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Fluctuations of Estimated Glomerular Filtration Rate Outside Kidney Disease Improving Global Outcomes Diagnostic Criteria for Acute Kidney Injury in End-Stage Liver Disease Outpatients and Outcome Postliver Transplantation

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Background. Renal dysfunction in end-stage liver disease (ESLD) results from systemic conditions that affect both liver and kidney with activation of vasoconstrictor systems. In this setting, estimated glomerular filtration rate (eGFR) may undergo variations often outside Kidney Disease Improving Global Outcomes criteria for acute kidney injury (AKI) diagnosis, whose meaning is not clear. The aim of this study was to evaluate eGFR variations in ESLD outpatients listed for liver transplant (liver Tx) and the association with post-Tx outcome. **Methods.** Fifty-one patients with ESLD were retrospectively evaluated from listing to transplant (L-Tx time), intraoperatively (Tx time), and up to 5 years post-Tx time. Variations between the highest and the lowest eGFR occurring in more than 48 hours, not satisfying Kidney Disease Improving Global Outcomes guideline, were considered as fluctuations (eGFR-F). Fluctuations of eGFR greater than 50% were defined as eGFR drops (DeGFR). Early graft dysfunction, AKI within 7 days, chronic kidney disease, and short- and long-term patient survivals were considered as outcomes. **Results.** All patients presented eGFR-F, whereas DeGFR were observed in 18 (35.3%) of 51 (DeGFR+ group). These patients presented higher levels of Model for End-stage Liver Disease score, pre-Tx bilirubin and significantly greater incidence of post-Tx AKI stages 2 to 3 compared with patients without drops (DeGFR–). DeGFR was the only independent predictive factor of the occurrence of post-Tx AKI. The occurrence of AKI post-Tx was associated with the development of chronic kidney disease at 3 months and 5 years post-Tx. **Conclusions.** Drops of eGFR are more frequently observed in patients with a worse degree of ESLD and are associated with a worse post-Tx kidney outcome.

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Renal dysfunction in end-stage liver disease (ESLD) can occur as a result of systemic conditions that affect both liver and kidney.[1] The progression of liver cirrhosis to severe portal hypertension with ascites results in splanchnic arterial vasodilation with reduced effective arterial blood volume.[1,2] This condition is associated with the activation of vasoconstrictor systems with decrease of renal blood flow, leading

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F.F. collected data, analyzed data, and wrote the article. F.M. collected the data. I.U. analyzed the data and wrote the article. A.Z. and A.C. collected data. E.P., S.G.C., and M.M. performed the hepatological evaluation of the patients. F.T. analyzed the data and wrote the article. I.N. analyzed the data. F.M., P.B.B., and M.R. performed the liver transplant. A.P.M. designed the research and wrote the article. Each author has reviewed the article, believes it represents a valid work, approves it for submission and declares no conflicts of interest.

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to chronic kidney ischemia.[3] In these scenario, patients are particularly prone to glomerular filtration rate (GFR) reduction with acute variations of serum creatinine (sCr) from baseline.[4] Changes in sCr have been recently reported to exert poor impact on patient's survival as demonstrated in nephrologic setting and should be considered.[1,4]

A variation of sCr of 0.3 mg/dL or greater from baseline within 48 hours has been validated by Kidney Disease Improving Global Outcomes (KDIGO) guideline as a criterion to define acute kidney injury (AKI).[5] In patients with ESLD, AKI has been associated with increased mortality and worsening of kidney function before and after liver transplantation (liver Tx).[4,6,7] Moreover, AKI has been recognized as an independent risk factor of post-Tx de novo chronic kidney disease (CKD).[8] Cirrhotic patients are characterized by an instable estimated-GFR (eGFR), with frequent isolated decreases. This is usually related to prerenal AKI, due to high dose of diuretics, acute infections, decompensated ascites, electrolyte and water imbalance, spontaneous bacterial peritonitis, and gastrointestinal bleedings, as can be diagnosed in hospitalized patients.[1] However, most patients with liver cirrhosis are managed as outpatients. In this setting, the assessment of parameters required for AKI diagnosis, such as baseline eGFR, its variations, and timing during follow-up, is challenging. As a result, AKI diagnosis according to KDIGO guideline is difficult due to the short time of observation required (48 hours),[5] generally not feasible in outpatients monitoring. The presence of isolated decreases of eGFR in patients with ESLD and their effects on renal function before and after liver Tx have been poorly studied and not completely clarified.

