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Early Tacrolimus Overexposure and Renal Allograft Outcomes in Kidney Transplant Recipients: A Single-Center Retrospective Study with Development of a Predictive Risk Model

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ABSTRACT

To investigate the link between early excessive tacrolimus blood levels (trough concentration surpassing 20 ng/mL within the first week after surgery) and long-term graft performance in renal transplant patients, and to build a risk estimation algorithm for identifying individuals prone to such early supratherapeutic concentrations. This investigation was designed as a single-center, retrospective cohort analysis encompassing 210 kidney graft recipients (105 overexposed, 105 unexposed) after propensity score matching. Renal functional metrics (eGFR and cystatin C) and rates of infectious complications over the 12-month follow-up were evaluated using linear mixed-effects modeling, with multiple imputation. A Cox proportional hazards regression employing LASSO-based predictor selection was constructed to estimate the probability of developing early supratherapeutic levels. Recipients in the overexposed category displayed significantly poorer eGFR at postoperative days 7, 30, and 90 (adjusted mean differences: −11.32, −10.20, and −10.75 mL/min/1.73 m², respectively) and correspondingly higher cystatin C values (0.83, 0.36, and 0.36 mg/L). By the conclusion of the first year, eGFR continued to be reduced (−7.54 mL/min/1.73 m², P = 0.038) while cystatin C remained elevated (0.40 mg/L, P = 0.043) in this group. The cumulative incidence of infections at one year was substantially higher among overexposed individuals (80.0% vs 52.3%; adjusted OR = 4.27, P < 0.001). The derived predictive tool highlighted three dominant risk factors: carrying the CYP3A5 *3/*3 genotype (HR = 2.19), a raised C-reactive protein on the first postoperative day (HR = 1.27), and an increased weight-adjusted tacrolimus dose (HR = 1.58), yielding a C-index of 0.716 and an optimism-corrected C-index of 0.728. Early tacrolimus levels in the supratherapeutic range are independently associated with worse graft functional recovery and a greater burden of infectious events during the initial year post-transplantation. A prediction instrument incorporating genotypic, inflammatory biomarker, and dosing data holds promise for enabling the timely identification of high-risk recipients.

Keywords: Therapeutic drug monitoring, Pharmacogenomics, Predictive model, Early exposure, Risk prediction

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Introduction

In kidney transplantation, calcineurin inhibitors are a fundamental component of maintenance immunosuppressive therapy, with tacrolimus (TAC) and mycophenolate commonly used as primary agents [1]. Data from the 2021 US Annual Data Report on kidney transplantation indicate that more than 90% of recipients are managed with TAC- and mycophenolate-based regimens [2]. Although the optimal approach to tacrolimus level management remains controversial, the majority of published studies [1, 3–5]. favor the maintenance of relatively higher exposure. In line with this evidence, current clinical guidelines [6] recommend higher tacrolimus trough

concentrations (C0) during the early post-transplant period to improve immunosuppressive effectiveness. This strategy has been further supported and refined by recent international consensus statements and review articles [7, 8].

Nevertheless, due to marked interindividual variability in tacrolimus metabolism, trough concentrations often exceed the recommended upper therapeutic range during the early post-transplantation period [9].

A tacrolimus trough concentration (C0) of approximately 15 ng/mL is generally regarded as the threshold at which toxicity begins to emerge. In contrast, values above 20 ng/mL are associated with a substantially increased risk of nephrotoxicity [10]. Despite this, international consensus guidelines still consider target C0 levels of up to 20 ng/mL acceptable during the early months following transplantation [7]. In parallel, Chinese clinical guidelines [11, 12]. Recommend maintaining tacrolimus concentrations within the range of 8–15 ng/mL in the immediate postoperative period, often guided by a "higher is safer" strategy aimed at reducing rejection risk.

Based on long-term institutional experience demonstrating a notable rise in adverse outcomes when C0 exceeds 20 ng/mL, the present study defines this level as the threshold for "high-risk exposure." Real-world evidence in kidney transplant populations [13–17] further indicates that a proportion of patients achieve tacrolimus concentrations close to or exceeding 20 ng/mL shortly after transplantation, which contrasts with conventional early therapeutic targets such as 8–12 ng/mL during the first three months [18].

These observations highlight the ongoing clinical dilemma of achieving adequate immunosuppression while avoiding tacrolimus-induced nephrotoxicity. However, the exact effect of early high-level exposure on graft outcomes remains uncertain. Whether it enhances recovery through stronger immunosuppressive control or contributes to functional deterioration through direct toxicity remains unclear and requires further investigation.

This study, conducted as a single-center retrospective cohort analysis, investigates how exposure to elevated tacrolimus concentrations in the early post-transplant period (defined as C0 > 20 ng/mL) influences kidney graft function, hematologic and metabolic profiles, and the occurrence of infections. Alongside outcome assessment, the study also focuses on constructing a model capable of identifying individuals at risk of developing early supratherapeutic tacrolimus levels. The results are expected to support the development of more individualized dosing strategies, with the ultimate goal of enhancing therapeutic safety and improving long-term transplant outcomes.

Materials and Methods

Study design

A single-center retrospective cohort design was used to examine the relationship between early tacrolimus exposure and post-transplant outcomes in kidney recipients. Patients were categorized according to early drug exposure during the first 7 days after transplantation. The exposure group included individuals with at least one tacrolimus trough concentration ≥ 20 ng/mL during this period, while the comparison group consisted of patients with trough levels consistently below this threshold.

The study population comprised adult kidney transplant recipients who underwent surgery between January 2019 and June 2023 and were identified through institutional records. Ethical approval was granted by the Ethics Committee of the First Clinical Medical College of Southern Medical University (NFEC 2024-390). As the analysis relied exclusively on pre-existing clinical data, involved no intervention, and posed minimal risk, the committee waived the requirement for informed consent. All data were anonymized before analysis to ensure confidentiality and patient privacy throughout the study process.

All grafts originated from voluntary deceased donors, with documented written consent obtained in accordance with applicable national regulations and the Declaration of Istanbul. To address potential confounding arising from baseline differences between groups, propensity score matching was performed before the outcome analysis. The selection and matching process is summarized in **Figure 1**. Following matching, the final dataset included 105 patients per group, yielding a total cohort of 210 kidney transplant recipients.

