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INTRODUCTION: **To analyze the impact of acute-on-chronic liver failure (ACLF) immediately before liver transplantation (LT) on short-term kidney function.**

METHODS: **In this retrospective study, we included 416 of 687 consecutive patients who had an estimated glomerular filtration rates (eGFRs) at 3-month post-LT. We compared the non-ACLF (N = 356), ACLF with eGFR ≥30 mL/min/1.73 m² (A-HGFR, N = 32), and ACLF with eGFR <30 mL/min/1.73 m² (A-LGFR, N = 28) groups at LT and for 2 kidney-related outcomes: (i) slope of eGFR by linear mixed model and (ii) time to development of composite kidney outcomes (eGFR < 15 mL/min/1.73 m² or need for dialysis).**

RESULTS: **The mean eGFRs at LT in non-ACLF, A-HGFR, and A-LGFR groups were significantly different as follows: 83.9 ± 29.5, 56.5 ± 31.2, and 21.6 ± 5.0 mL/min/1.73 m², respectively. The eGFR slope significantly increased in A-LGFR group (+7.26 mL/min/1.73 m²/mo), whereas it remained stable in A-HGFR group (+1.05 mL/min/1.73 m²/mo) and significantly declined in non-ACLF group (−7.61 mL/min/1.73 m²/mo) by the first 3-month period. On the other hand, the eGFR slope in all groups stabilized after 3 months post-LT. A-LGFR group showed significantly increased risk of developing composite kidney outcomes in adjusted analysis (hazard ratio = 3.61, 95% confidence interval: 1.35–9.70) compared with the non-ACLF group. However, this significance disappeared after the further adjustment for eGFR at 3-month post-LT (hazard ratio = 1.91, 95% confidence interval: 0.70–5.23).**

DISCUSSION: **The slopes of eGFR before 3-month post-LT were significantly different among non-ACLF, A-HGFR, and A-LGFR groups. The renal dysfunction in A-LGFR group stabilized after partial recovery by 3-month post-LT (eGFR reset point).**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A289, http://links.lww.com/CTG/A288

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INTRODUCTION

Acute kidney injury (AKI) before liver transplantation (LT) has a significant impact not only on renal outcomes but also on patient survival and resource utilization (1–5). Approximately 25% of patients had an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m² at LT, with 10%–20% requiring dialysis immediate post-LT (4,6). The incidence of end-stage renal disease is approximately 1%–3% at 1 year and 5.9% at 5 years after LT (2,7).

Evolving demographics and the underlying causes of AKI in patients with end-stage liver disease likely contribute to significant chronic kidney disease (CKD) after LT (6,8,9). There is growing evidence for structural changes secondary to the inflammatory processes underlying AKI (8,10,11). Hepatorenal syndrome, an important cause of AKI in end-stage liver disease, portends high mortality without LT. However, pure hepatorenal syndrome is a functional disorder because of hemodynamic changes without

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structural damage to glomeruli or tubules; most of these patients might recover completely after LT (12).

Acute-on-chronic liver failure (ACLF) is a syndrome defined as acute decompensation with multiple organ failures occurring on top of preexisting chronic liver disease (cirrhosis), caused by either hepatic (alcohol abuse and hepatitis flare) or extrahepatic insults (infection) (13). AKI occurring in the patients with ACLF could have an increased risk of kidney dysfunction related to inflammatory kidney injury (8). Structural damage and inflammation arising from ischemia, endothelial dysfunction, and oxidative stress could lead to acute tubular injury/necrosis (8,14). The ACLF definition and grading characterized by organ failures by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium reflect the involvement of inflammatory processes underlying its pathophysiology (15). The post-LT kidney function in patients with ACLF under the EASL-CLIF guidelines remains unclear.

We postulated that patients with ACLF as defined by EASL-CLIF undergoing LT will have worse kidney function in the post-LT period. We, therefore, conducted a retrospective cohort study at a high-volume transplant center to assess kidney-related outcomes in those with and without ACLF pre-LT.

METHODS

Selection of patients and data source

In this single-center, retrospective cohort study, consecutive patients 18 years or older (April 2006–March 2013) with chronic liver disease undergoing their first LT from a deceased donor were included. Patients with multiorgan transplantation were excluded. Of the 687 recipients who fulfilled the criteria, 416 with complete longitudinal renal function data were included (Figure 1). Patients with missing serum creatinine at 3 months after LT (±30 days from 90 days after LT) were excluded for the analysis because the outcome of interest of this study was to assess the slope of kidney function until at least 3 months after LT. Those who died, underwent re-LT, and were lost to follow-up by 3 months after LT were also excluded from the analysis (Figure 1). We have presented the baseline characteristics between the analysis cohort (N = 416) and the excluded cohort (N = 271) to evaluate any possibilities of selection bias (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A289).

Local electronic medical record was queried until March 6, 2019, to obtain baseline demographic and clinical data. Presence of pre-LT dialysis was defined as dialysis therapy 48 hours before LT. Diabetes was defined based on diagnosis code, use of antidiabetic medication, and hemoglobin A1c (≥6.5%). Model for end-stage liver disease (MELD) score just before LT was calculated using the original formula (16). Living donor liver transplants were not included in this study.

Kidney function was calculated at the time of LT as eGFR by 4 variable version of the Modification of Diet in Renal Disease Study equation formula (17,18). For the purpose of the analysis, the upper limit of eGFR was capped at 150 mL/min/1.73 m^2. All patients were maintained on the local immunosuppression protocol published elsewhere (19).