Therefore, the aim of this study was to evaluate eGFR variations in ESLD and investigate the association with post-Tx outcome, in terms of early and long-term renal function and patient survival.

MATERIALS AND METHODS

This is a single-center study from a cohort of 112 waitlisted patients for liver Tx in the Liver Unit of Sapienza University of Rome. From this cohort, all patients transplanted (whole liver) from donation after brain-death donors from October 2008 to October 2011 were considered (59 patients). Acute liver failure (4 patients) and combined liver-kidney Txs (4 patients) were excluded (Figure 1).

We retrospectively evaluated 51 liver Tx recipients as follows: from listing to Tx (L-Tx time), intraoperatively (Tx time) and up to 5 years post-Tx time.

Data Collected From L-Tx Time

During L-Tx time, patients were clinically assessed every 3 months in the outpatient setting on the basis of the nephrologic form developed in our renal outpatient clinic,[9] with blood test done every 4 to 6 weeks.

Renal function was evaluated assessing sCr level measured by enzymatic assay and GFR estimated by the 4 variables of Modification of Diet in Renal Disease 4 formula Study equation.[10]

CKD was defined as a reduction of the eGFR less than 60 mL/min per 1.73 m^2 longer than 3 months and classified in stages according to KDIGO guidelines. Worsening of CKD was defined as progression to a higher CKD stage.[11] We considered in each patient:

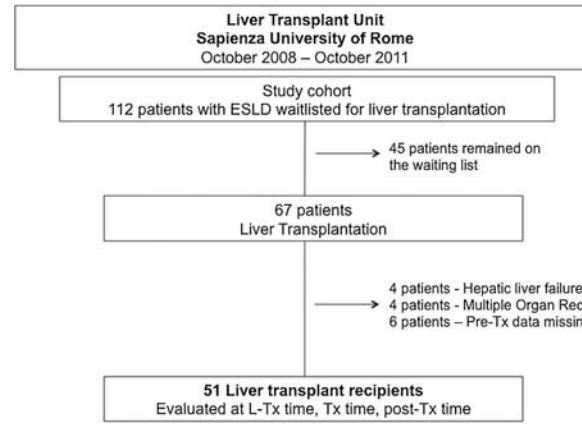

FIGURE 1. Process of patient selection. pre-Tx, before liver transplantation; L-Tx time, from listing to transplant time; Tx time, intraoperatively time; post-Tx time, up to 5 years postoperatively.

- eGFR at listing (eGFR-list);
- eGFR at Tx (eGFR-Tx);
- maximum eGFR (eGFR-max) defined as the highest value of GFR estimated on the basis of the lowest value of sCr collected during L-Tx time. It was considered as the baseline eGFR according to KDIGO guideline[5] and the looking back reference, standard method[12];
- minimum eGFR (eGFR-min) defined as the lowest value of GFR estimated on the basis of highest value of sCr collected during L-Tx time;
- variations of eGFR observed during L-Tx time were defined as fluctuations of eGFR (eGFR-F). These were considered as a percentage of variation between the lowest and the highest eGFR, estimated on the basis of maximum and minimum value of sCr among all values collected, respectively. Fluctuations of eGFR, more than 50% from maximum, were defined as eGFR drops (DeGFR).

Data Collected Intraoperatively During Liver Transplantion (Tx Time)

Data regarding the number of transfused units of packed red blood cell, fresh-frozen plasma, crystalloids or colloids, inotropic drug administered during Tx time, and the donor risk index (DRI) score were collected.

