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## ORIGINAL ARTICLE

# Measurement of glomerular filtration rate in lung transplant recipients highlights a dramatic loss of renal function after transplantation

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## ABSTRACT

**Background.** Chronic kidney disease (CKD) after lung transplantation (LT) is underestimated. The aim of the present study was to measure the loss of glomerular filtration rate (GFR) 1 year after LT and to identify the risk factors for developing Stage  $\geq 3$  CKD.

**Methods.** LT patients in the University Hospital of Lyon had a pre- and post-transplantation measurement of their GFR (mGFR), and GFR was also estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

**Results.** During the study period, 111 patients were lung transplant candidates, of which 91 had a pre-transplantation mGFR, and 29 had a mGFR at 1 year after LT. Six patients underwent maintenance haemodialysis after transplantation. Mean mGFR was 106 mL/min/1.73 m<sup>2</sup> before LT and 58 mL/min/1.73 m<sup>2</sup> 1 year after LT ( $P < 0.05$ ) with a mean loss of 48 mL/min/1.73 m<sup>2</sup> per patient. The risk of developing Stage  $\geq 3$  CKD after LT was higher in patients with lower pre-LT mGFR (odds ratio for each 1 mL/min/1.73 m<sup>2</sup> increase: 0.94, 95% confidence interval 0.88–0.99). Receiver operator characteristics curves for the sensitivity and specificity of eGFR and mGFR for the prediction of CKD Stage  $\geq 3$  after LT found that pre-LT mGFR of 101 mL/min/1.73 m<sup>2</sup> and pre-LT eGFR of 124 mL/min/1.73 m<sup>2</sup> were the optimal thresholds for predicting Stage  $\geq 3$  CKD after LT.

**Conclusion.** The present study underlines the value of mGFR in the pre-LT stage and found major renal function loss after LT, and consequently two-thirds of patients have Stage  $\geq 3$  CKD at 1 year. All patients with a pre-LT mGFR  $< 90$  mL/min/1.73 m<sup>2</sup> warrant particular attention.

**Keywords:** chronic kidney disease, epidemiology, lung transplant, measured GFR

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## INTRODUCTION

Lung transplantation (LT) is an established treatment for patients with end-stage lung disease and the median survival is 6 years [1]. Graft rejection prevention requires high doses of immunosuppressive therapies leading to increased direct toxicity and infectious complications [2]. Chronic kidney disease (CKD) remains one of the most common complications in lung transplant patients. At 5 years post-transplant, 14% have a serum creatinine levels  $>220\ \mu\text{mol/L}$ , 2.4% are on maintenance dialysis and 0.9% require kidney transplantation [1, 3]. The use of calcineurin inhibitors (cyclosporine or tacrolimus) has been reported to be the main cause of post-transplantation renal dysfunction [2]. However, few studies have focused on the immediate renal outcomes of LT in the first year of transplantation. Ojo *et al.* [4] found that age, post-operative acute kidney injury (AKI), pre-morbid hypertension and diabetes mellitus were associated with an increase in the frequency of CKD onset after LT; furthermore, chronic renal failure was associated with a 4-fold increase in mortality [relative risk of death, 4.55; 95% confidence interval (CI) 4.38–4.74] [4]. Sikma *et al.* [5] identified early high serum level of tacrolimus as a significant risk factor for the onset of AKI. Moreover, 46% of LT had AKI and the recovery rate after AKI was low (19%), with a cumulative incidence of severe CKD at 1 year of 15% [5]. Solé *et al.* [6] found that older recipient age, low body mass index (BMI) and use of cyclosporine/azathioprine were associated with the onset of CKD after LT; 50% of LT patients had developed CKD at 6 months and almost 80% at 2 years.

Furthermore, because low estimated glomerular filtration rate (eGFR) before LT is associated with worse outcome and mortality, a reliable detection of an impaired renal function before LT is critical [7]. However, most LT recipients have previously experienced a long period of debilitating chronic pulmonary disease, and their muscular mass is decreased, which renders the use of serum creatinine level for the estimation of GFR unreliable. Inulin or iothexol clearance remains the gold standard for the measurement of GFR, and as it is completely independent of muscular mass, it can perfectly describe GFR in LT candidates. Thus, Degen *et al.* [8] found that eGFR using Cockcroft and Gault and Modification of Diet in Renal Disease (MDRD) formulas have a poor performance compared with measured GFR (mGFR) in LT recipients, while the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was considered to have satisfactory performance pre-LT, although the accuracy was poor.