Risk stratification (exposure)

Patients were first stratified into ACLF and non-ACLF groups using the EASL-CLIF Consortium definition shown elsewhere (15,20). Second, the ACLF group was further divided into 2 groups according to eGFR at LT for the analysis as follows; (i) ACLF with eGFR ≥30 mL/min/1.73 m^2 at LT (A-HGFR group) and (ii) ACLF with eGFR <30 mL/min/1.73 m^2 at LT (A-LGFR group).

Outcomes

The primary outcome of interest was eGFR slope after LT up to 12 months in the non-ACLF, A-HGFR, and A-LGFR groups. Additional outcome measures included the following: (i) The mean eGFR at LT and 12 months after LT compared between 3 groups. (The eGFR at LT was captured at just before LT. The eGFR at 12 months was accepted the nearest day of 12 months ± 120 days after LT as a window period.) (ii) The time from LT to onset of composite kidney outcome. Composite kidney outcome was defined as time to initiation of maintenance dialysis or reaching to CKD stage

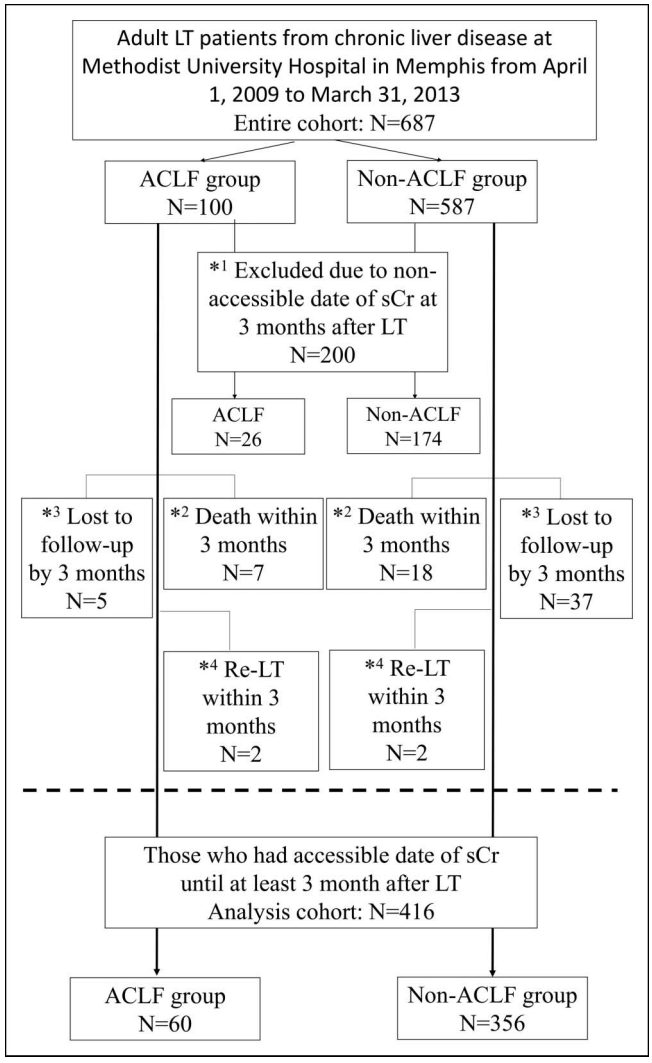

Figure 1. Study flowchart. We focused on the trajectory of kidney function at least 3 months after LT. Thus, those who had serum creatinine of 3 months after LT were included. We accepted the window period for 3 months after LT as ± 30 days. Furthermore, we excluded *1: Those without accessible date of sCr at 3 months after LT (actually, they could be captured at least once after this period); *2: Those who died within 3 months after LT; *3: Those who were lost to follow-up until 3 months after LT; *4: Those who underwent re-LT within 3 months after LT. After elimination by above-mentioned reasons, 416 patients were analyzed for kidney function-related outcomes. ACLF, acute on chronic liver failure; LT, liver transplantation; sCr, serum creatinine; Tx, transplantation.

5 defined as eGFR of less than 15 mL/min/1.73 m^2 (measurements taken on 2 occasions at least 90 days apart) (21), whichever occurred first. Maintenance dialysis was defined as continuous dialysis for at least 3 months or longer (first date) or a diagnosis of incidence of end-stage renal disease with dialysis on electronic medical record.

Statistical analysis

Pre-LT characteristics were summarized and stratified according to the non-ACLF, A-HGFR, and A-LGFR groups and presented as mean ± SD or median and interquartile range for continuous variables and numbers and percentages for categorical variables. Differences between the non-ACLF group and A-HGFR and A-LGFR groups were assessed separately by Student *t* test, Mann-Whitney test for continuous variables, or χ^2 test for categorical variables.

The eGFR slope was calculated using a general linear mixed model from longitudinal eGFR data after LT in all analysis cohort (N = 416). We calculated the mean response profile of GFR and generated spaghetti plots by GFR groups, and identified a reset point at 3 months after LT. We compared the slopes of eGFR before and after the reset point using MIXED procedure in SAS to compare eGFR data both within the groups and across the groups. We then checked the additive effect of potential confounders (e.g., age and diabetes) on the mean response eGFR profiles over time. Finally, we probed whether effect of GFR groups at LT on mean response profiles differed across the covariate levels (i.e., the interactive GFR groups at LT and covariate effect).

