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# Postoperative Fluid Accumulation is Associated With Underestimation of AKI Severity in Lung Transplant Recipients

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## ABSTRACT

**Background:** Post-lung transplantation (LTx) fluid accumulation can lead to dilution of serum creatinine (SCr). We hypothesized that fluid accumulation might impact the diagnosis, staging, and outcome of posttransplant acute kidney injury (AKI).

**Methods:** In this retrospective study, we analyzed data from 131 adult LTx patients at a single German lung center between 2005 and 2018. We assessed the occurrence of AKI within 7 days posttransplant, both before and after SCr-adjustment for fluid balance (FB), and investigated its impact on all-cause mortality. Transient and persistent AKIs were defined as return to baseline kidney function or continuation of AKI beyond 72 h of onset, respectively.

**Results:** AKI was diagnosed in 58.8% of patients according to crude SCr values. When considering FB-adjusted SCr values, AKI severity was underestimated in 20.6% of patients, that is, AKI was detected in an additional 6.9% of patients and led to AKI upstaging in 23.4% of cases. Patients initially underestimated but detected with AKI only after FB adjustment had higher mortality compared to those who did not meet AKI criteria (hazard ratio [HR] 2.98; 95% confidence interval [CI] 1.06, 8.36; $p = 0.038$).

**Abbreviations:** ADQI, Acute Dialysis Quality Initiative; FB, fluid balance; KDIGO, Kidney Disease: Improving Global Outcomes; LAS, lung allocation score; LTx, lung transplantation; POD, postoperative day; RRT, renal replacement therapy; UKGM, University Hospital Giessen and Marburg; UO, urine output.

Matthias Hecker and Faeq Husain-Syed contributed equally to this study.

Persistent AKI was associated with higher mortality than transient AKI, regardless of using crude or adjusted SCr values ($p < 0.05$). Persistent AKI emerged as an independent risk factor for mortality (HR 2.35; 95% CI 1.29, 4.30; $p = 0.005$).
**Conclusion:** Adjusting for FB and evaluating renal recovery patterns post-AKI may enhance the sensitivity of AKI detection. This approach could help identify patients with poor prognosis and potentially improve outcomes in lung transplant recipients.
**Trial Registration:** ClinicalTrials.gov identifier: NCT03039959, NCT03046277.

## 1 | Introduction

Posttransplant acute kidney injury (AKI) affects up to two-thirds of patients undergoing lung transplantation (LTx) and has a substantial impact on postoperative survival, risk of chronic kidney disease (CKD), and long-term morbidity [1–5]. The risk factors for AKI are complex and include pretransplant kidney function, recipient demographics and comorbidities, perioperative hemodynamics, and exposure to nephrotoxic substances [4, 6]. Early recognition of AKI has been shown to improve chances of renal recovery in hospitalized patients [7].

AKI is diagnosed and staged according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI consensus criteria, which are based on absolute or relative changes in 7-day serum creatinine (SCr) concentrations or urine output (UO) [8]. However, fluid accumulation in the perioperative and intensive care unit (ICU) settings can lead to the dilution of SCr concentration and an overestimation of kidney function [9]. Hence, fluid accumulation may mask and/or delay the diagnosis of AKI or result in an underestimation of its severity [10, 11]. FB adjustment of SCr can overcome this limitation [11], but whether this leads to an improved recognition of LTx recipients at risk of adverse outcomes is unknown. Additionally, the duration of AKI is associated with adverse short- and long-term outcomes, but it is not included in the KDIGO criteria [12, 13]. Differentiation between persistent and transient (self-limiting) AKI might improve the identification of LTx patients at risk of poor outcomes, even among AKI cases of similar severity.

Although the dilutional effects of fluid accumulation on SCr have been consistently demonstrated [10, 11, 14, 15], no study has investigated whether FB-adjusted SCr improves the detection of AKI in patients undergoing LTx. Therefore, we aimed to evaluate whether FB-adjusted SCr impacts AKI classification after LTx and improves the identification of high-risk patients. In addition, we evaluated whether persistent AKI was associated with worse outcomes than transient AKI.

## 2 | Materials and Methods

### 2.1 | Study Design and Participants

This single-center, retrospective, cohort study included consecutive patients aged ≥18 years who underwent LTx from March 2005 to December 2018 and received aftercare at the outpatient pulmonary clinic of University Hospital Giessen and Marburg (UKGM), Giessen, Germany. Kidney function was monitored from prior to LTx to up to 365 days after LTx. All-cause mortality was monitored through December 2019. We excluded patients with missing kidney results required for AKI ascertainment (i.e., baseline SCr, and SCr and UO values for the first 7 days post-LTx) and those who died within 7 days after LTx. Patients without an indwelling urinary catheter for a minimum of 7 days were also excluded.

The study adheres to the principles of the Declaration of Helsinki and was approved by the research ethics committee Justus-Liebig-University Giessen (no. AZ 35/17). The need for informed consent was waived. The study is in compliance with the ISHLT ethics statement [16].