Although post-LT onset of CKD seems to be associated with pre-LT GFR [6], and eGFR is reported to be unreliable in these patients [8], there is no published study that has investigated loss of renal function using mGFR. The aim of the present study was therefore to determine the loss of renal function, as assessed by eGFR and mGFR at 1 year after LT, and also to identify the risk factors of the onset of CKD and end-stage renal disease (ESRD) requiring maintenance haemodialysis (HD) among LT recipients.

## MATERIALS AND METHODS

### Data collection

Between January 2012 and April 2016, we retrospectively included all LT recipients referred to our unit with pre-LT mGFR, and collected all available pre- and post-LT eGFR (CKD-EPI) and mGFR (inulin or iothexol clearance) results. Post-LT GFR was

assessed at 1 year after LT. Demographic, medical and biological findings were collected retrospectively. CKD was defined according to the KDIGO definition [9]. AKI was defined according to the KDIGO classification [10], and events occurring within the first 30 days after LT were considered in the present study. CKD was also defined according to the KDIGO classification, and CKD Stages 1 and 2 was defined by the presence of an albuminuria [9]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethical committee.

### GFR estimation and measurement

All plasma creatinine values were obtained in clinically stabilized patients using the Siemens enzymatic method (on the Dimension Vista System, Siemens Healthcare, Erlangen, Germany) traceable to National Institute of Standards and Technology Creatinine Standard Reference Materials 914 (verified with National Institute of Standards and Technology SRM 967) with calibration certified by isotope dilution mass spectrometry. mGFR was performed by the gold standard methods: inulin (pre-LT) or iothexol (pre-LT and post-LT) clearance measurements [11]. mGFR was indexed (mGFR) to the body surface area (BSA) as determined by the Dubois and Dubois BSA formula  $[0.0071843 \times \text{total body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}]$  [12]. GFR was also estimated (eGFR) by the CKD-EPI formula as previously described [13].

### Statistical analyses

Statistical analyses were performed using Prism software, version 6 (GraphPad software, La Jolla, CA, USA) and the R software (R foundation for Statistical Computing, Vienna, Austria). Simple comparisons were performed using Student's *t*-test. Variables associated with Stage  $\geq 3$  CKD at 1 year after LT were evaluated in univariate analysis; odds ratios were computed using the Woolf logit method [14]. Variables with a  $P < 0.20$  in univariate analysis were included in multivariate models of Stage  $\geq 3$  CKD at 1 year after LT. Akaike and Bayesian information criteria were calculated for each model. Receiver operator characteristics (ROC) curves for the prediction of Stage  $\geq 3$  CKD at 1 year of LT were built for eGFR and mGFR before LT.

## RESULTS

### Population characteristics

A total of 111 patients were candidates for a LT between January 2012 and April 2016. Among these, 91 were transplanted and had a pre-transplantation mGFR available and were included. Twenty-nine (32%) had an available mGFR at 1 year of transplantation (Supplementary data, Figure S1). Principal demographic and clinical characteristics are presented in Table 1. At the time of censoring, 13 patients had died (14%) and 6 (7%) were on maintenance HD.

### Loss of renal function after LT

Mean  $\pm$  standard deviation (SD) mGFR was  $106 \pm 24\ \text{mL/min}/1.73\ \text{m}^2$  before LT and  $58 \pm 17\ \text{mL/min}/1.73\ \text{m}^2$  at 1 year after transplantation ( $n=29$ ); the mean decrease for individual patients was  $48 \pm 22\ \text{mL/min}/1.73\ \text{m}^2$  ( $P < 0.05$ ; Figure 1A). Stage  $\geq 3$  CKD was present in 7% (6/91) of patients before LT, and 66% (23/35) after LT. All LT recipients had a decrease of  $\geq 25\%$  in their baseline mGFR at 1 year after LT and 60% had lost  $\geq 50\%$ .

