituted by multiple imputation (n=5 dataset) procedures using the Stata (Stata Corporation, College Station, TX) "mi" set of commands in sensitivity analyses.(19, 20)

Reported *P* values were two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 13.1 (STATA Corporation, College Station, TX).

Results

Baseline Characteristics

The mean±SD age of the cohort at baseline was 58±8 years, 55% were male, 80% were Caucasian. The average MELD score was 24±9, and 52% of the patients were diabetic. Baseline characteristics of recipients categorized by renal dysfunction are shown in Table 1. The recipients with preserved renal function (Group II) were more likely to be male and Caucasian and had lower prevalence of diabetes and lower exception MELD score compared to recipients in Group I and Group III.

Death with Functioning Graft and All-Cause Mortality in the Study Cohort

During the entire follow-up period (median=1,816 days (5 years), interquartile range (IQR): 1,090 – 2,723 days (3-7.5 years)) following transplantation, a total of 1,065 (26%) deaths occurred (crude incidence rate, 50 per 1000 patient-years; 95% confidence interval [CI]: 47-53). The crude mortality rate was the highest in recipients who underwent SLK transplantation, 118 (38%) deaths (77 per 1000 patient-years, 95% CI: 64-92), followed by recipients with Group I, 284 (34%) deaths (66 per 1000 patient-years, 95% CI: 59-74), while the lowest mortality rate was observed in recipients who had Group II, 663 (27%) deaths (43 per 1000 patient-years, 95% CI: 40-47) as shown in the Kaplan-Meier survival curve (Figure 2).

Compared to recipients in Group I, recipients in Group II had 33% lower risk for death with functioning graft, [Sub-Hazard Ratio (SHR) (95% CI): 0.67 (0.58-0.77)] while recipients in Group III had similar risk for death with functioning graft [SHR (95% CI): 1.18 (0.96-1.46)] using unadjusted competing risk regression model (Table 2). Similar trend was observed after adjustment in our adjusted model (Table 2) and also for all-cause mortality using Cox proportional regression models (Table S1). Additionally, compared to in Group I

recipients, recipients in Group II had 24% lower risk for death with functioning graft (SHR 95% CI: 0.76 [0.62-0.93]), while in Group III recipients had similar risk for death with functioning graft (SHR 95% CI: 1.21 [0.97-1.50]) in our multiple imputed adjusted competing risk regression model (Table 2). Qualitatively, similar results were found for all-cause mortality using multiple imputed adjusted Cox proportional regression model (Table S1). Finally, similar to the entire cohort, in Group II recipients had lower risk for death with functioning graft while in Group III recipients had similar risk for death with functioning graft compared to in Group I recipients in most of the subgroups (Figure 3). Similar qualitative results were found for all-cause mortality using Cox proportional regression models (Figure S1).

Graft Loss in the Study Cohort

During the entire follow-up period following transplantation, a total of 113 (26%) graft loss occurred (crude incidence rate, 5.4 per 1000 patient-years; 95% confidence interval [CI]: 4.5-6.4). The crude graft loss rate was the lowest in Group III recipients, 3 (1%) graft losses (2.0 per 1000 patient-years, 95% CI: 0.6-6.1), followed by in Group I recipients, 21 (2.5%) graft losses (4.9 per 1000 patient-years, 95% CI: 3.2-7.5), while the highest graft loss rate was observed in in Group II recipients, 89 (3.6%) graft losses (5.8 per 1000 patient-years, 95% CI: 4.7-7.2).

Compared to in Group I recipients, recipients with in Group II [SHR (95% CI): 1.39 (0.86-2.23)] and in Group III recipients [SHR (95% CI): 0.38 (0.11-1.29)] had similar graft loss risk, respectively, using unadjusted competing risk regression model (Table 3). Similar results were observed after adjustment in our adjusted model and also in our multiple imputed adjusted competing risk regression model (Table 3). Finally, similar to the entire cohort, in

Group II recipients and in Group III recipients had similar graft loss risk compare to in Group I recipients in most of the subgroups (Figure 4).

Kidney Transplantation Free Survival in the Study Cohort

Group I recipients had lowest probability for kidney transplant free survival while in Group II recipients had the highest probability during the 8 years follow-up period as showed in Figure 5.