### 2.2 | Data Collection

Patient data and the most recent lung allocation score (LAS) were manually abstracted from medical records, de-identified and pseudoanonymized, and stored in a password-protected dataset. The highest creatinine values were used if multiple measurements were available. Patients were categorized into three groups based on the underlying end-stage lung disease, according to the national legislation for organ transplantation [17]. Lung function testing, diagnosis and classification of pulmonary hypertension, right heart catheterization, and 6-min walk distance were assessed [18–20]. For pretransplant screening, all patients aged ≥40 years underwent diagnostic coronary angiography, and data on coronary artery disease were extracted from their electronic medical records. Age was defined as the patient's age on the date of LTx. The most recent body weight prior to LTx was abstracted from medical records. Hypertension and diabetes mellitus diagnosis was abstracted from medical records, or defined by the use of anti-hypertensives or diabetic medications. Information about the use of potentially nephrotoxic medications (such as intravenous aminoglycosides, colistin, vancomycin, and iodinated contrast media) within 1 week prior to LTx, loop diuretics and thiazides, mechanical ventilation, and extracorporeal membrane oxygenation were collected. Vasopressor and inotropes use was defined as the cumulative dose of norepinephrine or epinephrine administered. The majority of patients underwent bilateral thoracotomy for LTx. The clamshell technique was avoided where possible and extracorporeal membrane oxygenation was restrictively utilized. Information about the surgical technique, perioperative and posttransplant parameters, immunosuppressive and antibiotic regimens, and laboratory methods are detailed in Supporting Information.

### 2.3 | Definition of Kidney Measures and Fluid Balance (FB)

AKI was defined as an increase in SCr by ≥0.3 mg/dL within 48 h or by ≥1.5 times the baseline within 7 days of LTx, or

UO < 0.5 mL/kg/h for 6 h [8]. In patients with multiple AKI episodes, the highest AKI stage was considered. AKI occurrence beyond 7 days was not considered. Baseline SCr was the mean SCr measured 7–365 days before LTx [21]. CKD was defined as eGFR values < 60 mL/min/1.73 $m^2$ for > 3 months pre-LTx [22]. Perioperative and posttransplant ICU clinical data for all patients were abstracted from the anesthesia and ICU documentation system (ICUData, IMESO-IT GmbH, Giessen, Germany), which remained consistent over the study period and facilitated automated FB documentation, encompassing hourly electronic charting of FB. Fluid output included urine, blood, loose stools, gastrointestinal fluids, and drainage from surgical drains, nasogastric tubes, and chest tubes, manually recorded by the ICU staff. Insensible fluid loss in the form of perspiration or evaporative water loss due to respiration was not routinely measured. Protocolized fluid management consisted of 0.9% saline, optionally with potassium supplementation. Synthetic colloids were not administered. As per standard protocol, all patients were retained in the ICU for a minimum of 7 days. Beyond this period, the necessity for ICU treatment was evaluated solely based on the requirement for mechanical ventilation and invasive hemodynamic monitoring. ICU FB data for Day 0–1 were grouped as Day 1, and data for the subsequent days were labeled as Days 2–7. Cumulative FB on Day 1 was calculated as the sum of the perioperative and ICU FB. Cumulative FB during the first 7 calendar days is referred to hereafter as cumulative FB at Day 7. The 7-day SCr values after LTx were adjusted to the daily FB values following the approach by Madeco et al. [11]. This adjustment assumes a total body water content of 60% of the patient's body weight before LTx:

$$\textbf{FB} - \textbf{adjusted SCr} = \text{crude SCr} \times \text{correction factor}$$

$$\text{Correction factor} = (\text{weight [kg] prior to LTx} \times 0.6 + \Sigma\,[\text{daily FB}\{\text{L}\}])/\text{weight prior to LTx} \times 0.6$$

The patients were categorized as (i) those not diagnosed with AKI before or after FB adjustment, (ii) those diagnosed with AKI only after FB adjustment, (iii) those diagnosed with AKI before, but not after FB adjustment, and (iv) those diagnosed with AKI both before and after FB adjustment.

AKI duration based on crude SCr was classified as transient (return to stage 0 AKI within 72 h from AKI onset, independent of AKI severity) or persistent AKI (continuation of AKI based on SCr or UO for ≥72 h from AKI onset, independent of AKI severity), as proposed by Hoste et al. [23]. Patients undergoing renal replacement therapy (RRT) within the first 7 days after surgery were classified as having persistent AKI. We conducted a sensitivity analysis to determine whether the association between AKI duration and mortality was affected when AKI was classified by FB-adjusted SCr. Furthermore, we evaluated whether the association between AKI duration and mortality differed when AKI was classified based on the Acute Dialysis Quality Initiative (ADQI) consensus definition (transient AKI, return to stage 0 AKI within 48 h from AKI onset; persistent AKI, continuation of AKI based on SCr or UO for ≥48 h from AKI onset) [24].

In a companion sensitivity analysis, we explored whether postoperative fluid overload defined as cumulative fluid accumulation > 10% of pre-LTx body weight was associated with mortality. We chose the 10% cut-off value as it has been consistently shown to be associated with adverse outcomes [25, 26]. Percentage of fluid overload was calculated as:

$$(\text{daily cumulative FB [L]}/\text{body weight [kg]}) * 100$$

RRT was initiated at the discretion of the attending physician (Supporting Information).

For longitudinal kidney function analyses, all available estimated glomerular filtration rate (eGFR) values (2009 CKD-epidemiology collaboration creatinine equation) [27] were obtained from the UKGM central laboratory records before and up to 365 days after LTx, with quarterly median values calculated.

We included a Strengthening the Reporting of Observational Studies in Epidemiology checklist for study quality (Table S1).