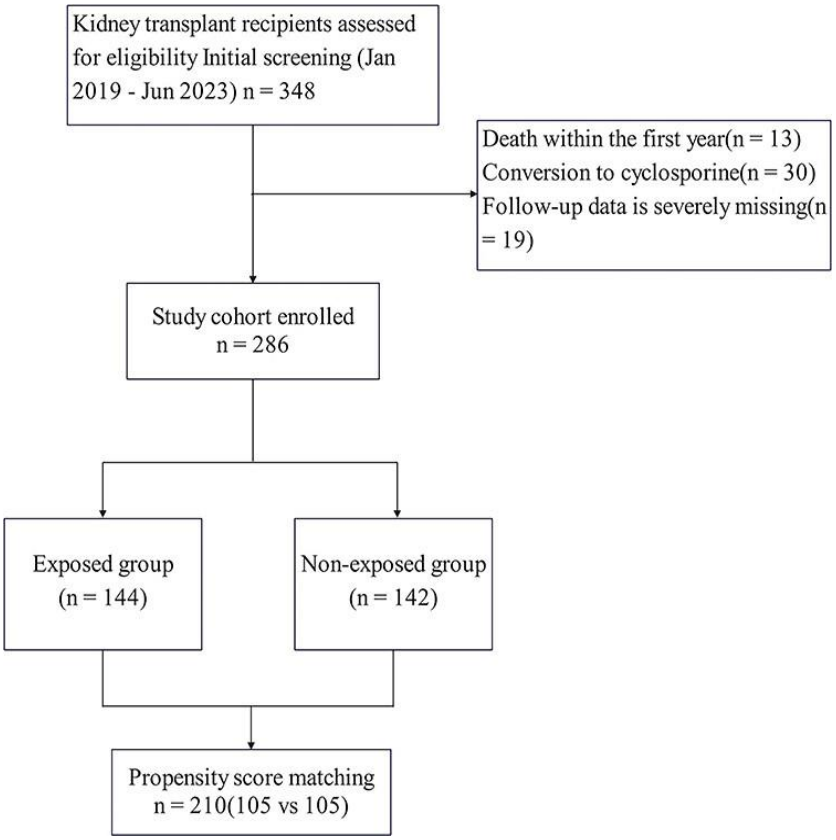

Figure 1. Study flow diagram.

Patient selection

Patient data were retrieved from the hospital's electronic medical records. The study population consisted of adult recipients undergoing their first kidney transplantation who were maintained on a tacrolimus-based immunosuppressive protocol throughout the initial post-transplant year, in combination with mycophenolate (MMF or MPS) and corticosteroids.

Individuals were excluded if their immunosuppressive regimen was changed immediately after surgery to cyclosporine or sirolimus, if they died within one year due to acute rejection or an unclear cause, or if their records lacked complete clinical information or essential laboratory follow-up data.

Cohort construction

Among all kidney transplants performed between January 2019 and June 2023, 286 patients met eligibility criteria and were included in the initial study population. This pre-matching cohort consisted of 144 individuals in the early high-tacrolimus exposure group and 142 in the non-exposed group and was subsequently used for propensity score-matching analysis.

Immunosuppressive regimen

Immunosuppressive induction followed a uniform protocol for all transplant recipients. At the time of surgery, patients received an intravenous dose of basiliximab (20 mg), which was repeated on postoperative day 4.

Corticosteroid induction was administered in a tapering intravenous regimen beginning with 1 g methylprednisolone on day 1, followed by 500 mg on day 2 and 250 mg on days 3 and 4. After transition to oral therapy on the first postoperative day, methylprednisolone was started at 20 mg/day and progressively reduced until a maintenance dose of 4 mg/day was achieved.

In selected cases requiring intensified immunosuppression, rabbit anti-thymocyte globulin (50 mg/day) was initiated during the early postoperative period (days 1–3), as determined by individual clinical assessment.

Maintenance immunosuppressive treatment began on the first day after surgery. Patients received tacrolimus orally in two divided doses, with a total daily amount ranging from 0.05 to 0.15 mg/kg. In parallel, enteric-coated mycophenolate sodium was prescribed at 0.5–0.75 g twice per day. Low-dose corticosteroids were also included

in the regimen, with either methylprednisolone (4–8 mg daily) or prednisone (5–10 mg daily), at the clinician's preference.

Infection prophylaxis

Standard postoperative antibacterial prophylaxis was administered to all recipients, using agents such as cefoperazone–sulbactam, meropenem, or linezolid, as indicated clinically. Prevention of opportunistic infections, including cytomegalovirus (CMV) disease and Pneumocystis jirovecii pneumonia (PJP), was achieved with oral valganciclovir, initiated within the first 10 days after transplantation and maintained for 3–6 months. In addition, trimethoprim–sulfamethoxazole (TMP–SMX) was routinely prescribed as prophylaxis for 6–12 months postoperatively.

Therapeutic drug monitoring and genotyping

Tacrolimus trough concentrations (C0) in whole blood were assessed once steady-state conditions were reached. For each measurement, 1.0 mL of venous blood was collected into EDTA-containing tubes immediately before the morning dose. Drug levels were determined using an enzyme-linked immunosorbent assay (ELISA) on a Siemens Syva Emit 2000 analyzer, following calibration and quality control procedures provided by Siemens Healthcare Diagnostics (Shanghai).

During the early postoperative hospitalization period, tacrolimus C0 was routinely monitored three times per week. Testing frequency was increased when concentrations exceeded 20 ng/mL or when clinically relevant adverse events were suspected.

CYP3A5 genotyping was performed for all participants. Genomic DNA was isolated from EDTA-anticoagulated peripheral blood using a standard nucleic acid extraction system. The CYP3A5*3 variant (6986A > G, rs776746) was identified using a commercial TaqMan-based assay (Beijing Huaxia Shidai Gene Co., Ltd., Medical Device Filing No. 20150009) employing fluorescence-labeled probes (FAM/HEX). Fluorescence detection was performed on the corresponding platform, with a signal intensity threshold of ≥1000 required for valid genotype determination. All procedures were conducted in strict accordance with the manufacturer's instructions.