Discussion

In this large national cohort of US liver transplant recipients with NASH, we found an association between pre-transplant renal dysfunction with death with functioning graft and all-cause mortality following LT, independent of demographics, comorbidities, and donor related variables. While patients with better renal function (eGFR≥30 ml/min/1.73m^2) at the time of LT experienced trend for lower risk for post-transplant death with functioning graft and all-cause mortality, recipients who underwent SLK experienced comparable risk of death with functioning graft and all-cause mortality versus recipients with renal dysfunction independent of other relevant risk factors. These associations were robust and present in almost all subgroup of the recipients. Additionally, we could not find any association between pre-transplant renal dysfunction and risk of graft loss in this cohort.

The presence and severity of NASH is associated with an increased risk and severity of CKD.(21) Therefore, it is not surprising to note the growing indication for SLK transplantation in NASH patients in the US.(16) NASH remains an independent risk factor for renal dysfunction after LT.(22) Although several published studies have reported the negative impact of renal failure on survival of patients undergoing LT,(23-27) specific mechanism of the degree or severity of renal dysfunction, and its relationship to survival probability following LT in recipients with NASH has not been well characterized. Studies are needed to examine mechanisms of these findings and develop strategies to improve renal outcomes in recipients for NASH.

The current study highlights the importance of pre-transplant renal dysfunction as an important predictor of post-transplant survival in liver transplant recipients with NASH. Our findings are further reinforced by an earlier study using UNOS-STAR data that reported that the presence of pre-transplant renal dysfunction was independently associated with lower survival following LT in alcohol related liver disease and NASH patients.(28) We, however,

did not detect any survival difference between the recipients with renal dysfunction before LT and recipients who received SLK transplantation. Similar results have been shown in non-NASH recipients as well.(29)

Several factors could have contributed to the poor survival outcome in NASH patients with renal dysfunction at the time of LT (eGFR <30 ml/min/1.73m^2/dialysis and/or underwent SLK transplantation) compared with LT recipients with better renal function (eGFR≥30 ml/min/1.73m^2). Firstly, LT recipients with pre-transplant CKD have a substantial burden of post-transplant renal dysfunction and high short-term mortality.(30) The presence of pre-transplant CKD in LT candidates with NASH may have contributed to the higher percentage of non-recovery of the renal insult after LT.(21) Secondly, NASH recipients have an increased risk of cardiovascular disease (CVD) mortality after LT explained by a high prevalence of comorbid cardio-metabolic risk factors such as renal dysfunction or presence of diabetes.(31) In fact, pre-transplant renal dysfunction was the strongest predictor of post-LT cardiovascular disease mortality in NASH recipients.(31) In addition, diabetes, either alone or in co-morbid association with obesity, is linked with significantly greater post-transplant mortality.(32, 33) The burden of diabetes could be even higher in NASH recipients receiving SLK transplantation. Higher proportion of SLK transplant recipients with NASH have diabetes in the UNOS-STAR cohort possibly due to long standing CKD related to diabetes.(31, 34) Hence, pre-transplant renal dysfunction along with presence of diabetes in LT candidates with NASH might result in additive deleterious consequences leading to lower overall survival.(31) Future studies should prospectively evaluate identification of other factors associated with outcomes in patients with NASH and pre-transplant renal dysfunction.

Our study identifies an inferior survival outcome in NASH patients undergoing LT with renal dysfunction (eGFR<30 ml/min/1.73m^2 or needing dialysis), but their outcome is no different than those with SLK transplantation. This study raises questions regarding the

current allocation policy in NASH candidates for LT in a resource poor setting for optimal utilization of the kidney allograft. It can be argued that considering similarly poor survival in NASH patients with eGFR<30 ml/min/1.73m^2 or those needing short-term dialysis compared to those who received SLK, consideration should be given for kidney after LT, particularly those with shorter duration on renal replacement therapy (as opposed to established ESRD). Although this notion has been argued against in previously published studies,(35) improved immunosuppression regimen (early use of mammalian target of rapamycin inhibitors in patients with renal impairment) in recent years might confer a better long-term outcome. *Sharma et al.* have reported, among recipients on renal replacement therapy before LT who survived after LT alone, the majority recovered their renal function within 6 months of LT. Longer pre-transplantation renal replacement therapy duration, advanced age, diabetes, and re-transplantation were significantly associated with an increased risk of renal non-recovery.(36) *Habib et al.* have reported that SLK transplantation improved 1-year survival only in low MELD (16 - 20) recipients but not in other groups.(37) The authors have concluded that performance of SLK transplantation should be limited to patients where a benefit in survival and post-transplant outcomes can be demonstrated. However, in our study MELD score did not modify the association between renal dysfunction and survival. Model for End-Stage Liver Disease prioritization of liver recipients with renal dysfunction has significantly increased utilization of SLK transplantation. With 20% short-term loss of kidney grafts after SLK transplantation, *Lunsford et al.* have suggested that renal transplantation should be deferred in liver recipients at high risk for renal allograft futility.(38) Consideration for a kidney allocation variance to allow for delayed renal transplantation after LT may prevent loss of scarce renal allografts. Without well-established listing guidelines, SLK transplantation potentially wastes renal allografts in both cases, high-acuity liver recipients at risk for early mortality and recipients who may regain native kidney function. Despite these

