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Renal Outcomes After Lung or Combined Heart-Lung Transplantation in Pulmonary Hypertension

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ABSTRACT

Renal impairment is considered a contra-indication for lung (LTX) or combined heart-lung (HLTX) transplantation due to increased mortality. We hypothesized that renal impairment in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) is the result of reduced cardiac output and should be partly reversible after LTX. We performed a retrospective analysis in 67 consecutive PAH and CTEPH patients who underwent (H)LTX, to investigate the postoperative evolution of renal function in function of baseline renal function using a mixed model effect test. Furthermore, we assessed potential predictors for postoperative renal dysfunction, renal replacement therapy (RRT) and mortality by multivariate analyses. Median baseline eGFR was 74 mL/min/1.73m^2. Fourteen patients were classified as KDIGO 3 preoperatively, 38 patients as KDIGO 2. Renal function significantly declined after 1 and 2 years in all patients. In patients with impaired renal function (KDIGO 2 and 3), we observed a significant improvement in eGFR 1 month after (H)LTX ($p = 0.02$ and $p = 0.04$, respectively). Baseline renal impairment ≤ 60 mL/min/1.73m^2 was associated with early RRT but not with further renal function deterioration, long-term RRT, or mortality. Age was a predictor of renal function decline and mortality. We conclude that renal function evolution can be biphasic after (H)LTX in PAH and CTEPH patients with baseline renal impairment, with initial improvement due to resolution of cardio-renal syndrome. Mild to moderate renal impairment was not significantly associated with renal deterioration or increased mortality.

Abbreviations: AKI, acute kidney injury; CKD-EPI, chronic kidney disease epidemiology collaboration; CNI, calcineurin inhibitor; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; ECLS, extra-corporeal life support; eGFR, estimated glomerular filtration rate; HLTX, heart-lung transplantation; ICU, intensive care unit; IQ, interquartile; ISHLT, International Society for Heart and Lung Transplantation; KDIGO, kidney disease improving global outcomes; LTX, lung transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RAP, right atrial pressure; RHC, right heart catheterization; RRT, renal replacement therapy; RV, right ventricle; SD, standard deviation.

L. Hardy and A.D'Haenens share first authorship.

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1 | Introduction

Pulmonary hypertension (PH) is defined by an increase in mean pulmonary arterial pressure (mPAP) > 20 mmHg as assessed by right heart catheterization (RHC) [1]. Physiologically the right ventricle (RV) is poorly equipped to deal with increasing pulmonary arterial pressures. The increasing afterload causes a rapid decline in stroke volume and cardiac output (CO), resulting in decreased organ perfusion and right-sided congestive heart failure [2].

Renal insufficiency is a common comorbidity in PH patients with an estimated prevalence between 4.5% and 36.0% [3, 4]. The degree of renal insufficiency is proportionately associated with increased mortality [3–5]. Renal dysfunction in PH is often related to a type 2 (chronic) cardiorenal syndrome, where chronic heart failure will eventually result in the development of chronic renal dysfunction. Severe PH is characterized by both a low CO and high right atrium pressure (RAP), leading to reduced renal perfusion and renal venous congestion, which will eventually damage the nephrons [6, 7].

Although the prognosis of pulmonary arterial hypertension (PAH) has improved in the last decades due to new treatment strategies, the disease remains incurable and causes severe morbidity. In addition, a minority of patients with chronic thromboembolic pulmonary hypertension (CTEPH) are insufficiently improved by the available medical treatments, balloon angioplasty, and/or pulmonary endarterectomy. A definitive treatment option in selected patients is lung (LTX) or heart-lung transplantation (HLTX). As the right heart shows a remarkable ability to recover after normalization of pulmonary arterial pressures [8], standard treatment nowadays is bilateral LTX; HLTX is mainly restricted to PAH associated with complex congenital heart disease [9–11]. Because of the scarcity of donor organs, the surgical complexity and inherent risk of transplantation, patients must undergo a rigorous selection. Moderate renal impairment, defined as an estimated glomerular filtration rate (eGFR) $< 60\,mL/min/1.73m^2$, is associated with worse 1- and 3-year survival after LTX for any indication and can be an argument to deem patients ineligible for transplantation [12, 13].

During the perioperative phase after (H)LTX, renal function can be affected by complications such as hypotension, subsequent ischemic acute kidney injury (AKI), and acute tubular necrosis. Moreover, the use of nephrotoxic medications such as calcineurin inhibitors (CNI) or certain antibiotics contributes to renal impairment after transplantation. Outcomes such as severe renal dysfunction and survival after (H)LTX are reported in the International Society for Heart and Lung Transplantation (ISHLT) registry for the general patient population, but no separate data have been reported for PAH/CTEPH patients specifically [14–16].