Data Collected Post-Tx Time

We evaluated post-Tx early renal function considering the occurrence of AKI according to KDIGO guideline as an increase in sCr by $\geq$ 0.3 mg/dL within 48 hours or an increase in sCr to $\geq$ 1.5 times baseline within the prior 7 days. AKI was classified into 3 stages: stage 1, increase of 0.3 mg/dl or greater or increase of 1.5- to 1.9-fold from baseline; stage 2, increase of twofold to 2.9-fold from baseline; stage 3, increase of more than threefold from baseline or 4.0 mg/dL or greater with an acute increase of at least 0.5 mg/dL or on renal replacement therapy.[5]

The occurrence of post-Tx CKD (at 6, 12, 24, 36, 60 months) was evaluated and staged according to the KDIGO guidelines.[13]

Early graft function was evaluated considering levels of aspartate aminotransferase, alanine aminotransferase, serum bilirubin, and International Normalized Ratio (INR) within 7 days post-Tx. We defined early graft dysfunction as the

presence of 1 or more of the following parameters: (i) total bilirubin ≥10 mg/dL on post-Tx day 7, (ii) INR of 1.6 or greater on post-Tx day 7, and (iii) aspartate aminotransferase or alanine aminotransferase of 2000 IU/mL or greater within the first week post-Tx.[14]

All patients received an immunosuppressive regimen based on intravenous basiliximab (20 mg) on postoperative days 0 and 4; mycophenolate mofetil if leucocytes were greater than 4000/mm^3 and delayed introduction of tacrolimus from postoperative day 5. The immunosuppression was adjusted in case of persisting renal dysfunction 7 days after liver Tx. Three months and 5 years post-Tx patient survivals were considered.

Statistical Analysis

Data are presented as median and interquartile range (IQR) for continuous variables and as frequency and percentage for categorical variables. Nonparametric methods were used for inferential analysis. The Mann-Whitney, Kruskal-Wallis, or Wilcoxon tests were used to compare distribution of continuous variables as appropriate. The Fisher exact and the χ^2 tests were used to evaluate associations between categorical variables, as appropriate. A univariate analysis was first performed to identify variables associated with each outcome considered. Odds ratio and 95% confidence intervals were estimated. A multivariate logistic regression was performed to identify independent predictors of outcome. The Cox regression model was used to determine the risk of death within 5 years post-Tx. All tests were performed using SPSS system 22.0 (SPSS Inc, Chicago, IL) with a P value less than 0.05 considered significant.

TABLE 1.

Demographic and clinical characteristics of 51 liver transplant recipients at L-Tx time and at Tx-time

	L-Tx time	Tx-time
Age, y	57.8 (50.1-61.0)	56.0 (51.1-61.3)
Gender (female)	8 (15.7)	8 (15.7)
BMI, kg/m^2	26.5 (22.6-31.1)	26.0 (23.6-30.8)
Hepatitis C virus	20 (39)	20 (39)
Alcoholic cirrhosis	7 (13.7)	7 (13.7)
Biliary sclerosis	3 (5.9)	3 (5.9)
Hepatocarcinoma	17 (33.3)	17 (33.3)
Diabetes	17 (33.3)	17 (33.3)
Hypertension	5 (9.8)	5 (9.8)
CKD	8 (15.7)	8 (15.7)
Ascites	20 (39.2)	20 (39.2)
Lab-MELD score	15.0 (11.0-19.0)	16.0 (13.0-22.0)
Bilirubin, mg/dL	2.9 (1.6-4.8)	3.0 (1.7-7.6)
INR	1.4 (1.3-1.6)	1.5 (1.3-1.8)
sCr, mg/dL	0.9 (0.7-1.0)	0.9 (0.6-1.1)
*e*GFR, mL/min	92.1 (71.3-108.2)	94.2 (73.6-142.4)
G1 (≥90)	26 (51.0%)	29 (56.9%)
G2 (60-89)	20 (39.2%)	15 (29.4%)
G3a (45-59)	3 (5.9%)	3 (5.9%)
G3b (30-44)	1 (2.0%)	3 (5.9%)
G4 (15-29)	1 (2.0%)	1 (2.0%)
G5 (<15)	0	0

Data are presented as median (IQR) and frequency (percentage) as appropriate.

