Original Article

Tacrolimus overdosing in lung transplant recipients: clinical manifestations and management

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Background: Tacrolimus is essential for preventing rejection after lung transplantation, but its narrow therapeutic index and interindividual variability increase the risk of overdose. Despite the frequency of overdose, the clinical impact of tacrolimus overdose remains poorly defined. This study aimed to systematically assess the frequency, severity, and clinical consequences of tacrolimus overdose in lung transplant recipients and to propose a structured management approach.

Methods: We conducted a retrospective single-center study involving 61 lung transplant recipients treated between January 2022 and December 2023. Tacrolimus overdose was defined as a trough level ≥15 µg/L, and classified as mild (15–<20 µg/L), moderate (20–<25 µg/L), or severe (≥25 µg/L). We analyzed clinical outcomes, renal function, and complications, with special attention to patients with cystic fibrosis (CF).

Results: Tacrolimus overdose occurred in 54 patients (88.5%), with a mean peak level of 22 µg/L (range, 10–39) at a median of 81 days post-transplant. Dose normalization required a mean of 11 days (range, 0–87). Acute kidney injury occurred in 37% of patients (odds ratio: 1.14, 95% confidence interval: 0.19–6.80; P>0.99) and was not statistically associated with overdose. None progressed to end-stage renal disease. All four CF patients experienced recurrent overdoses, including moderate and severe episodes. One patient developed posterior reversible encephalopathy syndrome. C-reactive protein levels were frequently elevated, while gastrointestinal and infectious complications were uncommon.

Conclusions: Tacrolimus overdose is common after lung transplantation. Although acute kidney injury was frequently observed, a statistically significant association could not be established in our cohort, particularly given the small sample size. CF patients appeared more vulnerable. Although severe complications are rare, they are clinically relevant. These findings underscore the importance of individualized monitoring and support a novel classification and management algorithm to guide prevention and treatment.

Keywords: Calcineurin inhibitors; immunosuppressive agents; therapeutic drug monitoring; acute kidney injury; neurotoxicity

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Introduction

Lung transplantation is a life-saving therapy for patients with end-stage lung disease. Advances in surgical techniques and immunosuppressive regimens have led to better outcomes over time. Among immunosuppressants, tacrolimus has become the preferred calcineurin inhibitor due to its superior efficacy in preventing chronic lung allograft dysfunction (CLAD), as shown in recent trials such as

ScanCLAD (1-3). However, the narrow therapeutic window and variable pharmacokinetics of tacrolimus complicate its clinical use. Supratherapeutic levels may lead to nephrotoxicity, neurotoxicity, and other complications, while subtherapeutic levels increase the risk of rejection. Factors such as drug interactions, gastrointestinal absorption, hematocrit changes, and genetic polymorphisms contribute to this variability, especially in the early post-transplant period. Although therapeutic drug monitoring is standard practice, there is no universally accepted definition of tacrolimus overdose, nor a structured protocol for its management in lung transplant recipients. The clinical consequences of overdose, including acute kidney injury and neurological complications, remain incompletely characterized. This study aims to systematically assess the frequency, severity, and outcomes of tacrolimus overdose in a real-world cohort of lung transplant recipients. We also propose a pragmatic severity classification and introduce a structured protocol for prevention and management. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-1253/rc).

Highlight box

Key findings

- Tacrolimus overdose (trough ≥15 µg/L) was observed in 88.5% of 61 lung transplant recipients; the mean peak was 22 µg/L, and normalization required 11 days on average. Acute kidney injury occurred in 37%, and one patient developed posterior reversible encephalopathy syndrome. All cystic fibrosis patients experienced recurrent, often moderate to severe overdoses.

What is known and what is new?

- Tacrolimus is the cornerstone calcineurin inhibitor after lung transplantation, but its narrow therapeutic index and large interindividual variability make patients vulnerable to both under- and overdosing. While nephrotoxicity and neurotoxicity are recognized complications, the real-world frequency and clinical consequences of tacrolimus overdose in lung transplant recipients have not been systematically assessed, and no standardized definition or management protocol exists. What is new?
- This study introduces a pragmatic three-tier classification of tacrolimus overdose (15–<20, 20–<25, and ≥25 µg/L), systematically evaluates its frequency and associated complications in a real-world lung transplant cohort, and proposes a structured management algorithm. The findings highlight that overdose is common, especially in cystic fibrosis recipients, and demonstrate that severe complications, although rare, require standardized preventive and therapeutic strategies.

What is the implication, and what should change now?