Renal insufficiency in PAH/CTEPH is particularly affected by hemodynamic status, which may dramatically improve after transplantation. Therefore, it is unclear whether the applied restrictions regarding renal dysfunction in the selection criteria for lung recipient selection are valid in the specific subsets of PAH and CTEPH patients.

The aim of this study was to explore both the effects of (H)LTX on renal function in PAH and CTEPH patients, and to investigate the effects of pre-existing renal dysfunction on outcomes after (H)LTX by a retrospective assessment in consecutive patients transplanted for PAH or CTEPH in our centre.

2 | Methods

2.1 | Study Design and Patient Population

All consecutive patients with PAH or CTEPH, who underwent (H)LTX at the University Hospitals Leuven between January 1, 1991 and September 30, 2019, were retrospectively screened for inclusion. Patients were excluded if data on preoperative serum creatinine were missing or if they underwent a simultaneous kidney transplantation. This study was approved by the local Ethics committee (S64227).

2.2 | Perioperative Patient Management

During the inclusion period, some evolutions have occurred regarding the surgical and medical management of transplant patients. From a surgical perspective, pulmonary hypertension patients initially received combined heart-lung transplantation; this was progressively changed to sequential single lung transplants starting from the 2000s. Transplantations were usually performed off-pump with the possibility of VA-ECMO if the patient required additional support. Cardiopulmonary bypass was restricted for combined cardiac surgeries or major blood loss. Until 2007, exclusively DBD donors were accepted; afterwards, DCD-III (cardiac arrest after planned withdrawal of life-sustaining treatment) and later DCD-IV donors (cardiac arrest in brain-dead patients) were accepted.

Regarding the medical management, the standard immunosuppressive regimen consisted of cyclosporine, methylprednisolone, and azathioprine until the 2000s. Starting from 2000, cyclosporine and azathioprine were progressively replaced by tacrolimus and mycophenolate mofetil. Since 2015, the slow-release form of tacrolimus is systematically used. Around 2017–2018, everolimus was briefly used in patients with decreased renal function as a sparing agent for CNI, but this was stopped due to a high frequency of adverse effects. All patients receive anti-thymocyte globulins for induction, except patients already under immunosuppressive medication before transplantation.

2.3 | Data Collection

Data were collected from the patients' medical files until December 31, 2021. Characteristics of interest included demographic information, PH diagnosis, last available RHC results, comorbidities, and baseline treatment. Creatinine serum levels were recorded at fixed times: on the day of transplantation before surgery, after 24 h, 48 h, 1 week, 1 month, 6 months, 1 year, and 2 years after transplantation. A time span of 2 weeks around the exact date was accepted for the creatinine levels at

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6 months, 1 year, and 2 years. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate GFR because of its close correlation with radionuclide GFR measurements and Cystatin C measurements in transplanted patients [17, 18]. AKI, as defined by the AKI Network, was scored in the first week after transplantation based on serum creatinine and urine output [19]. Chronic renal impairment was classified according to the Kidney Disease Improving Global Outcomes classification (KDIGO) [20]. Regarding the perioperative course, transplantation type, mode, and duration of extra-corporeal life support (ECLS), immunosuppression type and dose at time of hospital discharge, number of packed cell transfusions in the first postoperative week, and length of stay in the ICU and the hospital were recorded. Furthermore, renal replacement therapy (RRT) initiation (either continuous veno-venous hemofiltration or intermittent haemodialysis), kidney transplantation, mortality, and cause of death were registered until censoring on December 31, 2021.

2.4 | Statistical Analyses

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., NC, USA). Normal distribution of the data was assessed using a Shapiro–Wilk test. Continuous characteristics were summarized using their mean and standard deviation (SD), or median and interquartile (IQ) according to the distribution of the data. Categorical data were summarized using observed frequencies and percentages. eGFR evolution after (H)LTX was analysed using a linear model, calculating predicted values conditional on baseline eGFR. The associations between baseline characteristics and renal deterioration, RRT, and mortality were assessed using a logistic or Cox regression. Firstly, a univariate analysis was performed. Predictors with a significance level of 10% were subsequently included in a multivariate analysis. Renal function was assessed at fixed timepoints. Response in renal function was defined as improvement in eGFR $> 60\,mL/min/1.73m^2$. Regarding RRT, separate analyses were performed for early and late dialysis, defined as dialysis within and later than 3 months after transplantation, respectively. Deaths without dialysis were censored at the time of death. Mortality rates were calculated using Kaplan–Meier methodology. Comparison of survival between groups was performed using the Log-rank Mantel–Cox test. Due to the exploratory nature of the study, no adjustments were made to the significance level to account for multiple testing. eGFR data during RRT are not representative of steady-state renal function and were therefore considered as missing data. Since RRT confounds eGFR values and is generally initiated in eGFR values below 10, the missing data were substituted with a value between 0 and 10 using multiple imputation methodology (100 imputations), assuming a uniform distribution of the values between 0 and 10. For a complete description of the statistical methodology, we refer to the Supporting Information S1.