Table 1. Clinical characteristics of LT recipients

Variable	Total population, n = 91	mGFR post-LT, n = 29	ESRD patients after LT, n = 6
Age, years	46.5 ± 14.8	43.8 ± 15.1	51.8 ± 9.7
Male sex, n (%)	49 (54)	11 (38)	4 (67)
BMI, kg/m <sup>2</sup>	20.5 ± 4.3	20.1 ± 4.3	22.7 ± 3.4
Primary pulmonary disease, n (%)			
Cystic fibrosis	32 (35)	16 (55)	1 (16)
Idiopathic pulmonary fibrosis	15 (16)	4 (14)	1 (17)
COPD	2 (2)	1 (3)	0
Pulmonary hypertension	6 (7)	1 (3)	0
Other	36 (40)	7 (24)	4 (67)
Type of lung transplant procedure, n (%)			
Single LT	26 (29)	5 (17)	0 (0)
Bilateral LT	56 (61)	20 (69)	4 (67)
Heart-LT	9 (10)	4 (14)	2 (33)
Comorbidities prior to LT, n (%)			
Stage ≥3 CKD	6 (7)	0 (0)	2 (33)
Albuminuria	23 (25)	8 (28)	5 (83)
Hypertension	5 (5)	1 (3)	1 (17)
Diabetes mellitus	14 (15)	11 (38)	1 (17)
Current smoker	6 (7)	5 (17)	1 (17)

Data are expressed as mean ± SD or n (%). COPD, chronic obstructive pulmonary disease.

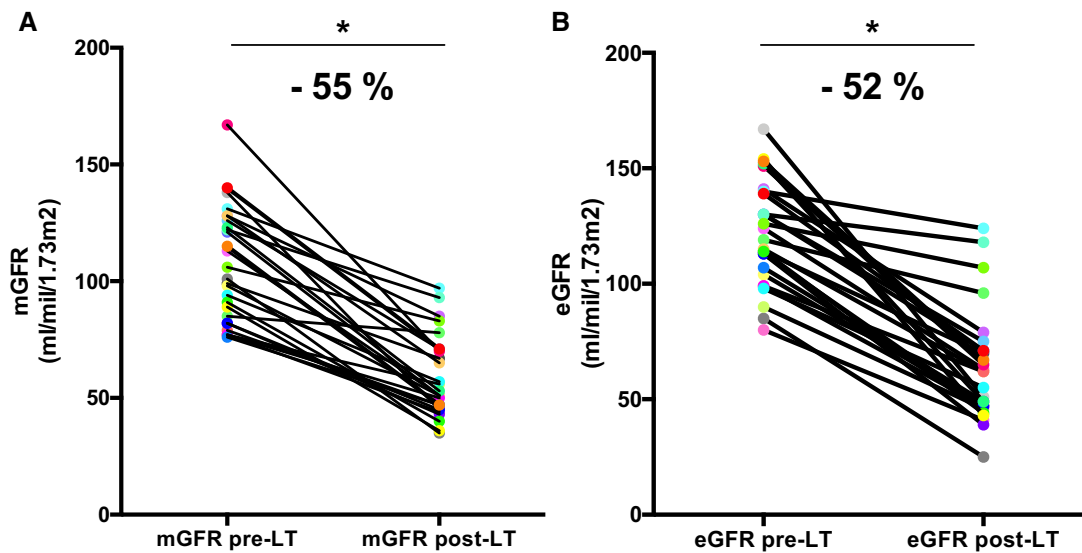


FIGURE 1: Loss of mGFR and eGFR renal function after LT. (A) The mean ± SD loss of renal function post-LT was  $48 \pm 22$  mL/min/1.73 m<sup>2</sup>, corresponding to a relative loss of 55%. Pre-LT and post-LT mGFR values were significantly different. mGFR was measured using either inulin or iothexol clearance (see Concise Method section). (B) The mean ± SD loss of renal function post-LT was  $58 \pm 27$  mL/min/1.73 m<sup>2</sup>, corresponding to a relative loss of 52%. Pre-LT and post-LT eGFR values were significantly different. eGFR was estimated with CKD-EPI formula (see Concise Method section). \* $P < 0.05$ , paired t-test.

Regarding eGFR, the difference between before and after LT was also significant; pre- and post-LT mean ± SD values were  $122 \pm 23$  and  $63 \pm 24$  mL/min/1.73 m<sup>2</sup> ( $n = 29$ ), respectively. Mean ± SD decrease for individual patients at 1 year after LT was  $58 \pm 27$  mL/min/1.73 m<sup>2</sup> ( $P < 0.05$ ; Figure 1B). According to the CKD-EPI formula estimation, 78% of the patients had a decrease of ≥25% of eGFR at 1 year after LT, and 37% had a decrease of ≥50%.