- Routine application of the grading system, paired with proactive dose adjustment, intensified renal and neurologic monitoring, and temporary calcineurin-inhibitor switching in severe cases, may curb toxicity without compromising rejection control. Cystic fibrosis patients warrant heightened surveillance. Prospective multicentre validation could harmonise tacrolimus management and improve long-term graft and patient survival.

Methods

We conducted a retrospective analysis on the medical records of 61 individuals who had undergone single or bilateral lung transplantation between January 2022 and December 2023 at the University Hospital Zurich in Zurich, Switzerland. The study population consisted solely of adults aged 18 years or older; all patients under 18 years were excluded. Tacrolimus was exclusively administered orally at 0.05 mg/kg BID in all patients; no intravenous formulations were used during the study period. Administration occurred 1 hour before or 2 hours after meals. Trough levels were measured daily post-transplant and then adjusted based on clinical stability.

The primary outcome was the frequency and severity of tacrolimus overdose episodes. Trough levels were measured daily during the first postoperative week, then every other day until stabilization, followed by weekly monitoring. Most overdoses occurred within the first three months post-transplantation. Tacrolimus overdose was defined as a level at least 2 µg/L above the highest point of the target range. The definition of overdose applied in this study is arbitrary and based on clinical judgment and institutional practice. While no universally accepted threshold exists, a cut-off of ≥15 µg/L was selected to enable systematic evaluation of supratherapeutic levels. Overdose severity was classified as mild for tacrolimus levels of 15–<20 µg/L, moderate for levels of 20–<25 µg/L, and severe for levels exceeding 25 µg/L.

Secondary outcomes included the effect of tacrolimus overdose on renal function, the frequency of other medical complications (gastrointestinal, neurological, etc.) and the time to normalization of the trough level after an overdose episode.

The preexisting relevant comorbidity was also documented, including pre-transplant chronic kidney disease (CKD), diabetes mellitus and arterial hypertension. Renal function was assessed through creatinine levels and estimated glomerular filtration rate (eGFR).

Given the distinct gastrointestinal absorption characteristics

Tacrolimus overdose severity grade	
Tacrolimus trough level (μg/L)	Overdose severity grade
15–<20	Mild
20–<25	Moderate
≥25	Severe

Monitoring in tacrolimus overdose
Signs and symptoms
Tremor, headache, nausea, emesis, electrocardiography (ECG) with corrected QT interval (QTc) prolongation, infections, urticaria, lethargy, posterior reversible encephalopathy syndrome (PRES)
Laboratory
Creatinine↑, estimated glomerular filtration rate (eGFR)↓, potassium↑, aspartate aminotransferase (AST)↑, alanine aminotransferase (ALT)↑, glucose↑, C-reactive protein (CRP)↑ in case of infection, in case of posterior reversible encephalopathy syndrome (PRES): exclude magnesium↓, calcium↑, cholesterol↑

Intervention when tacrolimus trough exceeds target by ≥2 μg/L
Treat as overdose if the trough exceeds the patient-specific upper target by ≥2 μg/L (even if absolute level <15 μg/L). Apply the severity grading once the absolute level is ≥15 μg/L. • Mild: reduce dose by 30–50%; check trough within 24–48 h. • Moderate: withhold 1–2 doses; resume at reduced dose once <15 μg/L; monitor renal function. • Severe: stop tacrolimus; daily neuro/renal checks; consider temporary switch to ciclosporin

Figure 1 Tacrolimus overdose severity grading and management cues.

in cystic fibrosis (CF) patients compared to those with other conditions requiring lung transplantation, we specifically examined tacrolimus overdose in CF versus non-CF patients. This differentiation allows for a more accurate assessment of tacrolimus overdose risk within these distinct groups. Patients with CF typically require higher tacrolimus doses to achieve therapeutic levels (4). Concurrent medications known to interact with tacrolimus, such as itraconazole, macrolides, statins, and proton pump inhibitors, were also documented. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the Canton of Zurich (Kantonale Ethikkommission Zürich, KEK-ZH) (No. 2024-00697). Written informed consent for the use of clinical data was obtained from all patients.

Tacrolimus overdose prevention and management protocol

Inconsistent tacrolimus dosing during the early post-transplant period remains a clinical challenge. Many centers rely on empirical dose titration, which leads to significant variability in drug exposure. This increases the risk of both acute cellular rejection due to subtherapeutic levels and toxicity when levels become excessive. While therapeutic drug monitoring is standard practice, a structured clinical response to tacrolimus overdose is lacking in most transplant programs.