3 | Results

3.1 | Patient Population

From the 81 patients who underwent (H)LTX for PAH or CTEPH in our centre, 13 were excluded based on missing creatinine data, and one based on a combined lung-kidney transplantation, leaving 67 eligible patients. Baseline characteristics and outcomes are summarized in Tables 1 and 2; baseline treatment is summarized in Supporting Information S1: Table S1. Sixty-one patients had PAH (91%) and 6 had CTEPH (9%). Mean age was 40 years (±13 years), and four patients (6%) were paediatric patients. Median baseline eGFR was $74\,mL/min/1{,}73m^2$ (range $41–149\,mL/min/1.73m^2$). Fourteen patients (21%) had a reduced baseline eGFR $< 60\,mL/min/1{,}73m^2$, corresponding to KDIGO 3; 38 patients (57%) had a reduced baseline eGFR between 60 and $89\,mL/min/1.73m^2$, corresponding to KDIGO 2. Median length of follow-up was 99 months (IQR 19–142 months); length of follow-up was not significantly different between KDIGO stages ($p = 0.72$).

3.2 | Evolution of Renal Function After Transplantation

In the entire population, there was no significant change in eGFR after 1 month ($+ 5.89\,mL/min/1.73m^2$, $p = 0.87$) (Figure 1, Supporting Information S1: Figure S1, Table S2). Renal function significantly declined after 1 and 2 years ($p = 0.01$ and $p = 0.0001$, respectively). When stratified according to baseline renal function, there was a significant improvement in renal function in patients with baseline renal impairment KDIGO 2 and 3 after 1 month ($+ 16.96\,mL/min/1.73m^2$, $p = 0.02$ and $+ 11.97\,mL/min/1.73m^2$, $p = 0.04$, respectively) (Figure 2 and Supporting Information S1: Table S3).

3.3 | Predictors for Renal Dysfunction After Transplantation

The association between the potential predictors of renal dysfunction and renal function evolution during 2-year follow-up can be found in Table 3. Univariate analysis demonstrated a significant correlation between renal function decline after transplantation and older age, higher diuretics dosing before transplantation, AKI within the first postoperative week, and higher tacrolimus dosing necessary to reach adequate trough levels (see also Supporting Information S1: Figures S2–S4). Only age and tacrolimus dose remained significant predictors after multivariable analysis. Baseline renal impairment was not predictive of later renal dysfunction.

3.4 | Predictors for Renal Replacement Therapy in the Postoperative Period

Sixteen (28%) out of 57 surviving patients required RRT within the first 3 months after (H)LTX, among whom three patients showed a persistent need for RRT after 3 months. In one of the patients requiring RRT in the acute postoperative period, renal function initially recovered but deteriorated again after 2.3 years, requiring long-term RRT again. In the long term, seven patients (12%) required chronic RRT later than 3 months after (H)LTX. The association between the baseline characteristics and RRT is reported in Table 4. Diuretics dose, baseline eGFR $< 74\,mL/min/1.73m^2$, and postoperative ECLS were

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TABLE 1 | Summary of the patient baseline characteristics.

Characteristics of interest	Total population	Number of patients with missing data
Female, *n* (%)	35 (52%)	0/67
Age, years	40 ± 13	0/67
Weight, kg	66 ± 16	0/67
Body mass index, kg/m²	23.4 ± 5.2	1/67
PH aetiology, *n* (%)		0/67
PAH	61 (91%)	
CTEPH	6 (9%)	
Comorbidities, *n* (%)		0/67
Diabetes mellitus	5 (7%)	
Systemic hypertension	9 (13%)	
Therapy at time of transplantation, *n* (%)		0/67
IV PCA monotherapy, *n* (%)	13 (20%)	
Oral monotherapy (ERA, PDE5i, or CCB), *n* (%)	5 (7%)	
Dual therapy including IV PCA, *n* (%)	12 (18%)	
Oral dual therapy (ERA, PDE5i, and/or CCB), *n* (%)	2 (3%)	
Triple therapy including IV PCA, *n* (%)	19 (28%)	
Quadruple therapy including IV PCA, *n* (%)	4 (6%)	
Bumetanide dose, mg (IQR)	1 (1–4)	
Baseline renal function		0/67
KDIGO 1 (eGFR ≥ 90 mL/min/1.73m²)	15 (22%)	
KDIGO 2 (eGFR 60–89 mL/min/1.73m²)	38 (57%)	
KDIGO 3 (eGFR 30–59 mL/min/1.73m²)	14 (21%)	
Prognostic parameters		
WHO functional class, *n* (%)		7/67
II	3 (5%)	
III	38 (63%)	
IV	19 (32%)	
6 min walking distance, m	318 ± 127	10/67
REVEAL 2.0 score (IQR)	10 (8–12)	7/67
Haemodynamic parameters		
mPAP, mmHg	60 ± 14	3/67
CI, L/min/m²	2.28 ± 1.06	6/67
RAP, mmHg (IQR)	11 (7–14)	4/67
PVR, WU (IQR)	11 (7.5–14.9)	6/67
Time from last RHC to transplantation, months (IQR)	10 (4–18)	3/67
Transplant type, *n* (%)		0/67
LTX	35 (52%)	
HLTX	32 (48%)	
ICU stay before transplantation, *n* (%)	12 (18%)	0/67
Number of packed cell transfusions, units	13 (7–28)	31/67
Tacrolimus dose, mg	8 (6–10)	22/67