#### Characteristics of LT recipients according to their post-LT CKD stage ( $n = 35$ )

In patients with post-LT CKD, LT recipients with Stage 1 or 2 CKD were significantly younger than those with Stage

≥3 CKD and maintenance HD patients at the time of transplantation, and had a higher pre-transplantation mGFR than both patients with Stage ≥3 CKD and maintenance HD patients (Supplementary data, Table S1). With pre-transplantation eGFR, only LT recipients with Stage 1 or 2 CKD had a higher pre-transplantation mGFR than maintenance HD patients. Patients requiring maintenance HD after LT had a lower mean ± SD pre-transplantation mGFR than patients with post-LT non-HD-dependent CKD ( $74 \pm 7$  versus  $108 \pm 5$  mL/min/1.73 m<sup>2</sup>;  $P < 0.05$ ). All patients requiring post-LT maintenance HD had initially presented a renal replacement therapy (RRT)-requiring AKI episode (Supplementary data, Table S1).

### Risk factors of CKD and ESRD after LT (n = 35)

In a univariate logistic regression, age at LT and pre-LT mGFR were associated with a higher risk of developing Stage  $\geq 3$  CKD after LT; cystic fibrosis and diabetes were associated with a lower risk (Table 2). Interestingly, pre-LT serum creatinine and eGFR were not associated with a higher risk of developing Stage  $\geq 3$  CKD after LT (Table 2). In a multivariate logistic regression adjusted on age, pre-LT mGFR remained significantly associated with a higher risk of developing Stage  $\geq 3$  CKD after LT, while eGFR did not (Table 2). In a multivariate linear regression, mGFR was also associated with a higher risk of developing Stage  $\geq 3$  CKD after LT, while eGFR was not (Supplementary data, Table S2).

ROC curves for the sensitivity and specificity of eGFR and mGFR for the prediction of CKD Stage  $\geq 3$  after LT found that pre-LT mGFR of 101 mL/min/1.73 m<sup>2</sup> was the optimal threshold for predicting Stage  $\geq 3$  CKD after LT (Supplementary data, Figure S2); sensitivity was 75% (95% CI 53–90) and specificity 82% (95% CI 48–98; Supplementary data, Table S3a). For eGFR, the optimal threshold was 124 mL/min/1.73 m<sup>2</sup> with sensitivity 67% (95% CI 45–84) and specificity 70% (95% CI 35–93; Supplementary data, Table S3b). There was no statistical difference between the two ROC curves (P = 0.07).

Pre-LT serum creatinine (1.17, 95% CI 1.06–1.38) and either eGFR per 1 mL/min/1.73 m<sup>2</sup> increase (0.94, 95% CI 0.88–0.99) or mGFR per 1 mL/min/1.73 m<sup>2</sup> increase (0.91, 95% CI 0.80–0.97) and length of stay in the intensive care unit per 1 day increase (1.08, 95% CI 1.02–1.17) were risk factors of developing ESRD after LT (P < 0.05, n = 35; Supplementary data, Table S4).

### Performance of eGFR before and after LT

The mean  $\pm$  SD pre-LT eGFR was significantly different from pre-LT mGFR (122  $\pm$  4 versus 106  $\pm$  5 mL/min/1.73 m<sup>2</sup>, respectively; n = 91, P < 0.05). There was no significant difference

between eGFR and mGFR when measured after LT (58  $\pm$  3 versus 63  $\pm$  5 mL/min/1.73 m<sup>2</sup>, respectively; n = 35, P = 0.3835).

Prior to LT (n = 91), the Bland–Altman plot indicates that, compared with mGFR, the mean  $\pm$  SD absolute bias of CKD-EPI eGFR was 18.7  $\pm$  17.7 mL/min/1.73 m<sup>2</sup>, precision 24 and P30 accuracy was 64%; for post-LT (n = 29), the mean  $\pm$  SD absolute bias was 5.0  $\pm$  11.1 mL/min/1.73 m<sup>2</sup>, precision was 18 and P30 accuracy was 85% (Figure 2). The mean bias between mGFR and eGFR was significantly higher in pre-LT than in post-LT (P < 0.0001).

Prior to LT, eGFR led to a misclassification of CKD stage in 29/91 patients (32%): 23 patients with Stage 1 CKD according to mGFR were classified as Stage 2 (24%), 3 patients with Stage 2 CKD were classified as 3a (3%) and 3 with Stage 1 CKD were classified as 3a (3%).