theoretical concerns, based on our study current UNOS allocation policy allowed similar survival outcomes (all-cause mortality) in SLK transplant patients with NASH compared to those with severe renal dysfunction receiving LT alone. In addition, Group III (SLK) patients have superior kidney transplant free survival (kidney re-transplant free survival in this group) compared to Group II (e GFR < 30) recipients with application of the current allocation policy, reaffirming validity of current UNOS policy in NASH patients.

Our study is unable to specifically address this question of renal allograft allocation in LT candidates with NASH. Future studies should be directed specifically to address which subgroup of LT candidates with NASH most benefit from SLK transplantation.

Our study is notable for its large sample size and event numbers, and for being representative of US LT recipients. We also used statistical approach with counts for competing events in case of graft loss or death with functioning graft. To our knowledge, this is the first study to assess the association between renal dysfunction before LT and death with functioning graft, all-cause mortality and graft loss after transplantation in recipients specifically in recipients with NASH. We used multiple imputation to increase the power of our analysis. While our main result showed only trend for lower mortality risk on patients with preserved renal function, the imputation increased the power and the result became significant without major change on the value of the point estimate.

This study also has several limitations that need to be acknowledged. First, because this was an observational study, only associations, but no cause-effect relationships, can be established. Second, our patients were US deceased donor LT recipients; hence, the results may not be generalizable to other recipient populations outside the US. Third, we were unable to assess the duration of renal dysfunction and pre-existing CKD before LT using the UNOS-STAR data. Fourth, etiology of death was not uniformly available in all patients, so we were unable to perform death cause specific analyses. Fifth, lack of data on immunosuppression

and incidence of renal dysfunction post-LT is also another glaring deficiency significantly limiting our ability to evaluate the cause of renal non-recovery. Sixth, we used estimated GFR in our analysis as renal data, and we did not have more granular, detailed data about the patient's underlying renal disease prior to their listing. Finally, as with all observational studies, we were not able to eliminate the possibility of unmeasured confounders.

Conclusion

In this large national cohort of US LT recipients with NASH, we found that recipients with more preserved renal function had lower mortality risk, but similar liver allograft loss risk after transplantation while recipients who received SLK had similar mortality and liver allograft loss risk, but superior kidney transplant free survival compared to recipients with severe renal dysfunction independent of demographics, comorbidities, and donor related data.

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Table 1: Baseline characteristics of the study population

	All Patients (*n*=4,088)	**Group I: eGFR < 30 mL/min/1.73 m^2 or dialysis (*n*=937)**	**Group II: eGFR ≥ 30 mL/min/1.73 m^2 (*n*=2,812)**	**Group III: SLK (*n*=339)**	**p for trend**
Sociodemographic data:					
Age; (years) mean±SD	58±8	58±8	58±8	59±8	0.02
Gender; (male) n (%)	2,236 (55)	407 (44)	1,656 (59)	173 (51)	<.001
Race/Ethnicity; n (%)					<.001
Caucasian	3,420 (80)	735 (80)	2,422 (87)	263 (78)	
African American	94 (3)	24 (3)	53 (2)	17 (5)	
Hispanics	455 (16)	144 (16)	261 (9)	50 (15)	
Others	88 (1)	15 (1)	64 (2)	9 (2)	
Education level; n (%)					0.46
Completion of high school or lower	1,764 (51)	401 (51)	1,210 (51)	153 (50)	
Attendance of college or technical school	810 (23)	168 (21)	576 (24)	66 (22)	
Bachelor's Degree or higher	903 (26)	215 (28)	604 (25)	84 (28)	
Comorbidities:					
Presence of diabetes mellitus; n (%)	2,116 (52)	483 (53)	1,403 (50)	230 (68)	<.001
Presence of ascites; n (%)	3,565 (89)	847 (94)	2,414 (87)	304 (90)	<.001
Malignancy; n (%)					0.02
No malignancy	3,577 (88)	835 (91)	2,439 (87)	277 (90)	
Malignancy present	309 (8)	58 (6)	230 (8)	19 (6)	