Abbreviations: CCB, calcium channel blocker; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; HLTX, combined heart-lung transplantation; ICU, intensive care unit; IV, intravenous; KDIGO, KDIGO chronic kidney disease stage; LTX, lung transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; sGCS, soluble guanylate cyclase stimulator; WU, Wood units.

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TABLE 2 | Renal and overall outcomes of patients after transplantation.

Outcomes	Total population incidence	Number of patients with missing data
AKI during the first week, *n* (%)	30 (46%)	2/67
RRT within first 3 months after transplantation, *n* (%)	16 (24%)	0/67
RRT during long-term follow-up, *n* (%)	23 (34%)	0/67
Time to RRT, days (IQR)	4 (2–1799)	0/67
Number of kidney transplantations, *n* (%)	3 (4%)	0/67
Length of ICU stay after transplantation, days	14 (9–23)	0/67
Need for ECLS after transplantation, *n* (%)	7 (10%)	0/67
Mortality		0/67
Overall, *n* (%)	39 (58%)	
Death within 90 days, *n* (%)	10 (15%)	
Death within 1 year, *n* (%)	14 (21%)	
Death within 2 years, n (%)	20 (30%)	
Cause of death		0/39
Respiratory	19 (48%)	
Hemorrhagic	6 (15%)	
Cardiogenic	4 (10%)	
Oncologic	2 (5%)	
Infection	1 (3%)	
Neurologic	1 (3%)	
PTLD	1 (3%)	
Renal	1 (3%)	
Unclear	4 (10%)	
Length of follow-up, months (IQR)	99 (19–142)	0/67

Abbreviations: AKI, Acute kidney injury; ECLS, extracorporeal life support; ICU, intensive care unit; PTLD, post-transplant lymphoproliferative disorder; RRT, renal replacement therapy.

significantly associated with a higher dialysis rate within 3 months in multivariable analysis.

3.5 | Predictors for Overall Mortality

Overall mortality rate was 21% after 1 year and 30% after 2 years. The associations between the baseline characteristics and mortality are summarized in Table 5. Older age, baseline eGFR $< 74\,mL/min/1.73m^2$, prolonged ICU stay, and RRT requirement within 3 months were associated with increased mortality after 1 year in a univariate analysis. Only age and RRT requirement remained significant predictors after multivariable analysis. When stratified according to KDIGO stage, the mortality rate was not significantly different in patients who had required RRT within 3 months compared to those who had not (KDIGO stage 2: $p = 0.44$; KDIGO stage 3: $p = 0.72$). Figure 3 shows the 2-year survival curve according to baseline eGFR using KDIGO classification. There was no significant difference between patients with normal renal function ($eGFR > 90\,mL/min/1.73m^2$) and patients with reduced renal function (KDIGO stage 2 and 3) ($p = 0.59$).

4 | Discussion

This explorative study aimed to investigate the evolution of renal function in PAH and CTEPH patients. In a cohort of 67 patients, we found a biphasic evolution in renal function after (H)LTX for PAH or CTEPH, with a trend towards early improvement in the general patient population and a significant improvement in patients with reduced renal function, followed by later progressive deterioration. This biphasic evolution reflects the clinical events encountered by the kidneys after transplantation: a first phase of relief from the cardio-renal syndrome, followed by the effects of the nephrotoxic medication (such as CNI) and other potential nephrotoxic events [21]. We also found that age and high tacrolimus dose were the only independent predictors of long-term renal dysfunction; however, there was no association with baseline renal impairment. The main predictors for short-term RRT after (H)LTX were reduced $eGFR < 74\,mL/min/1.73m^2$ before transplantation, high doses of diuretics before (H)LTX, and postoperative ECLS, suggesting that perioperative context and PH severity play a role in RRT initiation with renal function as a surrogate marker of the clinical severity. Finally, we did not observe any significant