Study endpoints

Primary endpoints

Renal allograft function was compared between the exposed and non-exposed arms at five time points spanning the first postoperative year: day 7, month 1, month 3, month 6, and month 12. Functional status was quantified through two complementary measures—estimated glomerular filtration rate (eGFR) and circulating cystatin C (CysC) levels. The eGFR computation employed the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation structured as follows: eGFR (mL/min/1.73 m²) = a × (Scr / b)^c × (0.993)^age. Within this formula, the coefficient a assumes values of 163 (Black males), 166 (Black females), 141 (non-Black males), and 144 (non-Black females); the divisor b is set at 0.9 mg/dL for males and 0.7 mg/dL for females; the exponent c adopts −0.411 (males with Scr ≤ 0.9 mg/dL), −1.209 (males with Scr > 0.9 mg/dL), −0.329 (females with Scr ≤ 0.7 mg/dL), or −1.209 (females with Scr > 0.7 mg/dL). Measurement of CysC was performed using a latex-enhanced immunoturbidimetric assay on either a Roche Cobas 8000 or a Beckman AU 5431 instrument.

Secondary endpoints

Additional outcomes of interest were selected based on their physiological relevance and clinical importance. These included: markers of hepatic integrity (alanine aminotransferase [ALT], aspartate aminotransferase [AST]); hematological indices (white blood cell count [WBC], hemoglobin [HGB], platelet count [PLT]); metabolic profile components (fasting blood glucose [Glu], triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C]); other determinants of renal status (serum uric acid, blood urea nitrogen, serum potassium [K^+]); and the cumulative rate of infectious complications. Infection status was ascertained from clinician-entered diagnoses in the electronic medical record, substantiated by corroborating laboratory data or imaging evidence.

Statistical analysis

Categorical measures are expressed as absolute numbers alongside their percentages, and between-group differences were tested with Pearson's chi-square or Fisher's exact test as dictated by the data structure.

Continuous measures are shown as the arithmetic mean accompanied by the standard deviation; comparisons across groups relied on the independent samples t-test or the Mann–Whitney U-test, with the choice guided by prior assessment of distributional normality (Shapiro–Wilk procedure) and variance equality (Levene's procedure).

To correct for baseline disparities, 1:1 propensity score matching without replacement was undertaken through the MatchIt toolkit. Logistic regression provided propensity scores, conditioned on age, sex, BMI, CRP, day-1 postoperative estimated glomerular filtration rate (eGFR), day-1 postoperative cystatin C (CysC), and the induction protocol. A caliper width of 0.2 standard deviations of the logit-transformed propensity score was specified to preserve matching fidelity. This approach yielded a balanced analytic sample of 105 individuals in each of the two study arms for the primary assessment.

The problem of incomplete data was handled via multiple imputation within the MICE framework, using the 2L.pan and 2L.norm routines to generate 20 completed datasets across 30 iterative cycles. The primary renal function endpoints (eGFR and CysC) were examined through linear mixed-effects models (LMMs) built with the lme4 library, specifying fixed terms for group, time point, and their interaction, alongside adjustment covariates consisting of age, sex, BMI, tacrolimus level, mycophenolic acid level, and induction regimen; a random intercept was placed on participant identifier. Longitudinal secondary outcomes were subjected to a parallel modeling strategy. Rubin's rules were applied to synthesize estimates from multiply imputed datasets.

A multivariable Cox proportional hazards formulation was constructed to forecast the hazard of encountering a supratherapeutic tacrolimus concentration (C0 > 20 ng/mL) within seven days of surgery. Variable selection leveraged LASSO regularization implemented via the glmnet package on each imputed dataset; predictors that survived selection in half or more of the imputed models were carried forward into the conclusive Cox model fitted with the survival suite. The C-index served as the measure of model discrimination, and internal validation used 500 bootstrap draws via the boot package. Calibration was inspected through a grouped calibration diagram.

To account for multiplicity in longitudinal contrasts, the Benjamini–Hochberg false discovery rate (FDR) correction was enforced separately within each outcome domain. Data processing and figure generation drew on the tidyverse. Every analysis was conducted within the R computing environment (version 4.5.0). Statistical significance was declared at a two-tailed FDR-adjusted P value below 0.05.

Results and Discussion

Patient characteristics

Table 1 displays the baseline characteristics of patients after propensity score matching [1]. When comparing the two groups, no significant differences emerged in demographic variables, starting kidney function, the majority of lab measurements, or the induction therapy given (all p values exceeded 0.05) [2]. That said, certain values were notably higher in the exposed group. These included white blood cell count (12.2 ± 4.0 vs. 11.1 ± 4.3 × 10^9/L, p = 0.030) [3], fasting glucose level (8.6 ± 2.6 vs. 7.5 ± 2.4 mmol/L, p = 0.003) [4], and the amount of tacrolimus administered daily (8.2 ± 1.5 vs. 7.7 ± 1.5 mg/d, p = 0.014) [5]. Also, a much larger fraction of the exposed group had the CYP3A5 *3/*3 genotype (68.3% versus 30.2%, p < 0.001) [6].

Table 1. Post-PSM characteristics of kidney transplant recipients.

Variable	P	Non-exposed group (n = 105)	Exposed group (n = 105)
Gender	0.882		
Male, n (%)		72 (68.6%)	70 (66.7%)
Female, n (%)		33 (31.4%)	35 (33.3%)
Age (years)	0.889	43.1 ± 11.3	43.3 ± 11.5
BMI	0.818	22.0 ± 3.2	21.9 ± 3.1
BSA (m2)	0.885	1.6 ± 0.2	1.6 ± 0.2
Weight (kg)	0.877	60.4 ± 11.0	60.7 ± 12.2
WBC (×109/L)	0.030	11.1 ± 4.3	12.2 ± 4.0
HGB (g/L)	0.106	105.9 ± 16.5	109.4 ± 16.5
PLT (×109/L)	0.462	192.9 ± 63.4	186.5 ± 60.3
HCT (L/L)	0.094	0.3 ± 0.1	0.3 ± 0.1
eGFR (mL/min/1.73m2)	0.599	7.8 ± 3.9	7.7 ± 3.9