For the time-to-event analysis, Kaplan-Meier curves and log-rank test were used to compare between the groups The start of the follow-up period was date of LT, and patients were followed up until the incidence of composite kidney outcome or other censoring events such as death, re-LT, loss to follow-up, or the end of follow-up period (12 months after LT), whichever occurred first. Unadjusted Cox regression analysis and adjusted analysis were performed to predict composite kidney outcomes with age, sex, and body mass index (BMI) (model 1) and additionally including eGFR at reset point (model 2). We further performed a sensitivity analysis in predicting composite kidney outcome based on absence or presence of diabetes mellitus (DM) and hypertension (HTN). Proportional hazards assumptions were tested using scaled Schoenfeld residuals. All covariates were tested for multicollinearity; the highest variance inflation factor was 1.16 (mean variance inflation factor = 1.08).

P values were 2-sided and considered significant at less than 0.05 for all analyses. All analyses were conducted in STATA Version 13 (STATA Corporation, College Station, TX) and SAS Version 9.4 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Committees of The University of Tennessee Health Science Center (14-03544-XP) *a priori*.

RESULTS

Characteristics at pre-LT

Table 1 displays the pre-LT characteristics of the non-ACLF, A-HGFR, and A-LGFR groups in the analysis cohort (N = 416). A total of 60 recipients were categorized as the ACLF group (14.4%). Of those, 32 recipients were categorized into A-HGFR group (7.7%) and 28 recipients A-LGFR group (6.7%). Compared with non-ACLF group, both A-HGFR and A-LGFR groups had significantly higher MELD scores that correspond to worse cirrhosis-related parameters and kidney function before LT. Donor characteristics were not significantly different between non-ACLF and both A-HGFR and A-LGFR groups.

Estimated GFR at each point and eGFR slope after LT

The mean eGFRs at LT in non-ACLF, A-HGFR, and A-LGFR groups were 83.9 ± 29.5, 56.5 ± 31.2, and 21.6 ± 5.0 mL/min/1.73 m^2, respectively. The eGFR slope significantly increased in the A-LGFR group (+7.26 in unadjusted and +7.67 mL/min/1.73 m^2/mo in adjusted analyses), whereas it almost remained stable in the A-HGFR group (+1.05 in unadjusted and +1.04 mL/min/1.73 m^2/mo in adjusted analyses) and significantly declined in the non-ACLF group (−7.61 in unadjusted and −7.60 mL/min/1.73 m^2/mo in adjusted analyses) until about 3 months post-LT, which was the reset point (Figure 2). The eGFR slopes before the reset point in the non-ACLF and A-LGFR groups were significantly different. On the other hand, eGFR slopes in all groups stabilized after reset point and were not significant (Table 2).

Table 3 summarizes the comparison of eGFR slopes between 3 groups. The eGFR slopes before the reset point were significantly different between the groups, whereas the trend disappeared after reset point in both unadjusted and adjusted models. Eventually, however, the mean eGFR at 12 months after LT in A-HGFR (62.0 ± 24.4 mL/min/1.73 m^2, N = 24) and A-LGFR groups (62.9 ± 27.5 mL/min/1.73 m^2, N = 14) were approximately 10 mL/min/1.73 m^2 lower than that in non-ACLF group (70.6 ± 22.6 mL/min/1.73 m^2, N = 288, P=NS).

Survival analysis for the composite kidney outcome based on main exposures

Figure 3 displays Kaplan-Meier curves for composite kidney outcome. Based on the whole analysis cohort (N = 416), the incidence of composite kidney outcome was 28 (75.9/1,000 person-years, 95% confidence interval [CI]: 52.4–110.0) in the first transplant year. The incidence was 58.9/1,000 person-years (95% CI: 37.6–92.3) in the non-ACLF group, 156.8/1,000 person-years (95% CI: 58.9–417.9) in the A-HGFR group, and 242.2/1,000 person-years (95% CI: 100.8–581.9) in the A-LGFR group. The incidence rate was significantly different among the 3 groups (Figure 3a; log-rank, $P = 0.010$). The A-HGFR group was not at increased risk of composite kidney outcome in both unadjusted and adjusted analyses (models 1 and 2), whereas A-LGFR group was at increased risk of composite kidney outcome in the unadjusted (hazard ratio [HR] = 3.76, 95% CI: 1.40–10.1) and age-, sex-, and BMI-adjusted analyses (HR = 3.61, 95% CI: 1.35–9.70) in model 1 (Figure 4). However, this significance disappeared in model 2 (model 1 plus eGFR at reset point) (HR = 1.91, 95% CI: 0.70–5.23) (Figure 4).

Survival analysis for composite kidney outcome: based on non-ACLF group vs ACLF group

Figure 3b shows Kaplan-Meier curve and log-rank test for the incidence of composited kidney outcome compared between non-ACLF and ACLF groups in the analysis cohort (N = 416). The ACLF group was at increased risk of the incidence of composited kidney outcome by unadjusted analysis (HR: 3.03, 95% CI: 1.37–6.70) and age-, sex-, and BMI-adjusted Cox regression analysis (HR: 3.19, 95% CI: 1.44–7.07) in model 1, whereas the significance disappeared after the adjustment with model 2 that includes eGFR at reset point (HR = 1.79, 95% CI: 0.80–4.01) (Figure 4).