To address this gap, we implemented a two-part clinical tool at our center in early 2023: (I) a severity grading system for tacrolimus overdose, and (II) a structured management algorithm that guides both prevention and intervention. The grading system is summarized in *Figure 1*.

Overdose severity classification

The tacrolimus overdose classification (mild, moderate, and severe) reflects institutional practice and serves to standardize the response to elevated levels. It should be emphasized that these thresholds are not based on prospective outcome data but are derived from pragmatic clinical use and internal consistency.

Prevention protocol

Preventive strategies focus on minimizing pharmacokinetic variability and include:

- Strict timing of tacrolimus administration in relation to meals (1 hour before or 2 hours after food).
- Avoidance or close monitoring of drug interactions (notably with itraconazole, macrolides, and proton pump inhibitors).
- Regular review of hematocrit levels and gastrointestinal symptoms, especially in the early postoperative period.
- Consistent and protocolized therapeutic drug monitoring, with daily trough levels during the first post-transplant week and stepwise extension thereafter.

Management protocol

In the event of overdose, management is adapted to severity:

- Mild overdose (15–<20 µg/L): Reduce tacrolimus dose by 30–50%, monitor trough levels daily or every other day. No additional interventions are usually required.
- Moderate overdose (20–<25 µg/L): Temporarily withhold 1–2 doses, resume at a reduced dose when trough level is <15 µg/L. Close renal function monitoring is recommended.
- Severe overdose (≥25 µg/L): Stop tacrolimus immediately. Initiate close clinical observation, including daily neurologic examination and renal function tests. Consider temporary conversion to cyclosporine in cases of persistent toxicity or significant symptoms (e.g., neurotoxicity, AKI). In rare cases, activated charcoal or hemoadsorption may be considered in consultation with toxicology.

Since its implementation in early 2023, this protocol has been applied to all lung transplant recipients at our center. While no formal statistical comparison was performed, a numerical decrease in the incidence of overdose has been observed. Prospective validation is planned.

Statistical analysis

Categorical variables were summarized as counts and percentages. Between-group comparisons (tacrolimus overdose *vs.* no overdose) were performed using Fisher's exact test, with two-sided P values <0.05 considered statistically significant. Because of the retrospective and exploratory design, no formal sample-size calculation was undertaken, and no multivariable, subgroup, or sensitivity analyses were performed. No missing data occurred; therefore, no imputation was required. In an exploratory post hoc analysis, we estimated the odds ratio (with exact 95% confidence interval) for acute kidney injury comparing patients with at least one overdose episode versus none; the P value for this comparison was obtained from Fisher's exact test.

Results

Table 1 summarizes the baseline demographic and clinical characteristics of the 61 lung transplant recipients included in the study. Tacrolimus overdose occurred in almost 90% of patients, with all cases deemed unintentional and without any signs of suicidal intent (standardly assessed in such contexts). Tacrolimus overdose typically occurred during the early postoperative phase, with a median onset at 81 days post-transplantation. The cohort showed a male predominance, with a male-to-female ratio of nearly 2:1. Nearly all patients received maintenance therapy with itraconazole and proton pump inhibitors, and a subset was additionally treated with macrolides (azithromycin) for their immunomodulatory properties.

Among the 61 transplant recipients, four patients (7%) had CF, and all experienced at least one episode of tacrolimus overdose. One CF patient had six episodes (four mild, one moderate, one severe), another had four (one mild, two moderate, one severe), one had three mild episodes, and one had a single mild episode. Tacrolimus overdose was a frequent occurrence in the cohort, typically presenting within the first three months after transplantation. Most episodes were mild, though moderate and severe cases also occurred. On average, normalization of tacrolimus levels required just over a week. Normalization was defined as the return of tacrolimus trough levels to the institutional target range. The observed variation in duration reflects differences in comorbidities, metabolism, and concurrent medication use. Full details are provided in *Table 2*.

Renal complications were common, with acute kidney injury occurring in over a third of patients. While CKD was less frequent, no patients progressed to end-stage renal disease. Other complications, such as hyperkalemia, gastrointestinal symptoms, neurological issues, and C-reactive protein (CRP) elevation, were observed sporadically. A detailed summary is presented in *Table 3*.