## 2.4 | Outcome Measures

SCr was measured directly after ICU admission and every morning thereafter, or if clinically indicated. Post-LTx UO was monitored via an indwelling urinary catheter. Outpatient follow-up was conducted through clinical visits and telephone interviews. SCr was monitored serially at least monthly in the first postoperative year and then every 1–3 months indefinitely thereafter, or as clinically indicated. For deaths outside the hospital, the general practitioner or family members were contacted by telephone to obtain details regarding the clinical course, date, and cause of death. The primary endpoint was all-cause mortality through December 2019. We secondarily investigated eGFR decline up to 1 year after LTx.

An adjudication committee comprising three expert nephrologists blinded to the clinical data reviewed the cases individually to confirm the baseline SCr, AKI diagnosis and staging, AKI duration, and eGFR decline. If two reviewers disagreed, the third reviewer provided their input and a consensus was reached.

## 2.5 | Statistical Analysis

Continuous baseline variables showed predominantly non-Gaussian distribution and were expressed as median (interquartile range [IQR]), whereas categorical variables were expressed as count (percentage). We compared these variables using Student's *t*-test and the Mann–Whitney *U* test or chi-square and Fisher exact tests for parametric and nonparametric continuous or categorical data, respectively. Mann–Whitney *U* test was used for comparison of characteristics in patients with and without underestimation of AKI severity. eGFR in the post-LTx phase was compared between patients with and without persistent or transient AKI using the Kruskal–Wallis test.

Univariate binary logistic regression analysis was performed to identify periprocedural, donor and recipient factors associated with the occurrence of AKI, AKI after FB correction, and duration of AKI. The goodness-of-fit for all independent variables was

assessed using the Hosmer–Lemeshow test, with a $p$-value > 0.05, indicating a good model fit. Variables with unclear relevance to the clinical endpoint were excluded from multivariate models, except in cases where a clear relationship was established. All variables demonstrating a significant association with the endpoint were included into a multivariate, stepwise, backward logistic regression model to identify independent predictors. Univariate Cox regression analysis was performed, encompassing relevant donor and recipient characteristics, along with perioperative parameters, to assess survival. Endpoints related to kidney function and covariates were selected for the inclusion in the multivariate model if the $p$-value in univariate analysis was below 0.05. Together with age and sex, these were included in a multivariate, stepwise, backward Cox regression model to identify independent predictors of mortality. In instances where variables showed multicollinearity ($R > 0.8$), the more reliable values were selected. Survival analyses were conducted using Kaplan–Meier plots (truncated at 200 months) and generalized Wilcoxon tests. Statistical significance was determined by $p$-values < 0.05. The distribution of crude AKI and AKI after FB correction across three different periods of the study duration was tested using the chi-square test. Missing data were treated as unavailable without replacement. All statistical analyses were performed using SPSS 28.0 (IBM Corp., Armonk, NY).

## 3 | Results

### 3.1 | Patient Characteristics and AKI Occurrence

Of the 156 patients undergoing LTx, 131 met the eligibility criteria. Twenty-two patients were excluded for missing critical values, 20 of those were from other LTx centers, and 2 patients who died within the first 7 days (Figure S1) (age: 58 [IQR, 50–62] years; males, 69 [52.7%]). End-stage interstitial lung disease, chronic obstructive pulmonary disease, and cystic fibrosis were the main indications for the LTx listing (LAS: 38 [IQR, 36–47]). The pretransplant eGFR was 107 (IQR, 80–137) mL/min/1.73 $m^2$. Pretransplant 24-h urinalysis data were available for 122 (93.1%) patients: the median creatinine clearance and proteinuria level were 95 (IQR, 72–125) mL/min and 84 (IQR, 50–152) mg/day, respectively (Table S2). Seven (5.3%) patients had mild CKD (baseline eGFR 49 [40–54] mL/min/1.73 $m^2$; creatinine clearance 62 [54–65] mL/min).

Post-LTx AKI occurred in 77 (58.8%) patients: 45 (34.4%) had stage 1 AKI; 32 (24.4%) had stage 2–3 AKI. About 9.1% (7/77) patients required RRT, accounting for 5.3% (7/131) of the entire cohort. The majority of AKI episodes (92.2%) was diagnosed within 48 h after LTx: 65 (84.4%) based on SCr values and 12 (15.6%) based on SCr and UO values. Throughout the study duration, the occurrence and severity of crude AKI and AKI after FB adjustment did not differ across three equal time periods (Figure S2). Multiple regression analysis showed that perioperative furosemide dose, mean FB, and serum sodium levels over postoperative days (POD) 1–7 were independent predictors of AKI (Table S3).

### 3.2 | Effects of Fluid Accumulation on SCr, AKI Diagnosis, and Mortality

The crude postoperative SCr and cumulative FB decreased from PODs 2–6 (Table 1). SCr values adjusted for FB were higher at each time point up to Day 6, which resulted in underestimation of SCr by 0.06 (range, −0.07 to 1.01) mg/dL on Day 2 to 0.001 (range, −0.20 to 0.77) on Day 6. Based on the FB-adjusted SCr levels, the total number of AKI cases increased by 6.9%, from 77 to 86 (Table S15): 9 patients were newly diagnosed with stage 1 AKI, whereas 18/77 patients were diagnosed with a higher AKI stage. Four of nine patients were diagnosed with new AKI at POD 1, whereas the remaining 5/9 patients were diagnosed at POD 2. In all 18/77 patients, the shift to the higher AKI stage occurred on the same day when the maximal AKI stage by crude SCr was determined. Twenty-seven patients (20.6%) in whom AKI severity was underestimated had higher perioperative FB and posttransplant FB on PODs 1 and 2, as well as a higher posttransplant cumulative FB on POD 7 (Table 2). None of the patients diagnosed with AKI based on crude SCr were downstaged after FB adjustment of SCr. Multiple regression analysis showed that the predictors of AKI based on FB-adjusted SCr were perioperative FB, cumulative furosemide dose during surgery, number of FFP units transfused, and mean POD 1–7 FB (Table S4).