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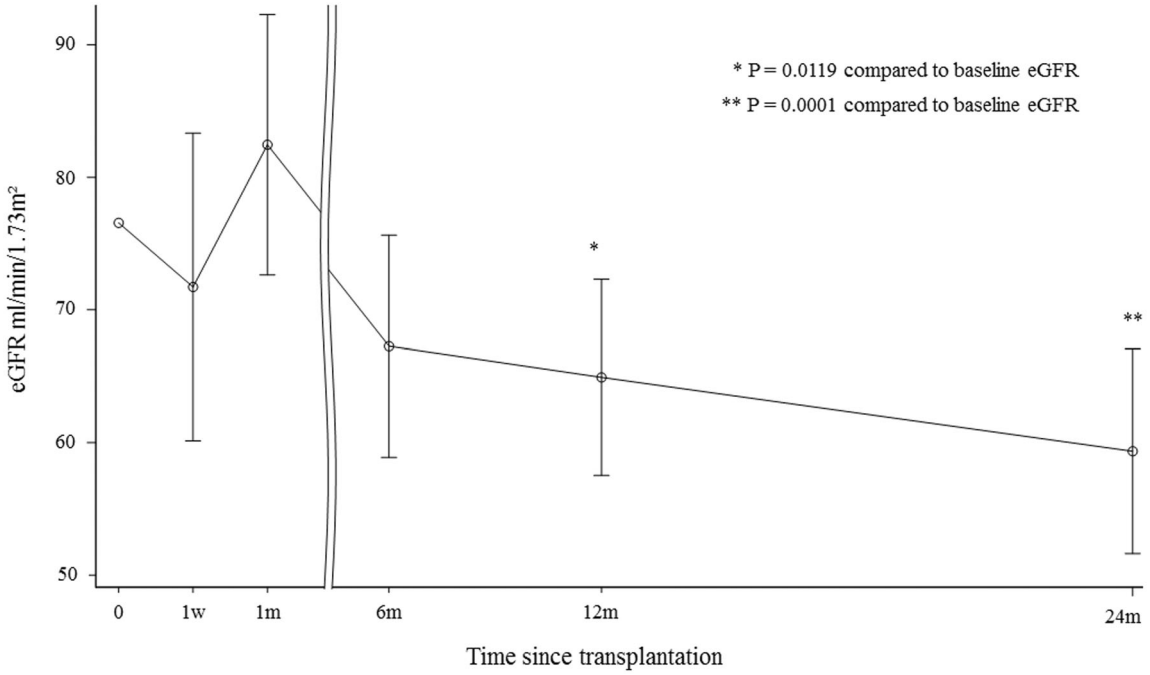

FIGURE 1 | Mean eGFR evolution in function of time after transplantation. This graph shows a nonsignificant trend towards eGFR improvement after 1 month in the overall population, followed by a significant decline after 1 and 2 years. *Note:* X-axis: 1w, 1 week after (H)LTX; 1m, 1 month; 6m, 6 months; 12m, 12 months; 24m, 24 months.

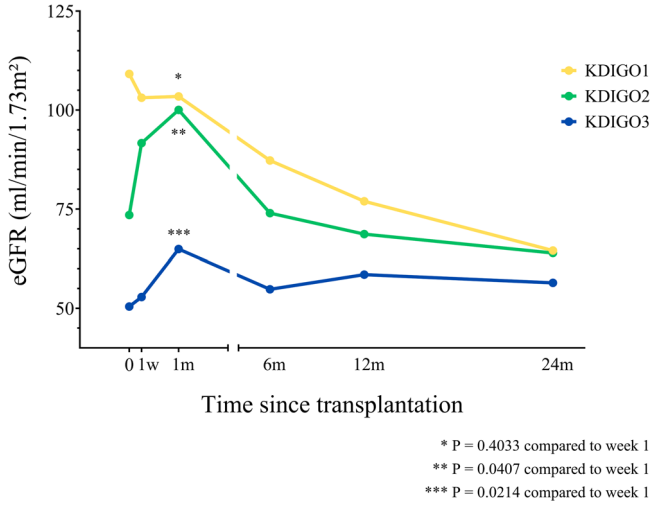

FIGURE 2 | Conditional predicted eGFR values in function of time, stratified according to baseline KDIGO classification. This graph shows a significant eGFR improvement after 1 month in patients with baseline renal impairment (KDIGO 2 and 3). *Note:* KDIGO stage 2: eGFR 60–89 mL/min/1.73 m²; KDIGO stage 3: eGFR 30–59 mL/min/1.73m². X-axis: 1w, 1 week after (H)LTX; 1m, 1 month; 6m, 6 months; 12m, 12 months; 24m, 24 months.

difference in the survival of patients with mild to moderate baseline renal impairment.