Table 1. Baseline characteristics at pre-LT for comparison between non-ACLF group and A-HGFR and A-LGFR groups at LT

	Non-ACLF group, N = 356	A-HGFR group, N = 32	*P* value[a]	A-LGFR group, N = 28	*P* value[b]
Variables					
Age, mean (SD)	54.6 (9.0)	53.1 (9.1)	0.358	54.0 (9.3)	0.710
Sex, female, n (%)	114 (32.0)	6 (18.8)	0.120	11 (39.3)	0.430
Race, n (%)			0.610		0.246
White	267 (75.0)	24 (75.0)		17 (60.7)	
African American	75 (21.1)	7 (21.9)		8 (28.6)	
Hispanic	10 (2.8)	0		2 (7.1)	
Other	4 (1.1)	1 (3.1)		1 (3.6)	
BMI (kg/m^2), mean (SD)	28.8 (5.8)	30.0 (6.2)	0.279	28.1 (5.7)	0.497
Cause of ESLD, n (%)			0.013		0.074
Alcoholic hepatitis	55 (15.5)	12 (37.5)		10 (35.7)	
HCV	180 (50.6)	10 (31.3)		10 (35.7)	
HCV/alcoholic hepatitis	13 (3.7)	2 (6.3)		0	
NASH/cryptogenic hepatitis	52 (14.6)	2 (6.3)		4 (14.3)	
Other	56 (15.7)	6 (18.8)		4 (14.3)	
Comorbidity: diabetes, n (%)	95 (26.7)	9 (28.1)	0.860	8 (28.6)	0.828
Comorbidity: hypertension, n (%)	146 (41.0)	11 (34.4)	0.464	6 (21.4)	0.041
MELD score, mean (SD)	16.2 (5.5)	27.8 (5.7)	<0.001	32.4 (7.4)	<0.001
Pretransplant ALT (IU/L), median (IQR)	38.5 (26.0, 60.0)	49.5 (28.5, 66.5)	0.310	35.0 (17.0, 52.5)	0.143
Pretransplant AST (IU/L), median (IQR)	64.0 (44.0, 92.5)	84.5 (49.0, 136.0)	0.059	66.0 (37.0, 114.0)	0.840
Pretransplant ALP (IU/L), median (IQR)	128.0 (96.0, 174.0)	113.5 (104.0, 157.5)	0.661	88.5 (74.0, 128.5)	0.003
Pretransplant bilirubin (mg/dL), median (IQR)	2.5 (1.6, 4.6)	10.4 (3.2, 22.9)	<0.001	7.5 (2.9, 21.4)	<0.001
Pretransplant PT-INR, mean (SD)	1.6 (0.5)	2.3 (0.8)	<0.001	2.1 (0.7)	<0.001
Pretransplant WBC ($10^3/\mu$L), mean (SD)	5.2 (2.2)	7.9 (5.6)	<0.001	7.5 (5.7)	<0.001
Pretransplant platelet ($10^3/\mu$L), median (IQR)	82.0 (58.0, 121.5)	68.5 (50.0, 107.5)	0.124	80.0 (58.5, 104.0)	0.256
Pretransplant creatinine (mg/dL), mean (SD)	1.0 (0.3)	1.6 (0.6)	<0.001	3.0 (0.6)	<0.001
Pretransplant eGFR (mL/min/1.73 m^2), mean (SD)	83.9 (29.5)	56.5 (31.2)	<0.001	21.6 (5.0)	<0.001
Pretransplant eGFR (mL/min/1.73 m^2), median (IQR)	81.7 (61.9, 104.2)	42.3 (33.6, 71.9)	<0.001	21.9 (17.5, 25.7)	<0.001
Hemodialysis before LT within 2 wk, n (%)	0	2 (6.3)	<0.001	6 (21.4)	<0.001
Hemodialysis before LT within 48 hr, n (%)	0	1 (3.1)	<0.001	5 (17.9)	<0.001
CLIF-SOFA score, mean (SD)	NA	10.3 (2.0)	NA	10.8 (2.2)	NA
The numbers of organ failure, median (IQR)	0	1.0 (1.0, 2.0)	<0.001	1.5 (1.0, 2.5)	<0.001
ACLF grade 1, n (%)	NA	18 (56.3)	NA	14 (50.0)	NA
ACLF grade 2, n (%)	NA	10 (31.3)	NA	7 (25.0)	NA
ACLF grade 3, n (%)	NA	4 (12.5)	NA	7 (25.0)	NA
Donor information					
Age, mean (SD)	42.0 (15.8)	39.5 (16.9)	0.401	37.5 (15.1)	0.152
Sex, female, n (%)	165 (46.4)	12 (37.5)	0.336	11 (39.3)	0.470

Table 1. (*continued*)

	Non-ACLF group, N = 356	A-HGFR group, N = 32	*P* value[a]	A-LGFR group, N = 28	*P* value[b]
Race, n (%)			0.565		0.751
White	268 (75.3)	24 (75.0)		22 (78.6)	
Hispanic	13 (3.7)	0		1 (3.6)	
African American	70 (19.7)	8 (125.0)		4 (14.3)	
Other	5 (1.4)	0		1 (3.6)	

ACLF, acute on chronic liver failure; A-HGFR, ACLF with eGFR >30 mL/min/1.73 m^2 group at LT; A-LGFR, ACLF with eGFR <30 mL/min/1.73 m^2 at LT group; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLIF-SOFA, chronic liver failure-sequential organ failure-assessment; eGFR, estimated glomerular filtration rate; ESLD, end-stage liver disease; HCV, hepatitis C virus; IQR, interquartile range; LT, liver transplantation; MELD, the model of end-stage liver disease; NA, not available; NASH, non-alcoholic steatohepatitis; PT-INR, prothrombin time-international normalized ratio; WBC, white cell count.
[a]*P* values are compared between non-ACLF group and A-HGFR group.
[b]*P* values are compared between non-ACLF group and A-LGFR group. *P* values for continuous variables with mean ± SD are results of *t* test and with median (IQR) are results of Mann-Whitney test, and categorical variables are χ^2 test.