During the follow-up period of 1597 days (592–2565), 56 (42.8%) of patients died (see Table S5 for the causes). The mortality rate of 9 of the 27 patients with newly diagnosed AKI after FB adjustment was higher than that in patients without AKI before or after FB adjustment (55.6% vs. 22.2%; $p = 0.012$) and similar to those with AKI both before and after FB adjustment (55.6% vs. 53.3%; $p = 0.55$; Figure 1). To ascertain the relationship between aspects of AKI and mortality, we utilized three different models for multivariate Cox regression analysis and confirmed the occurrence of AKI stages 2–3 (hazard ratio [HR] 3.35; 95% CI 1.64, 6.86; $p < 0.001$) and newly diagnosed AKI after FB adjustment (HR 2.98; 95% CI 1.06, 8.36; $p = 0.038$) as independent risk factors for mortality with varying covariates (Table S6 Models 2 and 3).

When examining fluid overload as a categorical variable, patients with fluid overload >10% at POD 2 had a higher crude mortality rate than those ≤10% (57.7% vs. 39.1%; $p = 0.027$; Figure S3). However, in multivariate Cox regression analysis, fluid overload at PODs 1–7 was not associated with increased mortality.

### 3.3 | Association of AKI Duration With Mortality

Among the 77 patients with AKI based on crude SCr, 42 (54.5%) and 35 (26.7%) were diagnosed with transient and persistent AKI, respectively. Patients with persistent AKI had a significantly higher probability of death than those with transient AKI (62.9% vs. 45.2%; $p = 0.049$) or those without AKI (62.9% vs. 27.8%; $p = 0.004$) (Figure S6). No difference in mortality rate was observed between the transient AKI and no-AKI group ($p = 0.37$). Patients who met both the SCr and UO criteria for AKI were more likely to have persistent AKI than those who met only the SCr criterion (Table S7). Furthermore, patients with persistent versus transient AKI were more likely to develop

**TABLE 1** | Daily postoperative FB and SCr (crude and FB-adjusted).

| | Post-LTx days | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** |
| **Cumulative FB (mL)**[a] | 3197 (1627–4850) | 3719 (1971–5740) | 2939 (368–5299) | 1736 (−697 to −4725) | 717 (−1536 to 3587) | 325 (−1870 to 2952) | 322 (−1959 to 2970) |
| **Crude SCr (mg/dL)** | 0.9 (0.7–1.1) | 0.9 (0.7–1.3) | 0.8 (0.6–1.4) | 0.8 (0.6–1.2) | 0.7 (0.6–1.1) | 0.7 (0.6–1.1) | 0.7 (0.5–0.9) |
| **FB-adjusted SCr (mg/dL)** | 1.0 (0.7–1.2) | 1.0 (0.7–1.5) | 0.9 (0.7–1.4) | 0.9 (0.6–1.3) | 0.8 (0.6–1.1) | 0.8 (0.6–1.1) | 0.7 (0.5–1.0) |
| **Absolute daily underestimation (mg/dL)**[b] | 0.06 (0.03–0.12) | 0.07 (0.03–0.18) | 0.05 (0.004–0.14) | 0.03 (−0.01 to 0.10) | 0.01 (−0.02 to 0.06) | 0.001 (−0.03 to 0.06) | 0.005 (−0.03 to 0.06) |
| **% Daily underestimation**[c] | 7.9 (3.8–12.5) | 9.1 (4.4–15.8) | 7.2 (0.6–13.7) | 4.3 (−1.3 to 11.3) | 2.1 (−3.5 to 9.8) | 0.2 (−4.5 to 8.6) | 0.1 (−4.5 to 8.1) |

*Note:* Values are presented as the median (interquartile range). SCr adjustment based on FB was performed as proposed by Macedo et al. [11]. To convert the SCr values to micromoles per liter, they need to be multiplied by 88.4.

Abbreviations: FB, fluid balance; ICU, intensive care unit; SCr, serum creatinine.

[a]Cumulative FB at Day 1 is the sum of the perioperative and posttransplant FB during ICU.

[b]Absolute daily underestimation = FB-adjusted SCr – crude SCr for the day.

[c]% Daily underestimation = ([FB-adjusted SCr – crude SCr for the day]/crude SCr for the day) * 100.

higher stages of AKI. Patients with persistent AKI were also more likely to have hypertension and coronary artery disease than those with transient AKI (Table S8). Cumulative survival curves stratified by AKI duration based on FB-adjusted SCr yielded similar results regarding persistent AKI. The main effect on outcome appeared to be the difference between transient and persistent AKI, with a higher probability of death among patients with transient AKI based on FB-adjusted SCr (Figure S4). AKI duration based on the ADQI consensus criteria did not modify the association between persistent AKI and mortality (Figure S5). In multivariate Cox regression analysis, persistent AKI was an independent risk factor for mortality (HR 2.35; 95% CI 1.29, 4.30; $p = 0.005$; Table S6 Model 3). Logistic regression analysis showed that coronary artery sclerosis, and mean POD 1–7 serum urea and uric acid levels were independent risk factors for persistent AKI (Table S16).