CysC (mg/L)	0.279	3.7 ± 1.7	3.9 ± 1.5
Urea (mmol/L)	0.762	19.5 ± 5.7	19.3 ± 6.2
UA (μmol/L)	0.450	468.6 ± 136.0	482.8 ± 137.3
Urine output (mL)	0.369	3877.6 ± 1993.4	3803.8 ± 2186.9
ALT (U/L)	0.969	14.5 ± 11.4	15.9 ± 14.4
AST (U/L)	0.328	17.1 ± 8.8	19.2 ± 13.0
ALB (g/L)	0.368	36.9 ± 5.6	35.9 ± 4.0
TBIL (umol/L)	0.102	9.4 ± 6.8	10.6 ± 7.0
GLU (mmol/L)	0.003	7.5 ± 2.4	8.6 ± 2.6
CRP (mg/L)	0.977	30.1 ± 25.0	29.6 ± 24.4
TAC dose (mg/d)	0.014	7.7 ± 1.5	8.2 ± 1.5
MPS dose (mg/d)	0.191	913.3 ± 183.7	946.3 ± 174.8
GC dose (mg/d)	0.675	1508.1 ± 63.6	1495.2 ± 125.6
Immune induction	0.889		
Monotherapy, n (%)		60 (57.1%)	58 (55.2%)
Dual Therapy, n (%)		45 (42.9%)	47 (44.8%)
Systolic blood pressure (mmHg)	0.675	146.4 ± 10.6	148.3 ± 11.9
Diastolic blood pressure (mmHg)	0.463	89.1 ± 10.0	90.0 ± 8.9
Diabetes, n (%)	1.000	19 (18.1%)	18 (17.1%)
Hypertension, n (%)	0.150	74 (70.5%)	84 (80.0%)
CYP3A5	< 0.001		
***1/*1+*1/*3**		44 (69.8%)	19 (31.7%)
***3/*3**		19 (30.2%)	41 (68.3%)

Notes: Monotherapy refers to basiliximab or rabbit anti-human thymocyte globulin, whereas dual therapy indicates the combination of basiliximab and rabbit anti-thymocyte globulin. The CYP3A5 *1/*1 and *1/*3 genotypes correspond to rapid/intermediate metabolizers, while the *3/*3 genotype is associated with slow metabolism.

Abbreviations: body mass index (BMI); body surface area (BSA); uric acid (UA); glucose (GLU); hematocrit (HCT); albumin (ALB); total bilirubin (TBIL); tacrolimus (TAC); mycophenolate sodium (MPS); glucocorticoids (GC).

Primary outcomes

Across all evaluated follow-up points (day 7 and months 1, 3, 6, and 12), patients without early high tacrolimus exposure consistently showed more favorable renal function. This was reflected in higher eGFR values and lower cystatin C levels throughout the observation period, including at 1 year (eGFR: 64.0 ± 21.9 vs 57.1 ± 25.6 mL/min/1.73 m²; CysC: 1.58 ± 0.48 vs 1.92 ± 0.93 mg/L).

Using linear mixed-effects modeling on imputed datasets, early supratherapeutic tacrolimus exposure was consistently linked to poorer renal outcomes **(Table 2).** The impact was most pronounced during the initial postoperative phase. In this period (day 7 to month 3), the exposed group showed a clear reduction in eGFR, with adjusted differences exceeding 10 mL/min/1.73 m² at each time point (all FDR-adjusted $P < 0.05$). At the same time, cystatin C levels were higher, indicating impaired renal function (all FDR-adjusted $P < 0.05$).

Although the gap between groups narrowed over time, it did not disappear. By 6 and 12 months, eGFR remained lower in the exposed group, and this difference remained statistically significant at 1 year (FDR-adjusted $P = 0.038$). A similar pattern was observed for cystatin C, which remained elevated at 1 year (FDR-adjusted $P = 0.043$), supporting a sustained negative effect of early high exposure on graft function.

Table 2. Adjusted renal function differences between groups over time (multiple imputation).

Time point	Outcome	FDR-adjusted P	Unadjusted P	Adjusted mean difference (95% CI)
7 days	eGFR	0.010	0.003	−11.32 (−18.37 to −4.28)
	CysC	< 0.001	< 0.001	0.83 (0.50 to 1.16)
1 month	eGFR	0.010	0.006	−10.20 (−17.15 to −3.25)
	CysC	0.043	0.033	0.36 (0.03 to 0.68)
3 months	eGFR	0.010	0.004	−10.75 (−17.72 to −3.77)
	CysC	0.043	0.035	0.36 (0.03 to 0.69)
6 months	eGFR	0.034	0.027	−8.01 (−15.01 to −1.01)
	CysC	0.086	0.086	0.28 (−0.04 to 0.61)
1 year	eGFR	0.038	0.038	−7.54 (−14.62 to −0.46)

CysC	0.043	0.022	0.40 (0.06 to 0.73)

Notes: Adjusted mean differences (95% CI) are expressed relative to the non-exposed group as the reference. Multiple comparisons were controlled using the Benjamini–Hochberg false discovery rate procedure across five tests. Linear mixed-effects models included adjustments for age, sex, body mass index, tacrolimus levels, and mycophenolic acid levels, with a subject-specific random intercept. Missing data were addressed through multiple imputation, generating 20 datasets.

For sensitivity purposes, the analysis was repeated using only participants with complete data .This approach yielded findings that aligned with the primary results, showing similar effect directions and maintaining statistical significance.

Secondary outcomes

All analyses were performed using covariate-adjusted mixed-effects models, with missing observations handled through multiple imputation (20 datasets).

When examining additional renal-related markers, a difference was evident only in the early postoperative period: serum urea levels were lower in patients without high tacrolimus exposure at day 7 (adjusted difference: −4.94 mg/dL, FDR-adjusted P = 0.0008). By contrast, at 12 months, potassium levels showed a slight reduction in the non-exposed group; however, this difference was not statistically significant (adjusted difference: −0.17 mmol/L, FDR-adjusted P = 0.174). No consistent or significant group differences were observed for the remaining secondary measures.

Across non-renal secondary endpoints, most variables remained stable between groups after adjustment for multiple comparisons. Liver enzyme levels (ALT and AST) together with metabolic indices such as glucose and lipid profiles showed no statistically meaningful separation after FDR correction.