Subgroup analysis for the incidence of composite kidney outcome

The presence of DM in the A-LGFR group was an independent and significant risk factor of the composite kidney outcome by unadjusted and adjusted Cox regression analyses in model 1 (adjusted for age, sex, and BMI). However, in model 2 (model 1 + eGFR at the reset point), the significance disappeared (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A288). There were no interactions between the presence and absence of DM or HTN between the groups (all *P* values for interaction >0.05).

DISCUSSION

In this retrospective cohort study, several intriguing observations can be inferred regarding posttransplant kidney function and outcome among LT recipients with ACLF. First, we noted the slope of eGFR among 3 groups stratified by ACLF and kidney function at LT were significantly different for the first 3 months after LT but stabilized thereafter in all 3 groups; hence, we called 3 months after LT as the eGFR reset point. Second, the ACLF group regardless of severity of kidney dysfunction at LT had a lower eGFR at 12 months after LT of nearly 10 mL/min/1.73 m^2 compared with non-ACLF group. Third, ACLF itself and ACLF with severe kidney dysfunction at LT were significant risk factors of the short-term kidney outcome; however, this association disappeared after adjustment of eGFR at reset point. Finally, kidney function at 3 months after LT is the pivotal predictor of the short-term kidney outcome in ACLF. To our knowledge, this is the first report of kidney outcome among LT recipients with and without ACLF based on EASL-CLIF Consortium definition.

Longenecker et al. (2) published the patterns of longitudinal kidney function 1 year before and after LT stratified by eGFR at LT, regardless of ACLF. They showed that the lower eGFR group at LT (eGFR < 60 mL/min/1.73 m^2) sharply recovered their eGFR and the higher eGFR group (eGFR > 60 mL/min/1.73 m^2) at LT suffered a decline in their eGFR within 3 months post-LT. In both groups,

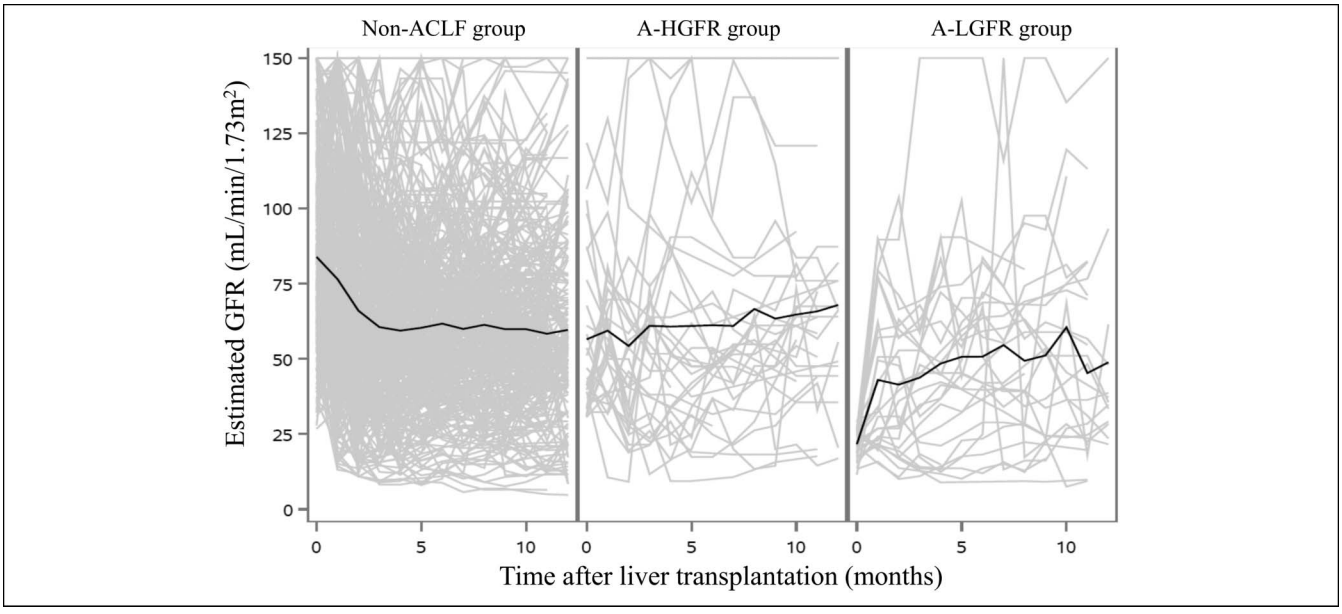

Figure 2. Estimated GFR slope in non-ACLF, A-HGFR, and A-LGFR groups. ACLF, acute on chronic liver failure; A-HGFR group, ACLF with eGFR ≥30 mL/min/1.73 m^2 at liver transplantation; A-LGFR group, ACLF with eGFR <30 mL/min/1.73 m^2 at liver transplantation; GFR, glomerular filtration rate.