BMI, body mass index; G1, GFR ≥ 90 mL/min; G2, GFR = 60-89 mL/min; G3a, GFR = 45-59 mL/min; G3b, GFR = 30-44 mL/min; G4, GFR = 15-29 mL/min; G5, GFR <15 mL/min.

RESULTS

Demographic and clinical characteristics of the 51 recipients at listing and Tx are shown in Table 1. The median L-Tx time was 254 days (IQR, 92-509).

A mean of 8 ± 3 tests were performed to assess patients' renal function during L-Tx time. All patients presented eGFR-F, ranging from median eGFR-max of 126.52 mL/min per 1.73 m^2 (IQR, 104.00-150.00) to median eGFR-min of 66.57 mL/min per 1.73 m^2 (IQR, 51.84-91.18).

Estimated GFR-Tx did not have a significantly different result compared with eGFR-list (P = 0.960). In all patients, eGFR-max never matched with eGFR-list or eGFR-Tx. Drops of eGFR were observed in 18 (35.3%) of 51 recipients. According to the presence of DeGFR, patients were divided into 2 groups: DeGFR+ and DeGFR–. Clinical parameters at L-Tx time, Tx time, and post-Tx time of the 2 groups (DeGFR+ vs DeGFR–) are reported in Table 2.

The number of sCr tests did not result in a difference between the 2 groups (P = 0.880). The DeGFR+ group presented a higher prevalence of CKD at listing compared with the DeGFR– group (6/18 patients, 33% vs 2/33 patients, 6%; P = 0.017). In both groups, no patients developed de novo CKD, neither a worsening of preexisting CKD, during L-Tx time.

During L-Tx time, patients in the DeGFR+ group presented a significantly higher Model for End-stage Liver Disease (MELD) score both at listing (P = 0.025) and at Tx (P = 0.033) compared with the DeGFR– group. Considering the single parameters of MELD score, significantly greater total bilirubin values at listing (P = 0.012) and at Tx (P = 0.047) were found in the DeGFR+ versus DeGFR– groups. No differences in INR and body mass index were observed between the 2 groups.

During Tx time, no differences in number of transfusions, inotropic support (dopamine), and DRI score were found in the DeGFR+ group compared with the DeGFR– group.

In post-Tx time, AKI occurred in 26 (51%) of 51 recipients. Among them, 15 (58%) of 26 presented AKI stage 1, 8 (31%) 26 in stage 2, and 3 (11%) 26 in stage 3. In particular, AKI stages 2 to 3 occurred in 8 (44%) of 18 DeGFR+ compared with 3 (9%) of 33 DeGFR– recipients (P = 0.007) (Table 2).

Early graft dysfunction occurred in 14 (27%) of 51 recipients with no differences between the 2 groups (P = 0.569). The logistic regression analysis of predictors of post-Tx AKI in 51 liver Tx recipients is reported in Table 3. Among all predictive factors, DeGFR only were associated with development of AKI post-Tx (P = 0.007) on the univariate analysis. The DeGFR+ group presented a higher prevalence of pre-Tx CKD (P = 0.010) but the occurrence of AKI was not significantly different in patients with and without CKD (P = 0.244). The multivariate logistic regression analysis, forced for age and sex, demonstrated that DeGFR were the only independent predictive factors of the occurrence of post-Tx AKI.

Estimated-GFR trend post-Tx (at 6, 12, 24, 36, 60 months) is shown in Figure 2. Patients with AKI post-Tx were associated with development of CKD from 3 months up to 5 years post-Tx (P = 0.004) (Figure 3).

Among all predictive factors, DeGFR were associated with development of long-term CKD post-Tx on the univariate analysis (P = 0.008) (Table 4).

TABLE 2.