A similar pattern was observed in hematological parameters. White blood cell and platelet counts did not demonstrate sustained between-group variation. Hemoglobin showed a short-term numerical difference at day 7, favoring the exposed group in unadjusted analysis (5.92 g/L increase, P = 0.044), but this signal disappeared after correction for multiple testing (FDR-adjusted P = 0.220).

In contrast to the generally neutral findings above, infection outcomes differed substantially. Over the 12-month follow-up, infections were more frequent in the exposed cohort (80.0% vs 52.3%). After covariate adjustment, exposure was associated with a markedly increased risk of infection.

Drug concentrations

During the follow-up period, tacrolimus (TAC) levels declined in both cohorts, reflecting dose adjustments after transplantation.

A difference between groups was limited to the immediate postoperative phase. At day 7, patients in the high-exposure group showed markedly greater TAC exposure than controls (12.88 ± 5.46 vs 10.12 ± 2.70 ng/mL, P < 0.001). However, this divergence was transient, and subsequent measurements showed rapid convergence in TAC concentrations between groups. From the first month onward, exposure profiles were largely indistinguishable, including at 12 months, where values were nearly identical (7.72 ± 2.13 vs 7.67 ± 1.67 ng/mL; all P > 0.05).

Mycophenolic acid (MPA) exposure remained stable over time and showed no meaningful separation between cohorts at any stage of follow-up. Concentration distributions were highly overlapping throughout the study period (2.68–3.44 vs 2.77–3.49 μg/mL), supporting the absence of between-group differences in MPA pharmacokinetics.

Sensitivity analysis

To test the robustness of the primary findings, a secondary analysis was performed using a more stringent exposure definition, setting the tacrolimus threshold at > 25 ng/mL.

Renal outcomes were then re-evaluated after multiple imputation using the same modeling framework. The results remained consistent with the main analysis, showing a persistent association between higher exposure and impaired graft function. In this sensitivity setting, eGFR remained lower in the exposed group at early and late follow-up points, including day 7, month 3, and year 1 (adjusted differences: −12.53, −8.79, and −8.90 mL/min/1.73 m²; all FDR-adjusted P < 0.07). In parallel, cystatin C was significantly elevated at day 7 (adjusted difference: 0.98 mg/L, FDR-adjusted P < 0.001).

Overall, the direction and magnitude of the effects were consistent with the primary results, reinforcing the stability and robustness of the observed associations.

Prediction model

The final predictive framework for early supratherapeutic tacrolimus exposure was constructed using a penalized Cox regression approach, with variable selection via LASSO before model fitting **(Figure 2).** This step allowed the model to focus on a limited set of consistently informative predictors rather than the full clinical spectrum.

Genetic variability in drug metabolism emerged as the dominant determinant, with the CYP3A5 *3/*3 genotype conferring the greatest increase in risk and indicating a markedly higher susceptibility profile. Alongside this, dosing intensity relative to body weight also played a substantial role, suggesting that early pharmacologic burden is a key driver of exposure risk. Inflammatory status shortly after surgery, as reflected in day 1 CRP levels, independently contributed to risk stratification, supporting a link between early systemic inflammation and altered tacrolimus handling.

In contrast, higher serum albumin was associated with a reduced risk, suggesting a potential buffering or stabilizing effect on drug exposure dynamics. Other demographic and clinical variables, including age, sex, metabolic comorbidities, body mass index, and induction immunosuppression, did not demonstrate independent predictive value and were excluded during selection.

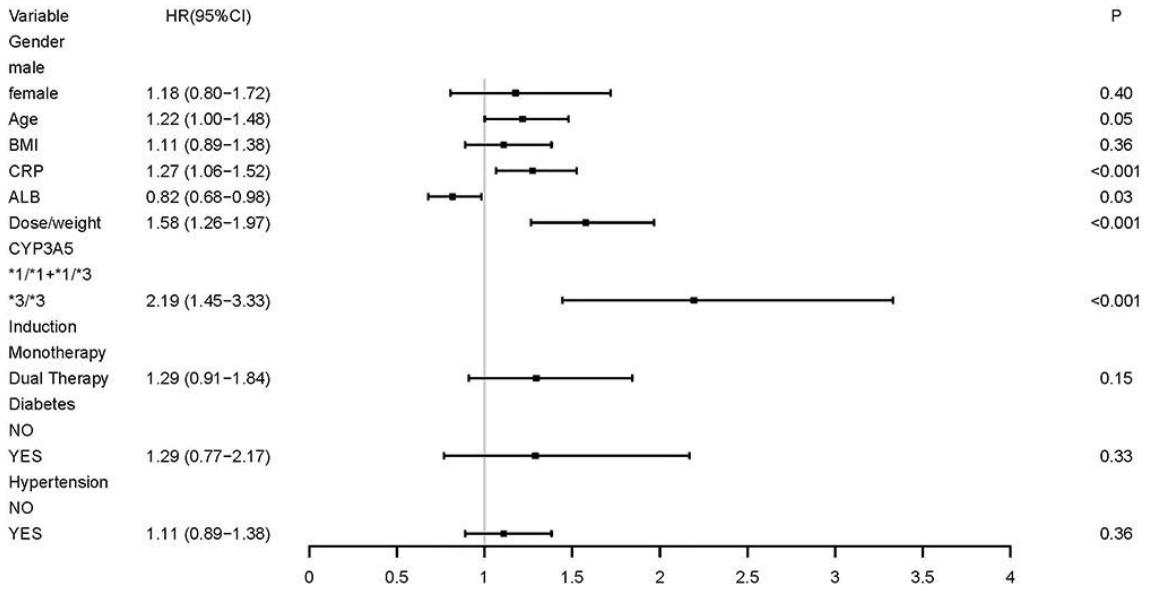

Figure 2. Forest plot illustrating predictors of early tacrolimus overexposure in kidney transplant recipients

Notes: Tacrolimus exposure was standardized to body weight (mg/kg/day). For CYP3A5, the *3/*3 genotype represents the homozygous variant, while *1/*1 and *1/*3 were used as the reference category (rapid/intermediate metabolizers); the *3/*3 genotype corresponds to the slow-metabolizer phenotype.