Table 2. Within-group comparisons of the eGFR slope using both unadjusted and adjusted analyses using piecewise linear mixed-effects model

	Non-ACLF group			A-HGFR group			A-LGFR group		
eGFR slope	Value[a]	SE	*P* value	Value[a]	SE	*P* value	Value[a]	SE	*P* value
Unadjusted analysis									
Slope before reset point	−7.61	0.55	<0.001	1.05	1.75	0.548	7.26	1.92	<0.001
Difference in the slope before and after the reset point	7.72	0.69	<0.001	−0.54	2.16	0.804	−6.42	2.39	0.008
Slope after the reset point	0.11	0.25	0.677	0.51	0.89	0.562	0.84	0.89	0.347
Adjusted analysis[b]									
Slope before reset point	−7.60	0.54	<0.001	1.04	1.74	0.549	7.67	1.76	<0.001
Difference in the slope before and after the reset point	7.67	0.68	<0.001	−0.51	2.15	0.812	−7.21	2.17	0.001
Slope after the reset point	0.07	0.24	0.778	0.53	0.87	0.542	0.46	0.71	0.522

Reset point is 3 months after LT. Number of Cr measurements used: Non-ACLF group = 3,353; A-HGFR group = 321, A-LGFR group = 305.
ACLF, acute on chronic liver failure; A-HGFR, ACLF with eGFR >30 mL/min/1.73 m^2 group at LT; A-LGFR, ACLF with eGFR <30 mL/min/1.73 m^2 at LT group; BMI, body mass index; eGFR, estimated glomerular filtration rate; LT, liver transplantation; MELD, the model of end-stage liver disease.
[a]Unit is mL/min/1.73 m^2/mo.
[b]Adjusted for age, race, sex, BMI, MELD score, hypertension, and diabetes.

eGFR stabilized after 3 months but was still lower in the lower pre-LT eGFR group (2). Although this study showed similar trends of the slope of kidney function, we could further delineate the relatively preserved eGFR in the A-HGFR group from those with severe kidney dysfunction and ACLF (A-LGFR group) when compared with the non-ACLF group. The slope of eGFR in A-HGFR group

Table 3. Across-group comparisons of the eGFR slope using both unadjusted and adjusted analyses using piecewise linear mixed-effects model

	Difference (mL/min/1.73 m^2/mo)	SE	*P* value
Unadjusted model			
eGFR slope before reset point			
A-HGFR group vs A-LGFR group	−6.30	2.66	0.018
Non-ACLF group vs A-LGFR group	−14.9	2.01	<0.001
Non-ACLF group vs A-HGFR group	−8.57	1.91	<0.001
eGFR slope after reset point			
A-HGFR group vs A-LGFR group	−0.25	1.24	0.839
Non-ACLF group vs A-LGFR group	−0.75	0.94	0.427
Non-ACLF group vs A-HGFR group	−0.50	0.88	0.574
Adjusted model[a]			
eGFR slope before reset point			
A-HGFR group vs A-LGFR group	−6.35	2.62	0.016
Non-ACLF group vs A-LGFR group	−14.9	1.98	<0.001
Non-ACLF group vs A-HGFR group	−8.55	1.89	<0.001
eGFR slope after reset point			
A-HGFR group vs A-LGFR group	−0.24	1.20	0.843
Non-ACLF group vs A-LGFR group	−0.81	0.91	0.373
Non-ACLF group vs A-HGFR group	−0.57	0.85	0.501

Reset point is 3 months after LT.
ACLF, acute on chronic liver failure; A-HGFR, ACLF with eGFR >30 mL/min/1.73 m^2 group at LT; A-LGFR, ACLF with eGFR <30 mL/min/1.73 m^2 at LT group; BMI, body mass index; eGFR, estimated glomerular filtration rate; LT, liver transplantation; MELD, the model of end-stage liver disease.
[a]Adjusted for age, race, sex, BMI, MELD score at LT, hypertension, and diabetes.