Table 1 Patient demographics

Characteristics	LTR without tacrolimus overdose	LTR with tacrolimus overdose
Demographic characteristics		
Number of patients	7 (11.5)	54 (88.5)
Age (years)	55.9±10.8	57.1±9.7
Sex (female)	2 (28.6)	20 (37)
Type of transplant (bilateral *vs.* single)	5 (71.4)	50 (92.6)
Body mass index (kg/m^2)	25.7±3.7	21.8±3.8
Clinical characteristics		
Underlying disease (non-CF *vs.* CF)	7 (100)	50 (92.6)
Preexistent CKD	1 (14.3)	2 (3.7)
Pre-transplant eGFR, mL/min per 1.73 m^2	95.9±19.2	102.5±15.9
Preexistent DM	1 (14.3)	4 (7.4)
Preexistent AHT	3 (42.9)	11 (20.4)
Treatment-related characteristics: comedication		
PPI	7 (100.0)	52 (96.3)
Itraconazole	6 (85.7)	54 (100.0)
Macrolide	0	7 (13)

Data are presented as n (%) or mean ± standard deviation. AHT, arterial hypertension; CF, cystic fibrosis; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LTR, lung transplant recipient; PPI, proton pump inhibitor.

Table 2 Frequency and severity of tacrolimus overdose episodes

Measure	Value
Incidence of overdose episodes among LTR	88.5%
Total number of overdose episodes	183
Severity of overdose, n (%)	
Mild	124 (67.8)
Moderate	31 (16.9)
Severe	28 (15.3)
Duration to normalization (days), mean ± SD	10.6±17.0

LTR, lung transplant recipients; SD, standard deviation.

Gastrointestinal symptoms, including nausea, vomiting, or diarrhea, were reported in 13% of patients with tacrolimus overdose but were absent in the non-overdose group. A single case of posterior reversible encephalopathy syndrome (PRES) was identified in one patient (2%), who presented with new-onset, right-sided visual disturbances. Ophthalmological evaluation confirmed visual impairment without an identifiable cause, and intraocular pressure was normal. Neurological assessment revealed impaired coordination, and magnetic resonance imaging (MRI) findings were consistent with PRES. The patient also exhibited uncontrolled, non-dipping hypertension. Two tacrolimus trough levels were elevated at 26.8 and 32.5 µg/L in the days preceding PRES, following a recent switch from cyclosporine in this patient, suggesting calcineurin inhibitor toxicity as the likely trigger. Tacrolimus was subsequently replaced with cyclosporine, and the patient underwent neurological rehabilitation with close monitoring and recovery was protracted over several months.

Discussion

This study examined the frequency and clinical implications of tacrolimus overdose in lung transplant recipients, highlighting several key findings.

Unintentional overdose was common, occurring in 88.5% of patients (*Table 1*). Overdoses were most often mild, though moderate and severe cases were also

Table 3 Effect of tacrolimus overdose on renal function and other medical complications

Measure	Non-overdose group (n=7)	Overdose group (n=54)	P value
Acute kidney injury	2 (28.6%)	20 (37%)	>0.99
hyperkalemia	2 (28.6%)	5 (9.3%)	0.18
PRES	0	1 (1.9%)	>0.99
Gastrointestinal symptoms	0	7 (13%)	0.59
Elevated CRP	5 (71.4%)	34 (63%)	>0.99

P values are two-sided and derived from Fisher's exact test. CRP, C-reactive protein; PRES, posterior reversible encephalopathy syndrome.

frequent enough to warrant concern. Given the absence of a standardized definition for tacrolimus overdose in the literature, the threshold used in this study reflects a pragmatic, institution-specific approach. While this enabled internal consistency, it may affect the generalizability of our findings. Notably, all patients with CF experienced one or more overdose episodes (*Table 2*), and male patients predominated in the affected group.

Renal complications

Although tacrolimus overdose and AKI frequently co-occurred, our analysis did not demonstrate a statistically significant association. These findings suggest a potential link, but should be interpreted with caution due to the limited sample size. This reflects findings from previous studies, where up to 50% of tacrolimus-treated patients developed nephrotoxicity. AKI is a known complication post-lung transplantation, and when persistent, can progress to CKD, contributing poorer long-term outcomes (5). Elevated tacrolimus trough levels have been linked to early AKI development (5), though additional factors—such as circulatory shock, systemic inflammation, and concurrent nephrotoxic drugs—also play a role. Recovery from AKI in this setting is often limited (5). Therefore, close monitoring and careful dose adjustments are essential, particularly in the early post-transplant period (5). Determining the exact contribution of tacrolimus to renal dysfunction can be complex, given the presence of other nephrotoxic agents (e.g., co-trimoxazole, valganciclovir) and comorbidities like diabetes (6).