### DISCUSSION

In the present study, a significant loss of renal function at 1 year of LT was observed. Consequently, we confirm the high prevalence of Stage  $\geq 3$  CKD among LT recipients according to mGFR. In the registry of the International Society for Heart and Lung Transplantation, the prevalence of renal dysfunction was relatively high, but notably lower than that found herein; the prevalence was 22.5% 1 year after LT and ~50% after 5 years. However, renal dysfunction definition in this registry was based on a creatinine level >220  $\mu$ mol/L, which is known to be subject to variations [1], and therefore the difference can then be explained by the definition of renal dysfunction used herein which is in accordance with KDIGO recommendations. It is also of note that Solé et al. [6] found Stage  $\geq 3$  CKD at 1 year of LT in 69% of LT patients based on MDRD GFR estimation.

We identified that mGFR <101 and consequently 90 mL/min/1.73 m<sup>2</sup> was associated with an increased risk of Stage  $\geq 3$  CKD at 1-year post-LT. As age before LT, cystic fibrosis and diabetes

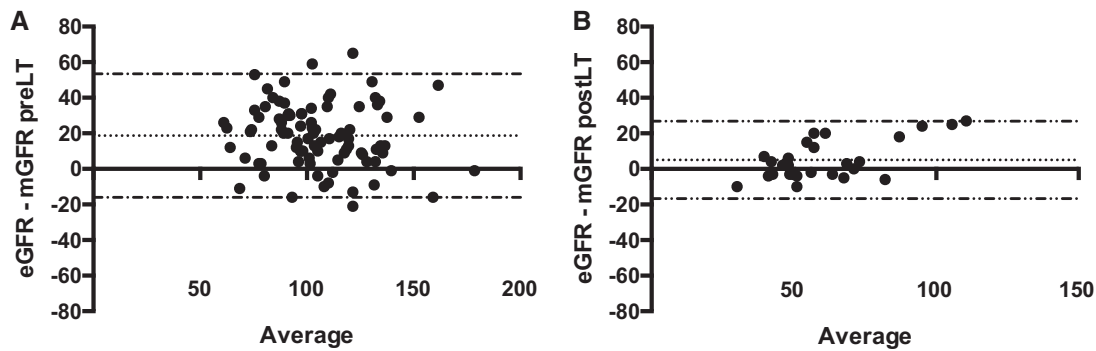
Table 2. Risk prediction of post-transplantation mGFR Stage  $\geq 3$  CKD, n = 35

	Univariate analysis		Multivariate analysis <sup>a</sup>			
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	AIC	BIC
Sex: male	0.32 (0.06–1.51)	0.16				
Age at time of LT (per 1 year)	1.09 (1.02–1.19)	0.02				
Age >50 years at time of LT	10 (1.45–203.74)	0.02				
BMI >18 kg/m <sup>2</sup> at time of LT	5.54 (1.20–25.69)	0.02				
Cystic fibrosis before LT	0.14 (0.02–0.75)	0.03				
Diabetes mellitus before LT	0.09 (0.01–0.53)	0.01				
Previous smoker	2.46 (0.29–52.83)	0.46				
Pre-LT serum creatinine (per 1 U increase)	1.03 (0.96–1.1)	0.45				
Pre-LT mGFR (per 1 mL/min/1.73 m <sup>2</sup> increase)	0.94 (0.88–0.98)	0.01	0.94 (0.88–0.99)	0.04	33.6	38.3
Pre-LT mGFR <90 mL/min/1.73 m <sup>2</sup>	8 (1.15–163.07)	0.07	10.7 (1.5–221.8)	0.04	37.6	42.3
Pre-LT mGFR <101 mL/min/1.73 m <sup>2</sup>	10.93 (2.16–85.04)	0.01				
Pre-LT eGFR (per 1 mL/min/1.73 m <sup>2</sup> increase)	0.97 (0.93–1.01)	0.17	1.00 (0.95–1.05)	0.96	39.4	44.0
Pre-LT eGFR <90 mL/min/1.73 m <sup>2</sup>	2.1 $\times$ 10 <sup>7</sup> (0+Inf)	0.99	2.8 $\times$ 10 <sup>7</sup> (0+Inf)	0.99	40.0	44.6
Pre-LT eGFR <124 mL/min/1.73 m <sup>2</sup>	4.67 (1.01–26.57)	0.06				
Pre-LT albuminuria (per 1 U increase)	1.06 (0.99–1.38)	0.33				
ECC >200 min	0.28 (0.05–1.38)	0.13				
Length of stay in ICU (per 1 day increase)	1.14 (1.01–1.42)	0.13				
Mean tacrolimus first month >10	0.9 (0.18–4.21)	0.43				
AKI after LT	1.6 (0.3–8.48)	0.57				

Methods: univariate and multivariate logistic regressions, P < 0.05 was considered as significant. eGFR and mGFR are expressed in mL/min/1.73 m<sup>2</sup>.