The final Cox proportional hazards model is expressed as: $h(t|X) = h_0(t)\exp(0.20\times\text{Age} + 0.24\times\text{CRP} + 0.46\times\text{TAC dose/weight} + 0.79\times\text{CYP3A5*3/*3} + 0.39\times\text{Hypertension} + 0.26\times\text{Dual induction} + 0.16\times\text{Female} - 0.20\times\text{Albumin} + 0.13\times\text{Total bilirubin} + 0.26\times\text{Diabetes} + 0.10\times\text{BMI})$.

The model's predictive ability was evaluated using the concordance index, which indicated moderate-to-good discrimination (C-index = 0.716). To assess potential overfitting, internal validation was performed using 500 bootstrap resamples. After correction, the optimism-adjusted C-index was 0.728, corresponding to a small negative optimism of −0.012.

The predicted probabilities closely matched the observed outcomes, indicating satisfactory calibration performance, with a mean absolute error of 0.027. It should be noted that validation was limited to internal resampling procedures and did not include external cohort confirmation.

This retrospective analysis, which applied propensity score matching alongside multiple imputation to mitigate confounding and handle absent data, indicates that renal transplant patients subjected to supratherapeutic tacrolimus trough levels early after surgery (C0 > 20 ng/mL within the initial 7 days) had meaningfully inferior short- and medium-term allograft performance when set against a matched cohort without such overexposure. This signal was consistently borne out by depressed eGFR values and elevated cystatin C (CysC) levels that persisted through the first post-transplant year. Beyond renal endpoints, early supratherapeutic levels were

robustly associated with a substantially greater infectious burden during the same year (80.0% vs 52.3%; adjusted OR = 4.27, 95% CI: 2.22–8.52, P < 0.001). By contrast, no appreciable correlations surfaced for glucoregulatory indices, lipid metabolism markers, or hepatic transaminases. Taken together, these data raise the possibility that early TAC overexposure presents a dual hazard: probable nephrotoxic insult that erodes graft performance and enhanced infection proneness, the latter plausibly driven by the drug's intense immunosuppressive action.

When weighing these associations, several study-level shortcomings deserve careful consideration. First, among the source population, nearly 70% of subjects in the unexposed arm maintained tacrolimus concentrations below 20 ng/mL throughout the initial postoperative year. As such, the analytical contrast effectively compares a group characterized by a "single early spike in exposure" with a referent largely composed of patients with "sustained low-level exposure." This configuration may seed selection bias and exaggerate the true magnitude of the effect. Second, although the measured covariates were well-balanced through propensity score matching, the possibility of unmeasured or suboptimally captured confounders—such as donor and recipient characteristics, subtle facets of medication-taking behavior, and so on—cannot be ruled out. Such inherent features of observational work demand caution when inferring causation. Still, the uniformity of effect direction, the durability of statistical significance through multiple time windows and sensitivity checks, and the underlying biological rationale collectively reinforce the clinical meaningfulness of what was observed.

The one-year mean eGFR in our propensity-matched unexposed arm (64.0 mL/min/1.73 m²) is comparable to the multicenter average of 51.1 ± 18.7 mL/min/1.73 m² reported elsewhere [19], confirming that our matched comparators achieved a representative and acceptable level of graft performance. The exposed arm, in contrast, showed a lower mean eGFR (57.1 ± 25.6 mL/min/1.73 m²). The adjusted between-group gap in eGFR, favoring the unexposed cohort, remained significant across repeated assessments as detailed in our main analysis. This reproducible pattern suggests that early tacrolimus levels above the therapeutic window are associated with a tangible and lasting decline in kidney allograft function during the first postoperative year.

The association between early TAC overexposure and impaired graft function was evident at virtually all evaluated postoperative time points in our sample. It was strongly underpinned by significantly reduced eGFR at every interval (day 7 through month 12) and elevated cystatin C at most time points (month 6 being the exception) in exposed versus matched unexposed individuals. The observed temporal pattern is mechanistically sound, aligning with TAC's well-recognized pharmacological footprint—afferent arteriolar narrowing and endothelial apoptosis [20]—processes thought to contribute to both hemodynamic compromise and incipient structural damage. Our clinical results echo earlier reports. Cosio and colleagues [21] described that early eGFR trajectories under comparatively intensive TAC regimens correlated with initial nephron loss. Steegh *et al.* [22] subsequently showed that peritubular capillary dropout shortly after engraftment tracked with long-term functional outcomes, a tissue-level finding that could underlie the sustained deficits we recorded. Adding further biological weight, cell culture experiments confirm that elevated tacrolimus levels can directly cause renal cellular injury [23].

A point of nuance in our dataset concerns the partial uncoupling of eGFR and CysC dynamics at the six-month evaluation, where eGFR remained significantly different between groups but CysC did not. This does not undermine the broader pattern; rather, it highlights the distinct informational contributions of the two markers. Creatinine-based eGFR and CysC capture glomerular filtration via distinct biological pathways and can be independently influenced by various clinical states. There is evidence that GFR-estimating formulas that integrate CysC perform more accurately in transplant recipients [24]. Thus, the joint longitudinal behavior of both measures likely renders a more complete picture of graft well-being. The enduring eGFR decrement points to a persistent functional limitation, whereas the CysC pattern may track more dynamic or subtle facets of injury. In aggregate, the evidence suggests that early exposure to supratherapeutic tacrolimus concentrations exerts an ongoing adverse influence on allograft function over the first year, with the precise signature of that influence shifting somewhat across complementary filtration markers.

Looking beyond eGFR and CysC, a significant elevation of serum urea was confined to day 7 post-surgery in the exposed arm (adjusted mean difference: 4.94 mg/dL; FDR-adjusted P = 0.0008). This probably reflects the kidney's acute functional state at that very early stage rather than a direct toxic action of TAC, a view consistent with urea's known responsiveness to substantial hemodynamic or functional perturbations [25, 26]. Serum potassium showed a downward numerical drift in exposed patients at the one-year mark (adjusted mean difference: −0.17 mmol/L), though this did not reach significance after multiplicity correction (FDR-adjusted P = 0.174). Tacrolimus labeling, as well as clinical reports, have documented hypokalemia as a potential adverse event [27], with proposed mechanisms involving tubular injury and consequent renal tubular acidosis [28, 29]. While the

trend we observed is consistent with this pharmacological profile, the lack of statistical significance in our data precludes drawing any firm conclusions.