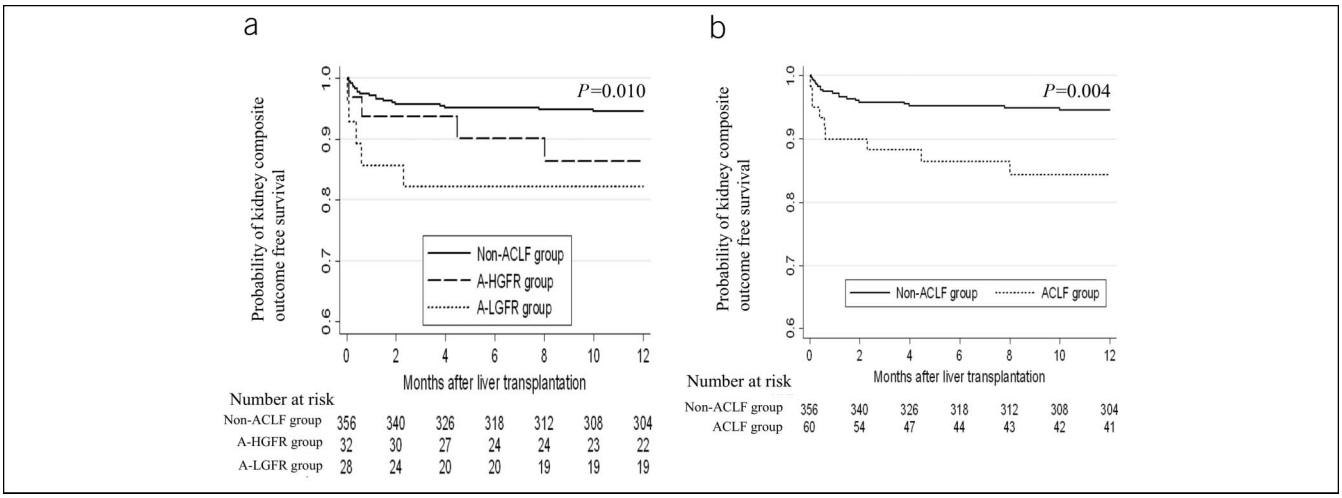

Figure 3. Kaplan-Meier curve for composite kidney outcomes compared between non-ACLF, A-HGFR, and A-LGFR groups. ACLF, acute on chronic liver failure; A-HGFR group, ACLF with eGFR ≥30 mL/min/1.73 m^2 at liver transplantation; A-LGFR group, ACLF with eGFR <30 mL/min/1.73 m^2 at liver transplantation; eGFR, estimated glomerular filtration rate.

essentially remained unchanged throughout the first transplant year, even though the mean eGFR at LT was below 60 mL/min/1.73 m^2 similar to the previous study. It seems the severity of pre-LT kidney dysfunction regardless of ACLF affect the recovery of eGFR after LT.

Regarding the permanent kidney damage, we noted a persistently lower eGFR, approximately 10 mL/min/1.73 m^2 in the ACLF group compared with that in the non-ACLF group at 12 months after LT. These trends obeyed the concept of kidney damage at LT that has evolved in the past few decades. Structural damage is now believed to arise not only as a result of CKD but also from acute tubular injury, previously considered a highly reversible condition. Basic experimental studies and clinical epidemiology reports have shown that acute tubular injury damage might not fully recover (10,22–24). We suspect that ACLF with AKI at onset can potentially result in sustained tubular damage through increased proinflammatory cytokines (8,14,25), resulting in severe and irreversible changes in kidney function compared with those without ACLF. Our stance here is only hypothesis driven based on theoretical considerations, and the findings of a persistently lower eGFR in the ACLF group compared with the non-ACLF group needs further confirmation in future studies.

Although kidney failure is a major component of the diagnosis of ACLF (15), there are no systematic studies examining consequent kidney function in ACLF patients post-LT. Bahirwani et al. (26) using a nonstandardized definition of ACLF (acute increasing MELD score more than 5 points within 4 weeks) investigated the longitudinal kidney function after LT patients with ACLF. They showed that the eGFR in the ACLF group from 3 months to 7 years after LT were comparable with those of the non-ACLF group at all time points despite a significant difference of eGFR at LT (26). On the other hand, we used EASL-CLIF Consortium definition to diagnose ACLF—currently, a widely used guideline in clinical practice

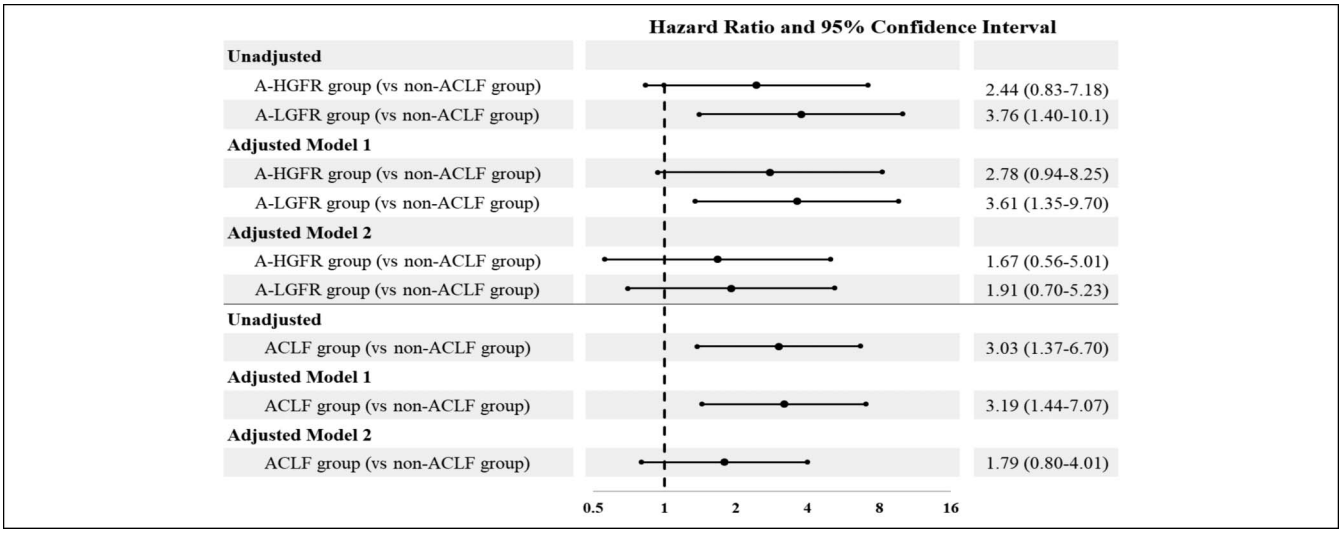

Figure 4. Hazard ratios, 95% CIs, and *P* values for composite kidney outcome by unadjusted and adjusted cox hazard regression model. Model 1 was adjusted by age and sex. Model 2 was adjusted model 1 and eGFR at reset point. 95% CI, 95% confidence interval; ACLF, acute-on-chronic liver failure; A-HGFR group, ACLF with eGFR ≥30 mL/min/1.73 m^2 at liver transplantation; A-LGFR group, ACLF with eGFR <30 mL/min/1.73 m^2 at liver transplantation; eGFR, estimated glomerular filtration rate.