CRP elevation and infection risk

CRP elevations were observed in both groups (71.4% in non-overdose *vs.* 63% in overdose group). Our data do not support a causal link between inflammation and tacrolimus overdose. Although tacrolimus levels may affect the risk of infection and rejection, these outcomes were not systematically assessed in this study. Prospective studies are needed to clarify these associations. Tacrolimus primarily suppresses cell-mediated immunity but can also impair humoral responses to a lesser extent. Non-infectious inflammatory reactions in the context of tacrolimus overdose have not been reported in the literature to date.

Studies have linked plasma tacrolimus levels to an increased risk of peripheral leukopenia (7) and identified hypogammaglobulinemia as a frequent finding in transplant recipients (8-11). However, the exact relationship between these immunological changes and susceptibility to inflammation or infection remains debated (12). In our cohort, although nephrotoxicity and elevated CRP were observed in a notable number of patients with tacrolimus overdose, these associations did not reach statistical significance—likely due to the limited sample size. As such, while our findings suggest a potential link between tacrolimus toxicity and these complications, larger studies are needed to validate and better define their clinical relevance and underlying mechanisms.

Neurological manifestations

Though uncommon, neurotoxicity remains a serious complication of tacrolimus overdose. It can occur even with tacrolimus trough levels in the therapeutic range, but severe manifestations are more often linked to elevated brain concentrations of tacrolimus. Tacrolimus inhibits p-glycoprotein expression in brain endothelial cells, compromising the blood-brain barrier and promoting vasogenic edema (13,14). Animal studies support a

correlation between tacrolimus brain concentration and symptom severity (15). Neurotoxic effects are more frequent in lung transplant recipients than in renal transplant recipients and are often associated with sustained levels above 15 µg/L (14,16).

PRES, first described in 1996 (17), is a rare but recognized complication of tacrolimus or ciclosporin therapy. While high tacrolimus levels are commonly implicated, other factors such as hypomagnesemia, hypercalcemia, hypercholesterolemia, renal failure, hypertension and sepsis may also contribute (18).

PRES presents with nonspecific symptoms such as headache, visual disturbances (in 39%), seizures (in up to 87%), and encephalopathy ranging from lethargy to coma (19).

Focal deficits, such as aphasia or hemiparesis, are reported in 19% of cases (18).

MRI is the preferred diagnostic modality due to superior sensitivity, though CT can also be diagnostic (18). While rare, PRES has been reported following intravenous immunoglobulin therapy and cytotoxic drugs (20,21). Accurate diagnosis requires clinical suspicion and the exclusion of alternative causes of acute neurological symptoms. Encephalopathy is typically defined as a disturbance of attention and orientation lasting ≥24 hours or causing significant clinical impact, excluding delayed awakening from anesthesia (22). In rare cases, PRES is lethal, so prompt therapeutic measures are mandatory. Given the potentially serious complications of tacrolimus toxicity, including neurotoxicity such as PRES, a structured protocol was introduced at our center to guide prevention and management. This protocol has been in routine use since early 2023 and is described in detail in the Methods section. The majority of patients in this cohort (92%) were transplanted before its implementation (23). While prospective validation is pending, initial experience suggests it may help reduce complication rates.

Study limitations

This study is limited by its retrospective design and relatively small cohort, which may reduce statistical power. Additionally, we did not assess genetic polymorphisms (e.g., *CYP3A5* variants), which are known to influence tacrolimus metabolism and could provide further insights into interindividual variability. Another limitation is that the proposed management protocol for tacrolimus overdose has not been prospectively validated, and its clinical application requires further investigation in larger, independent cohorts.

Future prospective studies with larger cohorts are needed to allow for more robust statistical modeling, including adjusted risk estimates and effect size interpretation with confidence intervals. Although suggestive of a mild increase in risk, the wide confidence interval and nonsignificant P value reflect the limited statistical power of this retrospective cohort. As such, these findings should be interpreted cautiously and warrant validation in larger, prospective studies using adjusted models.

Conclusions

Tacrolimus overdose is a frequent occurrence after lung transplantation, typically within the first three postoperative months. While acute kidney injury and neurotoxicity were observed, severe complications remain uncommon. Our findings underscore the need for vigilant monitoring, individualized dosing, and a structured management approach. Prospective multicenter studies are warranted to validate the proposed classification and protocol.

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Footnote

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conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the Canton of Zurich (Kantonale Ethikkommission Zürich, KEK-ZH) (No. 2024-00697). Written informed consent for use of clinical data was obtained from all patients.

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