Few studies have reported the evolution of renal function after (H)LTX in PH patients [14, 22–25], and even less have reported on long-term evolution [26]. The current study found that renal function seems to improve shortly after (H)LTX with deterioration at 1 year after transplantation. This supports the hypothesis that renal insufficiency in PH is mediated by hemodynamic status. However, it is possible that muscle wasting in the postoperative hospitalization has partly affected this evolution, since lower creatinine levels may have resulted in an overestimation of eGFR [27]. However, the already short-term improvement observed in our study may suggest that the effect of muscle wasting plays only a minimal role.

Broekroeflofs et al. directly measured the GFR in a cohort of 57 patients during a 2- year follow-up after LTX in end-stage pulmonary hypertension, emphysema, or cystic fibrosis [26]. The GFR decline during the first month after transplantation was less pronounced in the eight patients with PH than in other groups of patients. The improvement of renal function after (H)LTX was not maintained during long-term follow-up. This is likely due to confounding factors gaining importance over time, such as the direct nephrotoxic effect of CNI and comorbidities such as diabetes or systemic arterial hypertension frequently observed after (H)LTX. Persistent higher tacrolimus dose requirements have been associated with the development of CNI nephrotoxicity in renal allografts [28] and early supratherapeutic tacrolimus concentrations with renal dysfunction in lung recipients [29]. Moreover, other interventions for severe PH, such as balloon pulmonary angioplasty in CTEPH, have demonstrated an improvement of renal function after treatment despite the use of nephrotoxic contrast agents [30, 31]. This also supports our findings that acute relief of cardio-renal dilemma may overcome perioperative damage of the kidney.

The association between diastolic pulmonary arterial pressure and 90-day mortality has been reported [32]. In our study, patients with the worst hemodynamic status as measured by invasive RHC measurements did not show a distinct improvement in renal function after transplantation. Accordingly,

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TABLE 3 | Association between baseline characteristics and renal dysfunction after 2 years.

Predictor	Univariate analysis *p* value	Multivariate analysis *p* value
Gender	0.41	
Age, years	**0.0001**	**0.001**
PH aetiology	0.87	
CI, L/min/m²	0.12	
mPAP, mmHg	0.23	
RAP, mmHg	0.52	
Prostacyclin treatment before transplantation	0.59	
Diabetes mellitus	0.43	
Baseline diuretics dose, mg	**0.04**	0.88
Transplant type, LTX vs. HLTX	0.85	
Need for ECLS after transplantation	0.76	
AKI within the first week	**0.001**	0.11
Tacrolimus dose, mg	**< 0.0001**	**< 0.0001**
PAH combination therapy	0.13	
Number of packed cell transfusions	0.74	

Note: Data were analysed using a logistic regression. Characteristics at a significance level of 10% according to univariate analysis were included in a multivariable analysis. Bold values indicate statistically significant.
Abbreviations: AKI, acute kidney injury; CI, cardiac index; ECLS, extracorporeal life support; HLTX, heart-lung transplantation; LTX, lung transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RAP, right atrial pressure.

TABLE 4 | Association between baseline characteristics and early and late renal replacement therapy.

	Early dialysis (≤ 3 months)				Late dialysis (> 3 months)	
	Univariate analysis		Multivariable analysis		Univariate analysis	
Predictor	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Gender, F vs. M	0.93 (0.35; 2.48)	0.88			3.79 (0.64; 22.33)	0.14
Age	1.13 (0.78; 1.65)	0.53			0.65 (0.34; 1.25)	0.20
PH aetiology, PAH vs. other	0.70 (0.23; 2.08)	0.43			1.59 (0.19; 13.34)	0.91
CI	0.64 (0.31; 1.31)	0.22			0.64 (0.18; 2.36)	0.51
mPAP	1.02 (0.99; 1.06)	0.22			1.01 (0.94; 1.08)	0.88
RAP	1.09 (1.00; 1.17)	0.04	0.99 (0.92; 1.07)	0.81	1.01 (0.86; 1.18)	0.93
Prostacyclins before TX	0.51 (0.19; 1.36)	0.18			1.79 (0.22; 14.90)	0.59
Diabetes mellitus	0.83 (0.11; 6.28)	0.86			1.63 (0.19; 13.59)	0.65
Diuretics dose	1.32 (1.13; 1.54)	**< 0.01**	1.55 (1.22; 1.98)	**< 0.01**	0.91 (0.66; 1.26)	0.56
Transplant type	0.92 (0.35; 2.46)	0.87			1.48 (0.33; 6.64)	0.61
Baseline eGFR[a]	0.97 (0.94; 0.99)	**0.02**	0.95 (0.91; 0.99)	**0.01**	1.04 (1.01; 1.07)	**< 0.001**
Postoperative ECLS use	5.64 (1.94; 16.39)	**< 0.01**	41.29 (8.09; 210.8)	**< 0.0001**	3.28 (0.37; 29.44)	0.29
AKI < 1 week	(not calculated)	0.99			1.98 (0.39; 10.03)	0.41
Tacrolimus dose	1.06 (0.91; 1.25)	0.45			0.82 (0.61; 1.12)	0.21
Packed cell transfusions	1.04 (1.00; 1.07)	**0.03**			0.94 (0.83; 1.06)	0.31