Additional pharmacodynamic facets of tacrolimus, beyond immunosuppression, include possible modulatory effects on blood cell production and infection liability. In our cohort, an early hemoglobin disparity emerged at day 7, with numerically higher values in the exposed arm (unadjusted P = 0.044). This signal, however, dissipated upon FDR-based multiple-testing adjustment (FDR-adjusted P = 0.220). Although preclinical studies have suggested that high TAC levels may stimulate certain hematopoietic progenitors in a dose-related manner [30], the transient, statistically non-significant signal in our clinical material is insufficient to substantiate a meaningful link between early supratherapeutic exposure and a clinically relevant enhancement of red cell production.

In keeping with tacrolimus's powerful immunosuppressive actions, our data revealed that early supratherapeutic exposure was closely associated with a heightened risk of infectious complications during the first year following transplantation. Within the propensity score-matched sample, the infection frequency was significantly higher in the exposed group than in the unexposed group (80.0% versus 52.3%; adjusted OR = 4.27, 95% CI: 2.22–8.52, P < 0.001). A numeric inclination toward more frequent viral infections was also apparent among exposed individuals. This observation harmonizes with earlier publications linking elevated tacrolimus blood levels to a greater hazard of opportunistic infections. Manitpisitkul *et al*. [31] reported that high tacrolimus exposure was significantly associated with BK polyomavirus-associated nephropathy in kidney recipients, and a meta-analysis by Datrino *et al*. [32] identified cytomegalovirus infection as the predominant pathogen under tacrolimus-based immunosuppressive protocols.

New-onset hyperglycemia after transplantation represents a well-characterized adverse outcome [33], and the diabetogenic potential of tacrolimus exceeds that of certain alternative immunosuppressive agents [33]. In our sample, however, fasting glucose concentrations did not differ meaningfully between exposed and unexposed subjects at any post-transplant assessment point after FDR correction (all FDR-adjusted P > 0.05). This null finding may be interpreted against the backdrop of the known concentration-dependent effects of tacrolimus on glucose handling, with disruptions in glycemic regulation reportedly more pronounced when circulating levels exceed 15 ng/mL [34]. Although the exposed arm exhibited higher initial concentrations in our study, average tacrolimus trough values in both arms settled at or below 15 ng/mL from day 7 onward through the one-year follow-up visit. The continued maintenance of drug levels within this comparatively modest range may partially account for the lack of an appreciable divergence in glucoregulatory outcomes between the two groups.

To probe the resilience of our principal observations, a supplementary sensitivity analysis was undertaken employing a stricter exposure definition of 25 ng/mL. The outputs reinforced the central association, particularly during the immediate postoperative window. At this more stringent threshold, early overexposure continued to show a significant relationship with diminished eGFR and increased cystatin C at day 7. Although statistical significance became attenuated at subsequent time points following rigorous multiplicity adjustment, the directional patterns for both eGFR and cystatin C across the entire follow-up period stayed concordant with those documented in the main analysis. The waning of significance at later intervals in this sensitivity evaluation may stem from two interconnected explanations. Firstly, adopting a higher cutpoint contracted the number of individuals classified as exposed, thereby eroding statistical power to identify enduring differences. Secondly, from a practical clinical standpoint, a trough value exceeding 25 ng/mL is very likely to prompt a prompt dose reduction, thereby abbreviating the duration of supratherapeutic exposure and possibly softening its longer-term measurable impact on kidney function. Taken as a whole, the uniformity of effect direction across analytic approaches, along with the robust early signal even at a more conservative cutoff, buttresses the inference that the relationship between early supratherapeutic tacrolimus levels and graft dysfunction is sturdy and not an artifact tied to a particular numerical boundary.

An additional objective of this investigation was to construct a predictive algorithm for early high TAC exposure. It is noteworthy that while existing instruments—such as population pharmacokinetic (PPK) models—have substantially advanced our understanding of factors such as CYP3A5 genotype and body habitus that govern tacrolimus handling [35], their core strength typically lies in characterizing and forecasting steady-state pharmacokinetic behavior. By contrast, the model presented here was deliberately designed to provide an early risk estimate, drawing on readily accessible information on the first postoperative day. One particular element we wished to explore was the contribution of the acute postoperative inflammatory milieu. We identified that a raised CRP value at this early stage was a significant predictor in our model. This finding aligns with earlier work by Chavant and colleagues in liver transplant recipients, which likewise documented a connection between

heightened CRP and tacrolimus overexposure [36]. Moreover, the model suggested a possible contributory role for serum albumin, a finding consonant with the established pharmacokinetics of tacrolimus, a drug extensively bound to plasma proteins [37]. Our model may thus serve as a complement to existing tools by concentrating on the dynamic and multifaceted perioperative phase.

With respect to potential translation into practice, and assuming subsequent validation, this model might be envisioned as a decision-support instrument to assist early bedside judgment. In practice, entry of readily obtainable parameters on the first day after surgery—such as CYP3A5 genotype, the weight-adjusted tacrolimus dose, CRP, and albumin levels—could provide an early signal of a patient's susceptibility to impending supratherapeutic exposure. Such forewarning might encourage clinicians to consider measures such as intensified monitoring or careful dose titration over the ensuing several days, potentially helping to avert the high trough concentrations linked with unfavorable sequelae in our dataset. We stress that this represents a prospective avenue only; the model requires thorough external corroboration and evaluation of its influence on clinical endpoints before any consideration of routine adoption. In line with tacrolimus's strong immunosuppressive potency, our findings showed that early supratherapeutic drug levels were closely correlated with a greater infection burden during the inaugural post-transplant year. Among the propensity-matched subset, the cumulative infection rate was markedly higher in the exposed arm than in the unexposed arm (80.0% vs. 52.3%; adjusted OR = 4.27, 95% CI: 2.22–8.52, $P < 0.001$). A numerical uptick in viral infections was likewise noted in the exposed cohort. These clinical observations dovetail with earlier evidence tying higher tacrolimus blood concentrations to an amplified risk of opportunistic infections. Manitpisitkul *et al.* [31] described a significant association between elevated tacrolimus exposure and BK polyomavirus-associated nephropathy in renal allograft recipients, while a meta-analysis by Datrinoa *et al.* [32] underscored the predominance of cytomegalovirus infection under tacrolimus-based immunosuppressive protocols.