Uncertain or missing data on malignancy	171 (4)	25 (3)	131 (5)	11 (4)	
Functional status; n (%)					<.001
Able to perform normal activities	955 (25)	7 (9)	818 (31)	60 (18)	
Unable to perform normal activities	2,907 (75)	788 (91)	1,848 (69)	271 (82)	
Presence of TIPS; n (%)	446 (11)	88 (10)	325 (12)	33 (10)	0.43
BMI; (kg/m^2) mean±SD	33±6	33±6	33±5	32±6	0.04
Exception MELD score; mean±SD	24±9	33±8	20±7	30±8	<.001
Laboratory data:					
Serum creatinine; (mg/dL) median (IQR)	1.3 (1.0-2.1)	2.7 (2.1-3.7)	1.1 (0.9-1.4)	3.4 (2.3-4.7)	<.001
Serum albumin; (g/dL) mean±SD	3.0±0.7	3.1±0.8	2.9±0.6	3.0±0.8	<.001
Serum bilirubin; (mg/dL) median (IQR)	4.1 (2.3-8.3)	6.5 (3.2-19.1)	3.8 (2.2-6.9)	3.2 (1.7-7.6)	<.001
INR; median (IQR)	1.7 (1.4-2.2)	1.9 (1.6-2.4)	1.7 (1.4-2.1)	1.7 (1.4-2.1)	<.001
Transplantation related data:					
Cold ischemic time; (hours) median (IQR)	6.7 (5.0-8.3)	6.5 (5.0-8.4)	6.0 (5.0-7.7)	6.0 (5.0-7.7)	0.05
Donor age; (years) mean±SD	43±17	41±17	44±17	37±15	0.67
Donor gender; (male) n (%)	2,407 (59)	532 (58)	1,662 (59)	213 (63)	0.29
Donor race/ethnicity; n (%)					0.001
Caucasian	2,749 (68)	609 (66)	1,903 (68)	237 (68)	
African American	769 (19)	155 (17)	562 (20)	52 (19)	
Hispanics	404 (10)	118 (13)	244 (9)	42 (10)	
Others	135 (3)	36 (4)	91 (3)	8 (3)	
Donor BMI; (kg/m^2) mean±SD	28±6	27±6	28±6	27±5	0.05
CMV mismatch; n (%)					0.047
D(-)/R(-)	443 (12)	98 (11)	307 (12)	38 (12)	

D(-) or D(+)/R(+)	2,485 (65)	588 (69)	1,677 (64)	220 (69)	
D(+)/R(-)	862 (23)	172 (20)	630 (24)	60 (19)	

Abbreviations: BMI: Body mass index; CMV: Cytomegalovirus; D: Donor; eGFR: estimated glomerular filtration rate; INR: International Normalized Ratio; IQR: Interquartile range; MELD: Model for End-Stage Liver Disease; R: Recipient; SD: standard deviation; SLK: simultaneous liver-kidney transplant; TIPS: Transjugular intrahepatic portosystemic shunt

Table 2: Association between renal function and death with functioning graft using competing risk regression model with different level of adjustment

***Reference:* Recipients who had eGFR< 30 ml/min./1.73m^2 and/or received dialysis**	**Sub-Hazard Ratios (SHRs)**	**95% Confidence Interval of SHRs**	**p-value**
Model 1 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.67	0.58-0.77	<.001
Simultaneous liver kidney transplantation	1.18	0.96-1.46	0.12
Model 2 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.66	0.57-0.76	<.001
Simultaneous liver kidney transplantation	1.11	0.90-1.38	0.32
Model 3 (n=3,793):			
eGFR ≥ 30 ml/min./1.73m^2	0.75	0.60-0.93	0.01
Simultaneous liver kidney transplantation	1.14	0.91-1.43	0.25
Model 4 (n=3,323):			
eGFR ≥ 30 ml/min./1.73m^2	0.81	0.64-1.02	0.08
Simultaneous liver kidney transplantation	1.23	0.96-1.57	0.11
Multiple imputation model (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.76	0.62-0.93	0.009
Simultaneous liver kidney transplantation	1.21	0.97-1.50	0.10

Variables adjusted for in different models:

Model 1: unadjusted;

Model 2: adjusted for age, sex, and race/ethnicity;

Model 3: adjusted for variables included in model 2 and additionally adjusted for comorbidities (malignancy and diabetes), model for end-stage liver disease score at the time of transplantation, presence of ascites at the time of transplantation, history of transjugular intrahepatic portosystemic shunt placement, functional status and laboratory data (albumin, international normalized ratio and serum bilirubin);

Model 4: adjusted for variables included in model 3 and additionally adjusted for donor related data (age, sex, race and body mass index of the donor), and transplantation related data (cold ischemic time and cytomegalovirus mismatches).