Demographic and clinical parameters considered during L-Tx time, Tx time, and post-Tx time in DeGFR+ versus DeGFR– group

	DeGFR+ group 18 pts	*DeGFR–* group 33 pts	
Time	**L-Tx time**		***p***
Age (years)	53.0 (50.0-59.3)	56.0 (51.7-59.9)	0.541
BMI (kg/m^2)	25.2 (23.7-29.8)	26.0 (24.1-30.0)	0.626
Hepatitis C Virus	8 (44.4)	14 (42.4)	0.889
Diabetes	6 (33.3)	11 (33.3)	0.625
Hypertension	2 (11.1)	3 (9.1)	0.817
*e*GFR-list (ml/min)	86.0 (67.5-131.8)	105.9 (81.0-124.9)	0.280
MELD-list	17.0 (14.0-20.0)	14.0 (11.0-17.0)	0.025
Bilirubin-list (mg/dl)	4.2 (2.7-6.0)	2.2 (1.5-3.89)	0.012
INR-list	1.44 (1.22-1.68)	1.37 (1.26-1.54)	0.269
sCr-list (mg/dl)	0.86 (0.65-1.00)	0.86 (0.76-1.20)	0.600
*e*GFR-Tx (ml/min)	78.8 (54.09-140.70)	106.28 (77.13-144.24)	0.233
MELD-Tx	20.0 (14.3-2.0)	15.0 (12.0-20.0)	0.033
Bilirubin-Tx (mg/dl)	6.7 (2.6-8.7)	2.6 (1.5-6.4)	0.047
INR-Tx	1.61 (1.28-1.92)	1.46 (1.31-1.56)	0.129
sCr-Tx (mg/dl)	0.95 (0.65-1.21)	0.80 (0.60-1.05)	0.464
CKD	6 (33.3)	2 (6.1)	0.010
Tx time			
PRBCs (units)	5 (3-7)	5 (3-6)	0.298
FFP (units)	10 (7-18)	12 (8-17)	0.061
Dopamine (mcg/kg)	233 (0-615)	320 (0-850)	0.078
DRI	1.442 (1.033-1.755)	1.476 (1.187-1.786)	0.644
Post-Tx time			
AKI post-Tx	10 (55.6)	16 (48.5)	0.629
Stages 2 and 3	8 (44.0)	3 (9.0)	0.007

Data are presented as median value (IQR) and frequency (percentage) as appropriate; p value were estimated.

post-Tx time, up to 1 week postoperatively; MELD-list, MELD at listing; MELD-Tx, MELD at transplant; Bilirubin-Tx, Bilirubin at transplant; Bilirubin-list, Bilirubin at listing; INR-list, INR at listing; INR-Tx, INR at transplant; sCr-list, sCr at listing; sCr-Tx, sCr at transplant; PRBC, packed red blood cell; FFP, fresh frozen plasma; Dopamine, total dose of dopamine administered during Tx time.

Three-month patient survival post-Tx was 96.1% (49/51 patients). No difference in survival was evidenced between the 2 groups (17/18, 94.4% in DeGFR+ vs 32/33, 97% in DeGFR–; $P = 0.648$).

Survival at 5 years post-Tx was 80.4% (41/51 patients), divided between the 2 groups as follows: 72.2% (13/18 patients) in DeGFR+ versus 84.8% (28/33 patients) in DeGFR– ($P = 0.220$).

DISCUSSION

Hemodynamic portal alterations in advanced cirrhosis include increased intrahepatic vascular resistance, splanchnic vasodilation, activation of vasoconstrictive, and antinatriuretic systems.[3] In this condition, patients are particularly prone to develop variations of eGFR.[15,16]

In liver Tx recipients, variations of eGFR have been extensively studied in the post-Tx period.[17-19] Sustained reductions, defined as rapid loss or abrupt decline of eGFR, have been demonstrated and studied at different time post-Tx.[18] These so-called events of eGFR have been associated with adverse clinical outcomes post-Tx.[17,19]

Kidney susceptibility to risk factors for renal damage is clinically highlighted by unstable eGFR in patients with ESLD, as it is frequently detected.[20] KDIGO guideline has been recently validated and proposed for nephrologic monitoring in patients with liver cirrhosis.[5] The Modification of Diet in Renal Disease 4 formula, a sCr-dependent formula, has been accepted to estimate GFR, showing the greater accuracy among different estimating equations.[21]

Most patients with liver cirrhosis are managed as outpatients. In this setting, the assessment of parameters required for AKI diagnosis, such as baseline eGFR, its variations, and timing during follow-up, are challenging.