<sup>a</sup>The multivariate model was adjusted for age.

AIC, Akaike information criterion; BIC, Bayesian information criterion; CF, cystic fibrosis; ECC, extra-corporeal circulation.



**FIGURE 2:** Bland-Altman plot of eGFR - mGFR in pre- and post-LT. (A) Mean bias was  $18.7 \pm 17.7$  mL/min/1.73 m<sup>2</sup> for eGFR versus mGFR in pre-LT patients. (B) Mean bias was  $5.0 \pm 11.1$  mL/min/1.73 m<sup>2</sup> for eGFR versus mGFR in post-LT patients. The solid line represents the mean difference and the dotted and dashed line the 95% limit of agreement. Pre-LT eGFR exhibited a significantly higher systematic bias and less accuracy compared with mGFR. Post-LT eGFR was as performant as mGFR.

mellitus were associated with CKD Stage >3 after LT in the univariate analysis, we performed a multivariate linear analysis that confirmed the significant association of mGFR. We also confirmed that eGFR was not relevant for evaluating the risk of CKD post-LT as the threshold value of risk was relatively high (124 mL/min/1.73 m<sup>2</sup>) and not associated with post-LT CKD (see Table 2). In the study reported by Ojo et al. [4], AKI was also associated with an increased risk of CKD after LT, while herein, this was only the case in patients requiring RRT for AKI (in univariate analysis). Surprisingly, extracorporeal circulation (ECC) was not associated with a higher risk of developing CKD after LT. However, as almost all the LT recipients underwent surgery with ECC, this factor was not discriminant. Moreover, no significant difference was observed regarding ECC duration or type (data not shown).

The relatively high level of mGFR found to be associated with the CKD risk can be explained by at least two related causes. First, a significant proportion of the cohort of LT recipients suffered from cystic fibrosis, which is known to be a condition at risk of renal dysfunction [15, 16]. In such patients, GFR is relatively high because of a glomerular hyperfiltration. Secondly, this can also be explained by a higher frailty of the kidneys in response to the necessary and multiple kidney injuries after LT (e.g. ECC, nephrotoxic antibiotics and immunosuppressive therapies). Nevertheless, as LT recipients with cystic fibrosis are younger (data not shown), this can explain why this was not associated with an elevated risk of developing Stage  $\geq 3$  CKD after LT herein.

Taken together, the results presented herein strengthen the real relevance of mGFR among LT recipient candidates, especially since a pre-LT Stage  $\geq 3$  CKD is reported to be associated with an increased mortality after LT elsewhere [7]. Our results confirmed that in a specific population (LT candidates herein), mGFR and especially with iohexol plasmatic clearance is easy to handle and critical to better classify patients' renal status [17, 18]. However, the impact of CKD after LT on mortality remains unclear. Among LT recipients, patients who required post-LT maintenance HD had a lower yet preserved pre-LT mGFR (i.e. CKD Stage II); these patients experienced AKI requiring RRT immediately after LT and were significantly older than those with post-LT CKD Stages 1 and 2. Thus, in pre-LT work-up, increased attention is warranted in any patient with an mGFR <90 mL/min/1.73 m<sup>2</sup> and older age as this association could be associated with maintenance HD after LT.

Despite interesting results, the present study does suffer from certain limitations. For instance, the single-centre design

limited the sample size, although relatively large for LT, which precluded more thorough statistical analysis. Moreover, the retrospective analysis of the data is likely to have led to measurement and selection bias. However, most of the results were consistent with the existing literature and we can rely on the reproducibility and accuracy of mGFR for the extrapolation of the results.

In conclusion, the present study underlines the value of mGFR in the pre-LT stage and found major renal function loss after LT, and consequently two-thirds of the patients have Stage  $\geq 3$  CKD at 1 year. All patients with a pre-LT mGFR <101 and consequently 90 mL/min/1.73 m<sup>2</sup> warrant particular attention.

## SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

## ACKNOWLEDGEMENTS

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## AUTHORS' CONTRIBUTIONS

N.F., F.G.-E. and S.L. designed the study, analysed the data and wrote the manuscript. J.F.M and F.P. helped in the data collection and revised the manuscript. L.J., L.D., F.G.-E. and E.K. carefully revised the manuscript. L.B. helped in statistical analysis and carefully revised the manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. The results presented in this article have not been published previously in whole or part, except in abstract format.

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