### 3.4 | Association of AKI Duration With eGFR Decline

Patients with AKI had significantly a higher eGFR decline in the first posttransplant year than those without AKI (Table S10). Significantly lower posttransplant eGFR values were observed in the persistent AKI than in the no-AKI group ($p < 0.05$), except in post-LTx 4–6 months (Figure 2 and Table S11). Posttransplant eGFR values did not differ between the persistent AKI and transient AKI group, except in post-LTx 1–3 months. No significant differences in posttransplant eGFR values or eGFR decline were observed between the transient AKI and the no-AKI group. Results were similar when examining eGFR decline relative to pretransplant values (Table S12). Results were unchanged when excluding patients with baseline CKD (Tables S13 and S14) and when AKI duration was classified by FB-adjusted SCr and the ADQI consensus criteria (results not shown). At 1 year post-LTx, CKD was present in 95/120 patients (79.1%).

## 4 | Discussion

In our study, we investigated whether FB adjustment of SCr values after LTx affects the diagnosis of AKI and enhances the identification of high-risk patients. Our results show that FB-adjusted SCr increased AKI sensitivity, resulting in a 6.9% increase in AKI prevalence and reclassification in 23.4% of LTx recipients. This highlights the potential risk of underdiagnosis and misclassification of AKI in this population. Given the strong association between AKI severity and morbidity and mortality, accurate post-LTx AKI classification is crucial for prognosis [28–30].

Furthermore, patients diagnosed with AKI only after FB adjustment had higher mortality rates than those without AKI (before and after FB adjustment). This aligns with previous studies in at-risk populations, where fluid accumulation was identified as a risk factor for increased AKI-associated mortality [10, 11, 14, 15, 31]. Fluid accumulation can lead to tissue edema, elevated renal interstitial pressure, and intrinsic renal compartment syndrome, ultimately impacting renal perfusion pressure and kidney function [32]. Established AKI, on the other hand, exacerbates fluid accumulation, electrolyte and acid–base disturbances, and cardiorenal syndrome, all negatively impacting survival. Notably, in regression analysis, AKI—rather than fluid accumulation—was identified as an independent risk factor for mortality. This suggests that fluid accumulation may primarily serve as an indicator of disease severity and underlying AKI.

Due to our study's retrospective design, we were unable to analyze the specific causes of fluid accumulation or explore all potential risk factors for AKI in our cohort. Although fluid accumulation may contribute to AKI, it is important to note that fluids are typically administered to address hypovolemia, which can harm the kidneys.

**TABLE 2** | Patient characteristics with and without underestimation of posttransplant AKI severity.

| | Underestimation of AKI severity ($n = 27$) | No underestimation of AKI severity ($n = 104$) | $p$-value |
|---|---|---|---|
| **Demographics** | | | |
| Age, years | 59 (54–62) | 58 (50–61) | 0.59 |
| Male, *n* (%) | 16 (59.3) | 46 (44.2) | 0.16 |
| Body mass index, kg/m$^2$ | 22.2 (19.2–26.0) | 24.8 (20.8–26.7) | 0.10 |
| **Comorbidities, *n* (%)** | | | |
| Underlying end-stage lung disease | | | 0.27 |
| *COPD* | 11 (40.7) | 26 (25.0) | |
| *Cystic fibrosis* | 3 (11.1) | 14 (13.5) | |
| *Lung fibrosis* | 13 (48.1) | 64 (61.5) | |
| Pulmonary hypertension | 9 (33.3) | 39 (37.5) | 0.69 |
| Hypertension | 9 (33.3) | 36 (34.6) | 0.90 |
| Diabetes mellitus | 3 (11.1) | 20 (19.2) | 0.32 |
| Coronary artery disease | 5 (17.9) | 12 (11.5) | 0.39 |
| **Pretransplant clinical data** | | | |
| Hospitalized before LTx, % | 14 (51.9) | 45 (43.3) | 0.42 |
| LAS[a] | 43.5 (31.8–42.3) | 37.1 (35–45.5) | 0.09 |
| Non-invasive ventilation, *n* (%) | 17 (63.0) | 59 (56.7) | 0.83 |
| Invasive ventilation, *n* (%) | 2 (7.4) | 10 (9.6) | |
| ECMO before transplantation, *n* (%) | 2 (7.4) | 5 (4.8) | 0.14 |
| Last mPAP, mm Hg | 27 (20–36) | 27 (23–35) | 0.69 |
| Last PAWP, mm Hg | 7 (5–14) | 8 (5–10) | 0.75 |
| **Pretransplant kidney function** | | | |
| Baseline SCr, mg/dL[b] | 0.6 (0.5–0.8) | 0.7 (0.5–0.9) | 0.10 |
| eGFR, mL/min/1.73 m$^2$ | 113 (99–151) | 106 (79–133) | **0.041** |
| Measured creatinine clearance, mL/min[c] | 98 (78–150) | 95 (70–122) | 0.13 |
| Proteinuria, mg/day[d] | 117 (80–189) | 86 (57–1178) | 0.32 |
| **Perioperative data** | | | |
| Single lung transplant, *n* (%) | 1 (3.7) | 8 (7.7) | 0.47 |
| Incision–suture time, min | 357 (327–429) | 337 (295–397) | 0.12 |
| Graft ischemic time, min | 360 (259–406) | 355 (270–390) | 0.96 |
| ECMO during surgery, *n* (%) | 8 (30.8) | 25 (24.0) | 0.60 |
| Duration of MAP < 60 mm Hg, min | 48 (15–85) | 33 (15–66) | 0.53 |
| IV furosemide dose during surgery, mg | 0 (0–10) | 0 (0–10) | 0.92 |
| Perioperative FB, mL | 2315 (1049–3718) | 1290 (650–2400) | **0.018** |
| Lowest hemoglobin, g/dL | 108 (96–116) | 110 (95–118) | 0.83 |
| Number of RBC units transfused, *n* (%) | 4 (2–8) | 3 (2–6) | 0.31 |
| **Posttransplant laboratory data** | | | |
| Day-1 crude SCr, mg/dL | 0.9 (0.6–1.0) | 0.9 (0.7–1.1) | 0.25 |
| Day-1 FB-corrected SCr, mg/dL | 1.0 (0.7–1.1) | 1.0 (0.7–1.2) | 0.66 |
| Day-2 crude SCr, mg/dL | 0.8 (0.7–1.2) | 0.9 (0.7–1.3) | 0.96 |
| Day-2 FB-corrected SCr, mg/dL | 1.0 (0.8–1.4) | 1.0 (0.7–1.5) | 0.49 |