Fluctuations of eGFR were present in all our patients, ranging from the median eGFR-max value of 127 mL/min per 1.73 m^2 to the eGFR-min of 67 mL/min per 1.73 m^2.

This range despite CKD patients results from combination of eGFR of patients affected by CKD (16%) and eGFR of patients with hyperfiltration (Hy) secondary to abnormal low sCr.[22-24] Hyperfiltration has been recognized as an important predictor of worst outcome and may result from the marked reduced hepatic synthesis of creatine due to the advanced degree of cirrhosis. For this reason, a low sCr level can be considered a marker of poor hepatic function.

Serum creatinine is a surrogate of renal function (eGFR) and is considered biased in patients with ESLD because of decreased hepatic synthesis of creatine, malnutrition, reduced muscle mass, low BMI, female gender, interference of high bilirubin values with sCr laboratory assay.[25,26] Nevertheless, in our study, sCr determination was performed with an enzymatic assay test instead of a colorimetric test because of bilirubin interference only for serum value greater than 20 mg/dL reported by technical specifications of the Laboratory

TABLE 3.

Univariate and multivariate logistic regression analysis of predictors of post-Tx AKI in 51 liver transplant recipients

	Univariate		Multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
L-Tx time				
Sex (female)	2.63 (0.52-13.32)	0.244	0.83 (0.13-5.38)	0.844
Age	1.00 (0.95-1.06)	0.988	1.01 (0.95-1.07)	0.716
eGFR-list	0.99 (0.97-1.01)	0.391		
MELD-list	1.07 (0.93-1.24)	0.358		
sCr-list	2.02 (0.21-19.44)	0.543		
Bilirubin-list	1.04 (0.93-1.16)	0.480		
INR-list	2.89 (0.48-17.37)	0.248		
eGFR-max	1.01 (0.98-1.03)	0.645		
eGFR-Tx	1.00 (0.99-1.01)	0.197		
MELD-Tx	1.01 (0.91-1.13)	0.799		
sCr-Tx	0.47 (0.08-2.69)	0.396		
Bilirubin-Tx	1.02(0.95-1.10)	0.656		
INR-Tx	1.71 (0.23-9.98)	0.550		
CKD	2.63 (0.52-13.32)	0.244		
DeGFR	8.00 (1.77-36.13)	0.007	8.87 (1.67-47.23)	0.011
Tx time				
PRBCs	1.17 (0.98-1.40)	0.090		
FFP	1.04 (0.97-1.11)	0.299		
Dopamine	1.00 (0.99-1.01)	0.978		

OR, 95% CI, and *P* value were estimated.

OR, odds ratio; 95% CI, 95% confidence intervals.

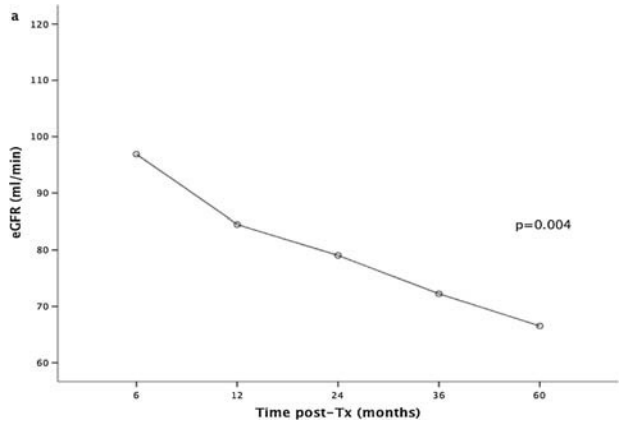

FIGURE 2. Estimated-GFR trend 5 years posttransplantation in all 51 liver transplant recipients. Time post-Tx at 6, 12, 24, 36, 60 months postoperatively.