Post-transplant disturbances in glucose metabolism represent a widely acknowledged complication [33], and the propensity of tacrolimus to precipitate new-onset diabetes surpasses that of certain other immunosuppressive drugs. [33] Nonetheless, fasting glucose measurements in our sample did not diverge significantly between the two study arms at any postoperative evaluation after FDR correction (all FDR-adjusted $P > 0.05$). This null result may be rationalized by the established concentration-dependent nature of tacrolimus-mediated glycemic effects, with disruptions to glucose control reportedly intensifying at blood levels above 15 ng/mL [34]. Although the exposed group exhibited higher initial concentrations in our analysis, the average tacrolimus trough values for both cohorts resided at or below 15 ng/mL from the seventh postoperative day onward through the entire first-year follow-up. This sustained occupancy of a relatively lower concentration band could partially explain why no meaningful between-group disparity in glucose-related outcomes was captured.

To test the durability of our core results, a sensitivity evaluation was conducted applying a more stringent exposure definition of 25 ng/mL. The outcomes corroborated the principal association, especially in the acute postoperative phase. Under this tighter criterion, early overexposure remained significantly associated with depressed eGFR and elevated cystatin C at day 7. While statistical significance receded at later observations after stringent multiplicity correction, the directional trends for both eGFR and cystatin C over the complete follow-up window remained aligned with those recorded in the primary analysis. The attenuation of statistical significance at more remote time points in this sensitivity assessment may be due to two interrelated factors. First, raising the threshold shrank the exposed cohort size, consequently diminishing statistical power to resolve persistent group differences. Second, from a clinical perspective, a trough measure exceeding 25 ng/mL almost invariably prompts an immediate dose reduction, thereby curtailing the window of overexposure and plausibly dampening its longer-term, quantifiable impact on renal function. Viewed as a whole, the uniformity of effect direction across analytic approaches, together with the pronounced early signal even at a more conservative exposure cutoff, reinforces the judgment that the observed association between early supratherapeutic tacrolimus concentrations and graft impairment is robust and not merely a function of a particular numerical threshold.

A further goal of this investigation was to devise a predictive tool for early high TAC exposure. It bears noting that while existing methodologies—including population pharmacokinetic (PPK) models—have substantially enriched our knowledge of determinants such as CYP3A5 genotype and body size that modulate tacrolimus disposition [35], their principal advantage often lies in delineating and forecasting steady-state pharmacokinetics. In contrast, the model advanced here was explicitly engineered to deliver an early risk estimate using variables readily available on postoperative day 1. A specific element we endeavored to probe was the contribution of the acute postoperative inflammatory cascade. Our analysis revealed that a higher CRP concentration at this early

time point was a meaningful predictor in the model. This finding resonates with earlier research by Chavant *et al*. in hepatic transplant patients, which also documented a connection between elevated CRP and supratherapeutic tacrolimus levels [36]. The model further suggested a possible influence of serum albumin, a result consistent with tacrolimus's known pharmacokinetic behavior as a highly protein-bound compound [37]. Our model might therefore supplement current tools by focusing on the volatile and complex perioperative period.

Regarding potential clinical translation, should further validation be forthcoming, this algorithm could be envisioned as an ancillary resource to inform early therapeutic decisions. Operationally, entering parameters easily collected on the first postoperative day—namely, CYP3A5 genotype, weight-normalized tacrolimus dose, CRP, and albumin concentrations—might generate an early alert regarding a patient's vulnerability to imminent supratherapeutic drug exposure. Such advance notice could prompt clinicians to adopt measures such as heightened surveillance or judicious dose adjustments over the subsequent days, thereby potentially circumventing the elevated trough levels associated with adverse consequences in our study. We underscore that this merely outlines a hypothetical future direction; rigorous external validation and demonstration of a favorable impact on clinical endpoints are indispensable prerequisites before any contemplation of routine application.

Several limitations of this study should be considered when interpreting the results. First, the way exposure was defined, together with the composition of the comparison group, may introduce selection-related bias, as discussed previously. In addition, although propensity score matching was applied to improve baseline comparability, residual confounding from variables not captured in the dataset cannot be ruled out.

Second, the retrospective nature of the analysis and its single-center setting may restrict the generalizability of the findings to other populations and clinical practices. Such a design may also be vulnerable to bias in data recording and outcome documentation inherent to routine clinical databases.

Finally, while the proposed prediction model showed encouraging performance in internal testing, its current form remains exploratory. External validation in independent cohorts and prospective evaluation are essential before any clinical application can be considered.

Despite these limitations, the study provides consistent observational evidence and supports a structured framework for early identification of patients at risk of excessive tacrolimus exposure after kidney transplantation.

Conclusion

In this single-center retrospective cohort of kidney transplant recipients, early exposure to supratherapeutic tacrolimus concentrations (> 20 ng/mL during the first postoperative week) was associated with less favorable clinical outcomes than in matched controls. Patients experiencing such exposure demonstrated persistently impaired graft function and a higher burden of infectious complications over the first year after transplantation.

Overall, these results indicate that excessive tacrolimus exposure in the early post-transplant period may have clinically relevant negative effects on both renal allograft performance and infection risk in this population.

To enable earlier identification of patients at risk for supratherapeutic tacrolimus exposure, we constructed a risk prediction model based on routinely obtainable clinical variables from postoperative day 1. The final model incorporated genetic variation in CYP3A5 (*3/*3 genotype), markers of early inflammatory response (CRP), and initial weight-adjusted tacrolimus dosing.

In internal validation, the model showed acceptable discriminative performance, suggesting its potential usefulness for early risk stratification. If further validated externally, it could support individualized postoperative management by identifying high-risk patients who may benefit from closer therapeutic monitoring and more conservative dose adjustment strategies during the early post-transplant period.

Taken together, these findings emphasize the importance of preventing excessive tacrolimus exposure in the early post-transplant period. Early supratherapeutic levels appear to be linked with both impaired graft performance and a higher infectious burden, underscoring the need for careful initial dosing.

The proposed predictive framework, pending external validation, may provide a practical means of identifying high-risk patients soon after transplantation. Such early stratification could help refine initial immunosuppressive management, aiming to improve renal allograft outcomes while minimizing infection-related complications.

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