(Continues)

**TABLE 2** | (Continued)

| | Underestimation of AKI severity ($n = 27$) | No underestimation of AKI severity ($n = 104$) | $p$-value |
|---|---|---|---|
| Day-1 FB, m[e] | 2690 (1590–3960) | 1570 (537–2620) | **0.003** |
| Day-2 FB, mL | 1475 (−251 to 2500) | 489 (−501 to 1412) | **0.040** |
| Cumulative FB at Day-7, mL | 1157 (−1126 to 5235) | −74 (−2243 to 2251) | **0.047** |
| Day-1 24-h UO, mL | 2800 (1490–3500) | 2495 (1725–3150) | 0.94 |
| Day-1 24-h UO, mL | 2470 (1958–3270) | 2820 (2077–3460) | 0.43 |
| Need for RRT in first 7 days, $n$ (%) | 0 (0) | 7 (6.7) | 0.15 |

*Note:* Values are the median (interquartile range) or $n$ (%). Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FB, fluid balance; IV, intravenous; LAS, lung allocation score; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RBC, red blood cells; RRT, renal replacement therapy; SCr, serum creatinine; UO, urine output.

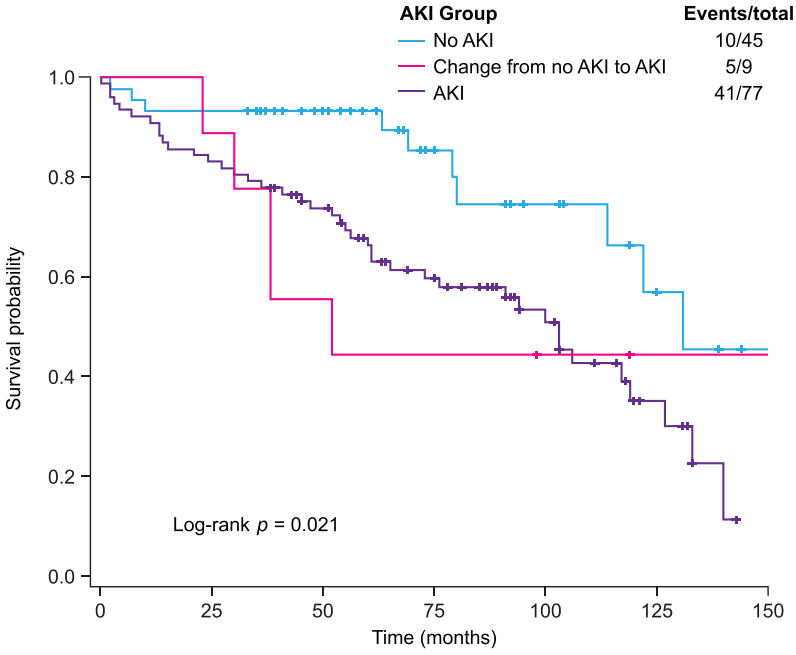
[a]LAS is a numerical value used by the United Network for Organ Sharing to assign relative priority for distributing donated lungs for transplantation and ranges from 0 to 1000, with a higher score indicating greater priority.

[b]Baseline SCr was the most recent SCr measured 7–365 days before LTx. To convert the values for SCr to μmol/L, multiply by 88.4.

[c]Creatinine clearance, derived from a 24-h urine collection, was available for 122 (93.1%) patients.

[d]Data on proteinuria, derived from a 24-h urine collection, was available for 112 (85.5%) patients.

[e]Posttransplant ICU FB on Day 1 without perioperative FB.




| Patients at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| No AKI (before and after FB adjustment) | 45 | 41 | 33 | 17 | 11 | 9 | 2 |
| New AKI diagnosis (after FB adjustment) | 9 | 7 | 5 | 4 | 2 | 1 | 1 |
| AKI (before and after FB adjustment) | 77 | 64 | 52 | 34 | 20 | 7 | 0 |

**FIGURE 1** | Kaplan–Meier estimate survival curves stratified by AKI status using crude and FB-adjusted SCr. The light blue, magenta, and lilac curves indicate the no AKI (according to both crude SCr and FB-adjusted SCr), newly diagnosed AKI (according to FB-adjusted SCr and crude SCr), and AKI (according to crude SCr and FB-adjusted SCr) groups, respectively. The log rank test was used to compute the $p$-values for the differences between groups according to AKI status. AKI, acute kidney injury; FB, fluid balance; SCr, serum creatinine.