Method. None of our patients presented these high values of bilirubin, as shown in Table 1.

Fluctuations of eGFR were always transient because eGFR returned to previous value after management of hydroelectrolytic balance. Principal management included reducing diuretic therapy and/or lactulose use, treating urinary tract infections, and other less severe infections. As shown in Table 1, these eGFR-F were not associated with worsening of renal function during L-Tx time as demonstrated by no significant differences in eGFR-list and sCr-list versus eGFR-Tx and sCr-Tx, median values.

Baseline eGFR is a very important nephrologic parameter in the evaluation of renal function, in particular for the diagnosis of acute renal dysfunction, which is focused on eGFR/sCr modifications from a previous value.[5,16,27,28]

During an episode of AKI, eGFR value shows an abrupt drop from values previously collected usually considered a baseline value. Therefore, AKI diagnosis or evaluations of eGFR modifications can only be performed retrospectively.

KDIGO guideline suggests to consider as baseline the lowest outpatient creatinine value between 7 and 365 days before the current value.[5] The so-called looking back method[13] is described as the best condition to consider eGFR-max as the baseline renal function.

In our study, we identified the eGFR-max as the highest value of eGFR among all values retrospectively collected during a median period of 254 days, corresponding to L-Tx time.

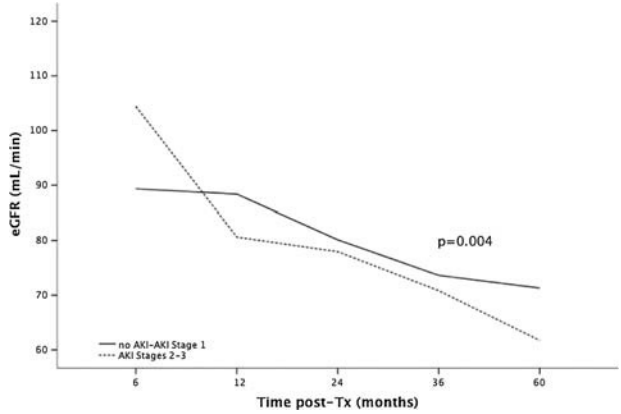

FIGURE 3. eGFR trend 5 years posttransplantation in patients with and without AKI post-Tx.

TABLE 4.

Univariate and multivariate logistic regression analysis of independent predictors of post-Tx CKD in 51 liver Tx recipients

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
L-Tx time				
Sex (female)	2.55 (0.31-20.99)	0.383		
Age	1.07 (0.96-1.18)	0.200		
eGFR-list	0.98 (0.95-1.01)	0.157		
MELD-list	0.99 (0.84-1.17)	0.931		
sCr-list	12.16 (0.67-218.13)	0.090		
Bilirubin-list	0.94 (0.76-1.17)	0.606		
INR-list	1.04 (0.13-8.17)	0.966		
eGFR-max	0.98 (0.96-1.00)	0.165		
eGFR-Tx	0.96 (0.94-0.99)	0.022	0.91 (0.79-1.04)	0.150
MELD-Tx	1.04 (0.93-1.18)	0.475		
sCr-Tx	23.99 (1.40-409.87)	0.028	0.01 (0.00-570.90)	0.190
Bilirubin-Tx	0.94 (0.80-1.09)	0.429		
INR-Tx	0.93 (0.09-9.71)	0.953		
CKD pre-Tx	13.71 (1.31-143.44)	0.029		
DeGFR	4.80 (1.03-22.37)	0.046	7.04 (0.88-56.48)	0.060
Tx time				
PRBCs	1.07 (0.94-1.23)	0.285		
FFP	1.03 (0.96-1.11)	0.409		
Dopamine	1.00 (0.98-1.08)	0.345		
Post-Tx time				
AKI post-Tx	1.97 (0.36-10.82)	0.436		

OR, 95% CI, and *P* value were estimated.