Note: Data were analysed using Cox regression. Characteristics at a significance level of 10% according to univariate analysis were included in a multivariable analysis. No multivariable analysis was applicable for late dialysis, considering only one predictor was significant. Bold values indicate statistically significant.
Abbreviations: AKI, acute kidney injury; CI, cardiac index; ECLS, extracorporeal life support; F, female; M, male; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RAP, right atrial pressure; TX, transplantation.
[a]Baseline renal impairment was associated with early dialysis, whereas increased renal function was associated with late dialysis.

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TABLE 5 | Association between the baseline characteristics and overall 1- and 2-year mortality.

	1 Year				2 Years			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Predictor	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
Gender, F vs. M	2.80 (0.78; 10.06)	0.11			2.89 (0.95; 8.82)	**0.06**	3.71 (0.65; 21.13)	0.14
Age	1.85 (1.07; 3.18)	**0.03**	3.16 (1.14; 8.77)	**0.03**	1.68 (1.06; 2.68)	**0.03**	1.37 (0.65; 2.90)	0.41
PH diagnosis	1.03 (0.10; 10.23)	0.50			0.73 (0.12; 4.58)	0.79		
CI	0.93 (0.49; 1.79)	0.84			0.78 (0.40; 1.51)	0.46		
mPAP	0.96 (0.92; 1.01)	0.13			0.94 (0.89; 0.99)	**0.01**	0.96 (0.90; 1.03)	0.30
RAP	1.03 (0.92; 1.14)	0.61			1.04 (0.95; 1.14)	0.43		
Baseline eGFR	0.97 (0.93; 1.01)	**0.09**	1.02 (0.96; 1.08)	0.49	0.98 (0.96; 1.01)	0.24		
Transplant type	0.89 (0.28; 2.90)	0.85			1.17 (0.41; 3.35)	0.77		
ICU before TX	1.33 (0.31; 5.77)	0.70			1.22 (0.32; 4.63)	0.77		
Postoperative ECLS use	3.34 (0.65; 17.11)	0.15			1.90 (0.38; 9.39)	0.43		
Length of ICU stay	1.03 (1.00; 1.06)	**0.04**	1.01 (0.97; 1.06)	0.54	1.02 (0.99; 1.05)	0.21		
RRT < 3 months	9.00 (2.34; 34.61)	**< 0.01**	23.80 (2.88; 196.8)	**< 0.01**	3.55 (1.08; 11.61)	**0.04**	17.34 (3.10; 97.16)	**0.001**

Note: Data were analysed using Cox regression. Characteristics at a significance level of 10% according to univariate analysis were included in a multivariable analysis. Bold values indicate statistically significant.
Abbreviations: CI, cardiac index; ECLS, extracorporeal life support; F, female; ICU, intensive care unit; M, male; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; RAP, right atrial pressure; RRT, renal replacement therapy; TX, transplantation.

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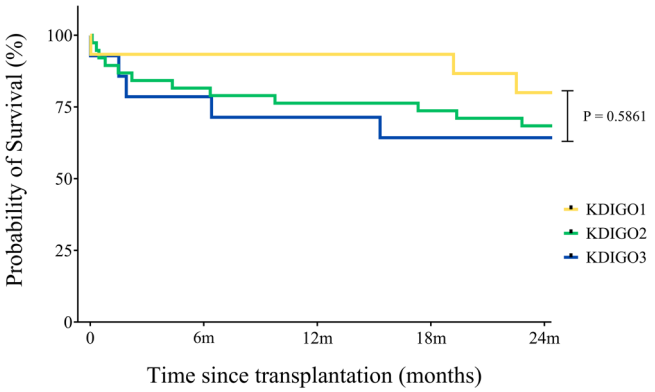

FIGURE 3 | Two-year survival curves in function of baseline renal function. This 2-year survival curve shows no significant survival disadvantage of patients with baseline renal impairment (KDIGO 2 and 3) compared with normal baseline renal function. *Note:* KDIGO 2: eGFR 60–89 mL/min/1.73 m²; KDIGO 3: eGFR 30–59 mL/min/1.73m².

reduced cardiac index (CI), higher mPAP, or increased RAP were not independently associated with worse renal outcomes. These findings are limited by the prolonged time between the last RHC and (H)LTX (median time 10 months), suggesting that the RHC results might not be representative of the hemodynamic situation at the time of transplantation.