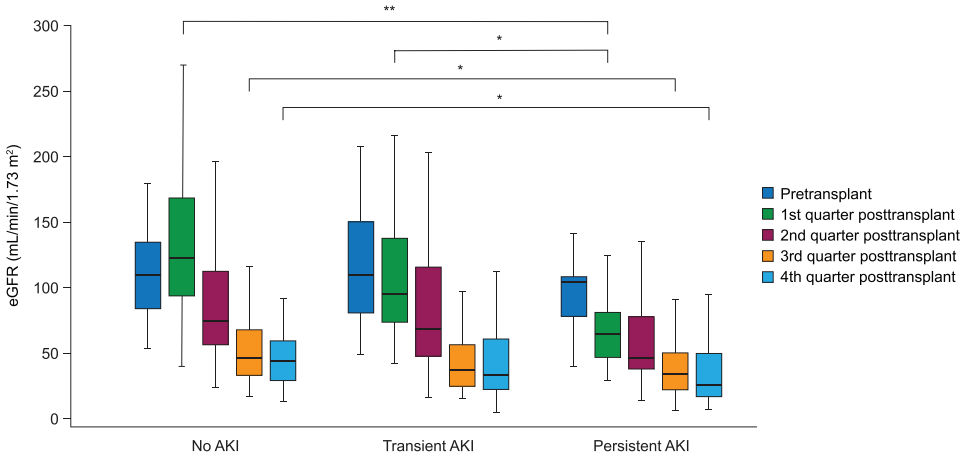



**FIGURE 2** | eGFR trajectory during the observational period stratified by AKI duration. The boxplots represent the pretransplant and quarterly posttransplant eGFR values up to 1 year after LTx stratified by AKI duration. No significant differences were observed between the transient AKI and no-AKI group at all time points. Definitions of transient AKI (i.e., return to stage 0 AKI within 72 h from AKI onset) and persistent AKI (i.e., continuation of AKI based on serum creatinine or urine output criteria for ≥72 h from AKI onset) were based on those proposed by Hoste et al. [23]. The boxes represent medians and interquartile ranges, and the whiskers represent the 1.5 interquartile range of the 25th quartile or 1.5 interquartile range of the 75th quartile. AKI diagnosis was based on the crude serum creatinine levels. eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation [27]. The numeric eGFR values are provided in Table S8. $*p < 0.05$ and $**p < 0.001$ for differences between the persistent AKI or transient AKI group versus the no-AKI group for any individual time point using the Kruskal–Wallis test. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; LTx, lung transplantation.

Hypovolemia during the perioperative period can stem from bleeding, volume loss, or surgical compression of major vessels/structures. Relative hypovolemia may also occur due to vasodilation and intravascular depletion triggered by surgical injury, mechanical circulatory support, new allograft, or sepsis, particularly during later stages of recovery. Moreover, perioperative ECMO, accounting for ~25% of our cohort, significantly contributes to fluid accumulation and poses an additional risk of injury.

The current AKI classification system lacks consideration for AKI duration, which is an important prognostic factor for kidney function recovery [33]. Therefore, another aim of this study was to compare the mortality rates of transient and persistent AKI. We found that patients with persistent AKI had a higher mortality rate than those without AKI. A recent meta-analysis demonstrated that AKI duration was independently associated with a higher risk of cardiovascular events and progression to CKD [34]. Additionally, among several distinct recovery phenotypes following stage 2 or 3 AKI, relapsing AKI and/or no recovery were associated with the highest risk for 1-year mortality (as high as 45%) [35]. Notably, in our work, the rate of persistent AKI did not change after SCr correction for FB and the main effect on outcome appeared to be the difference between transient and persistent AKI. Thus, though volume expansion may decrease SCr and delay AKI diagnosis, after a few days, the creatinine steady state is established with and without fluid loading [36]. Therefore, persistent AKI might appear regardless of FB correction and the clinical relevance of AKI detection by FB correction may mainly increase the diagnosis of transient AKI. Further investigation is needed to evaluate the role of FB-corrected SCr in the classification of AKI duration.

In our cohort, the pre-LTx prevalence of CKD aligned previous reports [37, 38]. However, compared to studies using measured GFR as gold standard, we observed a higher mean GFR decline (−63 vs. −48 mL/min/1.73 $m^2$) and greater CKD prevalence (79% vs. 66%) at 1 year posttransplant [38, 39]. These differences may stem from patient characteristics: for example, the patients in our cohort were older and had a higher number of comorbidities. The differences in GFR trajectories may also be explained by an overestimation of kidney function based on SCr due to pretransplant sarcopenia and subsequent muscle mass gain during rehabilitation post-LTx. Cystatin C assessment might have mitigated this limitation, as it is less affected by muscle mass than creatinine and thus provides an alternative approach to estimate GFR. However, corticosteroid use can increase cystatin C levels, potentially leading to an underestimation of GFR [40]. Regarding GFR trajectories, persistent AKI led to the greatest eGFR decline, independent of baseline CKD. Notably, however, substantial eGFR decline occurred even in patients without posttransplant AKI, suggesting that other mechanisms (e.g., recurrent AKI, calcineurin inhibitor nephrotoxicity, critical illness, and native kidney polyoma nephropathy) may also contribute to CKD progression [41, 42]. Furthermore, novel urinary biomarkers and kidney function tests, such as the evaluation of renal functional reserve, have been identified as potential tools to complement SCr in providing a more precise assessment of AKI trajectories and AKI–CKD transition [43, 44]. However, data in lung transplant recipients remain limited [45, 46]. Our study has several strengths. We present the first study investigating the association of post-LTx outcomes with FB, AKI diagnosis and staging, and AKI duration. We rigorously diagnosed AKI and obtained consistent results across different definitions of transient and persistent AKI. However, our study's limitations include its retrospective and single-center design, small sample