Furthermore, the retrospective assessment of eGFR-max in outpatients with ESLD during L-Tx time has allowed the identification of eGFR events characterized by a transient significant reduction of eGFR more than 50%, outside KDIGO criteria, defined as DeGFR.

These drops were found in 35% of our patients and were not associated with the worsening of renal function during L-Tx time, whereas drops were associated with the worse post-Tx kidney outcome, as shown in Table 3.

In DeGFR+ group compared with DeGFR- group, we observed at listing and at Tx higher MELD score due to higher bilirubin values and not related to a higher sCr values. This higher MELD score reflects the advanced degree of ESLD. In these patients, renal and hepatic functions are closely intertwined, as confirmed by the association between renal dysfunction and higher MELD score highlighted in previous studies.[29-31]

In our study, we demonstrated that patients in DeGFR+ group are sicker patients characterized by a worse degree of liver dysfunction and particularly prone to eGFR modification during L-Tx time.

Furthermore, eGFR drops were associated with early occurrence of post-Tx AKI stages 2 to 3 ($P = 0.007$). Although in DeGFR+ group, we found a higher prevalence of pre-Tx CKD, the occurrence of post-Tx AKI was not significantly different among DeGFR+ patients with and without CKD.

We cannot exclude that eGFR drops represented undiagnosed episodes of AKI outside KDIGO diagnostic criteria or occurrence of acute kidney disease (AKD). As defined by KDIGO guideline,[5] the term "acute kidney disease" (AKD) refers to kidney damage present more than 1 month and less than 3 months (unlike CKD).[11]

In a study on patients affected by kidney disease with biopsy-proven evidence of acute diffuse parenchymal damage, 35% of the cases did not meet the KDIGO criteria for AKI.[32] These non-AKI cases of acute kidney damage had similar outcomes to AKI, so the authors emphasized that the division between AKI and AKD may be arbitrary, as also suggested by the KDIGO guideline.[5] Moreover, in a large study on 104 764 inpatients with de novo AKI, including AKI stage 1 (increase in sCr $\geq$ 0.3 mg/dL within 48 hours), the apparent recovery of kidney function remained an independent risk factor for poor kidney outcome at 1 year.[33]

Our results seem to be in agreement with literature, in fact, our cases could be considered as AKD patients.[34] The eGFR returned to previous value in a period no longer than 3 months and the poor outcome is confirmed by the occurrence of de novo post-Tx AKI.

The diagnostic accuracy for AKI could be improved by the possible role of new biomarkers discovered in the past few years, as urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, liver fatty acid binding protein, and interleukin-18.[34] However, they are expensive and need to be validated in general population and in patients with cirrhosis. We expect the combination of several urinary biomarkers and early diagnosis to significantly contribute to the differential diagnosis of kidney dysfunction in the near future and improve the nephrologist monitoring pre- and post-Tx.

In conclusion, eGFR-F are common in outpatients with ESLD who received transplantation and are not indicative of worsening of renal function from listing to liver Tx. However, DeGFR are more frequent in patients with worse condition of ESLD and may be associated with worse post-Tx kidney outcome.

The collection of several eGFR values, instead of considering a single eGFR value, may help to understand the dynamics of variations in kidney function and may add prognostic information. A closer nephrologic monitoring of cirrhotic patient candidates to receive liver Tx may help to identify the actual eGFR-max value and define DeGFR.

Calcineurin inhibitors have a crucial role in the immunosuppression after liver Tx and its nephrotoxicity is a well-known risk factor of kidney dysfunction post-Tx. In our patients, the introduction of tacrolimus was delayed after the onset of AKI according to other transplant centers, then the exposure to tacrolimus did not influence AKI development in our population.[35-37]

This study is affected by some limitations. First, the small sample size of the study may affect the strength of our conclusion, but this is a single-center study, and all our patients were listed and transplanted in the Liver Unit of Sapienza University of Rome. Second, the retrospective study design may be considered a limitation, but in this case, it has represented the best condition to evaluate the eGFR-max among several eGFR values collected over time. Further and larger analyses are required to evaluate the impact of pre-Tx DeGFR on early and long-term post-Tx outcome.

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