and more accurate representative of a systemic organ failure syndrome with underlying inflammatory processes (15). Although this study also showed no statistical difference of eGFR between non-ACLF and both A-HGFR and A-LGFR groups at 12 months after LT, it has provided a more accurate picture of kidney function after LT among patients with ACLF.

Moreover, we were interested in investigating whether eGFR at reset point is a cofounder or mediator of post-LT longitudinal renal dysfunction. Thus, we adjusted eGFR at the reset point in adjusted model 2 for multivariable analysis and noted that the point estimates of all HR shifted toward nonsignificance (Figure 4). Based on the time course of pathophysiology after LT and rapid recovery of eGFR despite low eGFR at LT, worsening kidney function at reset point would be the most powerful mediator (predictor) for long-term risk of progression to advanced kidney failure regardless of ACLF. In other words, not only ACLF with severe kidney dysfunction at LT (e.g., A-LGFR group) but also ACLF with non-recovered kidney function at reset point (e.g., ACLF with eGFR <30 mL/min/1.73 m^2 at reset point) affects the chronic kidney damage after LT.

Recipients with known risk factors of renal function decline such as the presence of DM presented a trend for higher risk in the ACLF group in the unadjusted and adjusted model 1 analyses, whereas the subgroup with HTN did not affect outcome (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A288). ACLF might be a synergistic risk factor along with DM. To explore this question, we need to conduct larger, prospective, multicenter cohort studies.

Although this is the first report describing longitudinal kidney function in patients with ACLF based on EASL-CLIF criteria, several limitations are apparent. First, the absence of the data on eGFR at 3 months after LT leading to exclusion in the analysis cohort might have introduced some selection bias, limiting the generalizability of the study. However, we have shown that there were no significant differences in the analysis and the excluded cohort except for race, which might not have significant impact on the longitudinal kidney function. Second, as in any retrospective cohort study, a causal relationship between ACLF and kidney-related outcomes cannot be inferred. Third, we were unable to assess whether patients had underlying CKD pre-LT in the ACLF group. However, our center follows the United Network for Organ Sharing guidelines for listing simultaneous liver–kidney transplantation (27–30). Consequently, patients with advanced CKD might not have been included in this study because we excluded patients with simultaneous liver–kidney transplantation from the current cohort. In addition, the impact of renal replacement therapy before LT could not be assessed because the number of patients who received renal replacement therapy within 2 weeks before LT was small. Finally, eGFR in our cohort might have been overestimated using the Modification of Diet in Renal Disease Study equation, potentially leading to type II error in the time-to-event analysis.

In conclusion, the trajectories of eGFR slopes were distinctly different in the first 3 months post-LT among non-ACLF, A-HGFR, and A-LGFR groups. Although ACLF itself might confer risk of permanent kidney dysfunction after LT, kidney dysfunction at 3 months after LT (reset point), which represents recovery or not from kidney dysfunction incurred at LT, could be the powerful predictor of long-term kidney-related prognosis. Future prospective studies in larger multicenter cohorts to rigorously elucidate the effect of ACLF pre-LT in short- and long-term renal function after LT are warranted.

CONFLICTS OF INTEREST

Guarantor of the article: Sanjaya K. Satapathy, MBBS, MD, DM, MS (Epi), FACG, FASGE, AGAF, FAASLD, has the full responsibility for this study.

Specific author contributions: M.Y., M.Z.M., and S.K.S participated in research design. M.Y., B.M., S.D.K., M.Z.M., U.A.A., and S.K.S participated in the writing of the paper. M.Y., M.Z.M., P.S.B.P., and S.K.S. participated in data analysis. S.N, S.K, D.M, and J.D.E participated in the performance of the research.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Systemic inflammatory response plays a central role in developing acute-on-chronic liver failure (ACLF).
- ✓ Acute kidney injury is an important component of ACLF.
- ✓ Complete recovery of acute kidney injury after liver transplantation (LT) in patients with ACLF is expected.

WHAT IS NEW HERE

- ✓ ACLF group regardless of severity of kidney dysfunction at LT had a lower estimated glomerular filtration rate (eGFR) at 12 months after LT of nearly 10 mL/min/1.73 m^2 compared with that of non-ACLF group.
- ✓ Kidney function at 3 months after LT is the pivotal predictor of the short-term kidney outcome in ACLF.
- ✓ The slope of eGFR among ACLF and non-ACLF groups significantly different for the first 3 months after LT but stable thereafter and this 3-month time point is called the eGFR reset point.

TRANSLATIONAL IMPACT

- ✓ The current study highlight the importance of the 3-month transition point of kidney function as the "eGFR reset point" in ACLF patients. Future studies studies should use this transition point as the baseline for monitoring post transplant renal dysfunction after LT in ACLF patients.

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