size, and inability to account for dosing changes in nephrotoxic medications and fluctuations in muscle mass, which could have affected kidney function trajectory. Additionally, we did not consider the impact of fluid types used for volume resuscitation on kidney function. Finally, true incidence of post-LTx CKD may have been miscalculated due to the reliance solely on serial eGFR measurements without considering albuminuria, as required by the KDIGO definitions [22]. Although we included reasonable risk factors for post-LTx AKI related to donors, recipients, and the perioperative period (many of which have been described previously [47–49]), this list remains incomplete due to the focus of our work.

## 5 | Conclusion

In this study, we found that FB adjustment improves the diagnostic accuracy of AKI in lung transplant recipients and confirmed that AKI severity and duration are related to postoperative morbidity and mortality. This has significant implications since timely recognition of AKI affects renal recovery and overall prognosis. Moreover, as FB adjustment is a noninvasive and relatively straightforward process, it would be easy to apply this in the clinical setting. Future investigations on larger cohorts should be conducted to determine whether optimized perioperative management based on FB adjustment leads to improved outcomes in LTx recipients.

### Author Contributions

Study concept and design: S.K., J.S., K.M., M.H., and F.H.-S. Literature research and clinical advice: S.K., J.S., H.G., M.M.W., M.W., S.E., M.S., M.R., C.K., I.A., A.H., W.P., M.O., R.M., C.R., H.-W.B., W.S., K.M., M.H., and F.H.-S. Acquisition, analysis, or interpretation of data: S.K., J.S., H.G., M.M.W., M.W., S.E., M.S., M.R., C.K., I.A., A.H., W.P., M.O., R.M., C.R., H.-W.B., W.S., K.M., M.H., and F.H.-S. Adjudication of kidney function: M.O., H.-W.B, and C.R. Drafting of the manuscript: S.K., J.S., M.H., and F.H.-S. Critical revision of the manuscript for important intellectual content: S.K., J.S., H.G., M.M.W., M.W., S.E., M.S., M.R., C.K., I.A., A.H., W.P., M.O., R.M., C.R., H.-W.B., W.S., K.M., M.H., and F.H.-S. Statistical analyses: S.K., H.G., and F.H.-S. Study supervision: S.K., K.M., and M.H. The authors shared the study design, data collection, data analysis, and data interpretation, as well as preparation, review, and approval of the manuscript. S.K. as the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. M.H. and F.H.-S. share the senior authorship of the work.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The authors have nothing to report.

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### Conflicts of Interest

Henning Gall has received personal fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, Pfizer, GossamerBio, all unrelated to this study. Martin Reichert was supported by the Justus-Liebig-University Giessen Clinician Scientist Program in Biomedical Research (JLU-CAREER) funded by the German Research Foundation (DFG No. GU405/14-1). Marlies Ostermann has received grants or contrasts from Fresenius Medical, Baxter, and Biomerieux, honoraria for lectures from Fresenius Medical, Baxter, Biomerieux, and Gilead, and is a member of Executive Committee of the Intensive Care Society UK, all unrelated to this study. Ravindra Mehta received research funding from the National Institute of Diabetes and Digestive and Kidney Diseases grant (R01DK131586), consulting fees from Baxter Inc, Renibus, Fresenius, Mallinckrodt, Alexion, and Rensym, and acts as an advisory board member for Guard, Novartis, Am Pharma, and Unicycive, and has stocks in Unicycive, all unrelated to this study. Claudio Ronco acts as an advisory board member for ASAHI, Baxter, GE, Jafron, and Medtronic and has received speaker fees from Astute, bioMérieux, B. Braun, CytoSorbents, ESTOR, FMC, and Toray, all unrelated to this study. Werner Seeger discloses personal consulting fees from United Therapeutics, Tiakis Biotech AG, Liquidia, Pieris Pharmaceuticals, Abivax, Pfitzer, Medspray BV, all unrelated to this study. Stefan Kuhnert received personal fees or lecture honoraria from AstraZeneca, GSK, Sanofi, and BerlinChemie, all unrelated to this study. Michael Sander has received grants from Edwards Lifesciences, Philipps Orion, Fisher & Peykel, Ratiopharm, Ferrer. Konstantin Mayer received honoraria for lectures from AstraZeneca, Abbott, Astellas, Baxter, Braun, BerlinChemie, Boehringer, Fresenius Kabi, GSK, MSD, Novartis, Nestle and Pfizer all unrelated to this study. Janine Sommerlad, Max M. Weder, Sebastian Eberle, Christian Koch, Michael Sander, Ingolf Askevold, Andreas Hecker, Winfried Padberg, Horst-Walter Birk, Matthias Hecker, and Faeq Husain-Syed have no competing interests.

### Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Supporting Information**

Additional supporting information can be found online in the Supporting Information section.