Reduced baseline eGFR < 74 mL/min/1.73m² was only associated with short-term dialysis. There was no significant association with renal function decline, long-term dialysis, or mortality. An association between baseline eGFR and 90-day mortality was also not corroborated by Girgis et al. [32]. The decision to start RRT in the ICU setting is based on a combination of laboratory values (such as renal function, electrolytes, acidaemia) and clinical parameters (such as urine output, fluid balance). The exact timing of RRT is often influenced by clinical gestalt, and we cannot dismiss a lower threshold to start RRT in patients with severe PAH, notably to preclude fluid overload and increasing risk of primary graft dysfunction [33]. In addition, the need for short-term RRT in patients with moderate renal impairment may be nuanced if there is no increased risk of long-term RRT or mortality, which appear to be more crucial end points than short-term dialysis. Although baseline renal function < 74 mL/min/1.73m² was not associated with mortality, the need for RRT within 3 months after (H)LTX was, in accordance with previous reports [34–37]. The underlying pathophysiology is not clear; it is postulated that the RRT requirement is a substitute for severe critical illness. While short-term RRT was significantly associated with mortality, baseline renal impairment was associated with short-term RRT but not with mortality. Considering the small patient numbers, it is not excluded that there would be an association in a larger patient sample. However, considering the multivariate analyses and presence of other confounding factors, short-term RRT should not simply be considered as a surrogate endpoint for mortality.

Lastly, age seems to be a more significant predictor of poor outcomes than baseline eGFR. Older age was significantly associated with renal function decline after 1 and 2 years and with increased 1-year mortality. These findings corroborate previous analyses reporting worse survival in older patients undergoing LTX [16, 38].

Our study presents a couple of limitations. Firstly, the patient population was highly selected and rather small, as expected considering the limited indication for transplantation in PAH and CTEPH patients and the monocentric analysis. Secondly, the retrospective nature of the study does not allow analysis of causal relationships. Moving forward, these findings should be confirmed in a prospective study, preferably with larger patient numbers, in which it would also be interesting to look into the involvement of nephrotoxic medications. However, PAH being a rare disease and transplantation an option only in very selected patients, the possibility to make such a study remains implausible. Thirdly, no control population was included. Notably, there is no representative control population available because PAH patients are typically younger, have less comorbidities, have different pathophysiological processes and treatments influencing the renal function, and receive more frequently HLTX compared to other transplant candidates, such as COPD, interstitial lung disease or cystic fibrosis patients. Fourthly, there was no ideal substitute for renal function during RRT. Creatinine clearance calculation based on 24-h urine collection or registration of urine output were only available in a minority of patients. Lastly, the standard of care in transplantation is rapidly changing, impacting the outcome of patients who were transplanted over a period of almost 30 years.

4.1 | Conclusion

This retrospective study is the first to investigate the impact of baseline renal insufficiency on LTX outcomes, specifically in patients with PAH and CTEPH. There was no significant association between baseline renal insufficiency < 74 mL/min/1.73m² and long-term renal function decline, long-term dialysis, or increased mortality after (H)LTX. Renal function even improved shortly after transplantation, supporting the hypothesis that renal insufficiency in PAH and CTEPH is mainly mediated by the hemodynamic condition. Even though our patient cohort is limited in size, these findings suggest that moderate renal impairment may not be justifiable as an absolute contraindication for (H)LTX in PH patients due to the potential for recovery after transplantation. Pre-transplant renal function must be considered with other comorbidities and risk factors in the recipient selection process and regarding the severity of RV impairment.

Author Contributions

The study and protocol were designed by A.D., M.D., and L.G. A.D. and L.H. were responsible for data extraction and review. A.B. performed the statistical analyses and contributed to the methods section. The results were critically reviewed and interpreted by L.G., M.D., A.D., and L.H. The manuscript was co-authored by A.D. and L.H. R.Q., G.A., C.B., G.C., D.K., G.D.V., T.V., L.J.C., D.V.R., B.M.V., G.V., L.D. and R.V. contributed to the critical revision of the manuscript and approved the article for final submission.

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Ethics Statement

Ethical approval was obtained by the local Ethics Committee of University Hospitals Leuven (S64227).

Conflicts of Interest

L.H. and R.V. received funding from the Research Foundation—Flanders (FWO) for this study. The other authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Figure S1: Boxplot of eGFR values in function of time. **Figure S2:** Plot of predicted mean eGFR values in function of age. **Figure S3:** Plot of predicted mean eGFR values in function of presence of acute kidney injury. **Figure S4:** Plot of predicted mean eGFR values in function of tacrolimus dose. **Table S1:** Results from the Longitudinal Linear eGFR Model. **Table S2:** Estimated eGFR changes between week 1 and month 1 according to baseline eGFR. **Table S3:** Estimated eGFR changes between week 1 and month 1 according to baseline eGFR.

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