Abbreviations: eGFR: estimated glomerular filtration rate; SHR: Sub-Hazard Ratio

Table 3: Association between renal function and graft loss using competing risk regression model with different level of adjustment

***Reference:* Recipients who had eGFR< 30 ml/min./1.73m^2 and/or received dialysis**	**Sub-Hazard Ratios (SHRs)**	**95% Confidence Interval of SHRs**	**p-value**
Model 1 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	1.39	0.86-2.23	0.18
Simultaneous liver kidney transplantation	0.38	0.11-1.29	0.12
Model 2 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	1.34	0.83-2.14	0.23
Simultaneous liver kidney transplantation	0.41	0.12-1.38	0.15
Model 3 (n=3,793):			
eGFR ≥ 30 ml/min./1.73m^2	1.29	0.65-2.57	0.47
Simultaneous liver kidney transplantation	0.45	0.13-1.51	0.19
Model 4 (n=3,323):			
eGFR ≥ 30 ml/min./1.73m^2	1.25	0.59-2.62	0.56
Simultaneous liver kidney transplantation	0.18	0.02-1.37	0.10
Multiple imputation model (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	1.40	0.70-2.80	0.34
Simultaneous liver kidney transplantation	0.47	0.14-1.58	0.23

Variables adjusted for in different models:

Model 1: unadjusted;

Model 2: adjusted for age, sex, and race/ethnicity;

Model 3: adjusted for variables included in model 2 and additionally adjusted for comorbidities (malignancy and diabetes), model for end-stage liver disease score at the time of transplantation, presence of ascites at the time of transplantation, history of transjugular intrahepatic portosystemic shunt placement, functional status and laboratory data (albumin, international normalized ratio and serum bilirubin);

Model 4: adjusted for variables included in model 3 and additionally adjusted for donor related data (age, sex, race and body mass index of the donor), and transplantation related data (cold ischemic time and cytomegalovirus mismatches).

Abbreviations: eGFR: estimated glomerular filtration rate; SHR: Sub-Hazard Ratio

Legend of Figures:

Figure 1: Flow chart of the study population

Abbreviations: eGFR: estimated glomerular filtration rate; HCC: hepatocellular carcinoma; SLK: simultaneous liver kidney transplantation; UNOS: United Network for Organ Sharing

*: some patients had more than one reason for exclusion

Figure 2: Probability of all-cause mortality of recipient with different kidney function

Abbreviations: eGFR: estimated glomerular filtration rate; SLK: simultaneous liver kidney transplantation; Tx: transplantation

Figure 3: Association of different renal function and death with functioning graft in unadjusted (panel A) and adjusted* (panel B) competing risk regression model in selected subgroups (reference category: recipients who had eGFR< 30 ml/min./1.73m^2 and/or received dialysis)

Abbreviations: eGFR: estimated glomerular filtration rate; MELD: Model for End-stage Liver Disease

*: adjusted for age, sex, race/ethnicity, comorbidities (malignancy and diabetes), model for end-stage liver disease score at the time of transplantation, presence of ascites at the time of transplantation, history of transjugular intrahepatic portosystemic shunt placement, functional status and laboratory data (albumin, international normalized ratio and serum bilirubin), donor related data (age, sex, race and body mass index of the donor), and transplantation related data (cold ischemic time and cytomegalovirus mismatches).

Figure 4: Association of different renal function and graft loss in unadjusted (panel A) and adjusted* (panel B) competing risk regression model in selected subgroups (reference category: recipients who had eGFR< 30 ml/min./1.73m^2 and/or received dialysis)

Abbreviations: eGFR: estimated glomerular filtration rate; MELD: Model for End-stage Liver Disease

*: adjusted for age, sex, race/ethnicity, comorbidities (malignancy and diabetes), model for end-stage liver disease score at the time of transplantation, presence of ascites at the time of transplantation, history of transjugular intrahepatic portosystemic shunt placement, functional status and laboratory data (albumin, international normalized ratio and serum bilirubin), donor related data (age, sex, race and body mass index of the donor), and transplantation related data (cold ischemic time and cytomegalovirus mismatches).

Figure 5: Probability of kidney transplant free survival of recipient with different kidney function

Abbreviations: eGFR: estimated glomerular filtration rate; SLK: simultaneous liver kidney transplantation; Tx: transplantation