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Article

TIM-3 Combined With Pan-Immune-Inflammation Value for Predicting Acute Rejection Risk After Kidney Transplantation

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Abstract

Aims/Background: Acute rejection remains a major obstacle affecting long-term graft survival after kidney transplantation, and current non-invasive predictive tools are still limited. This study aimed to investigate the predictive value of early postoperative urinary soluble T-cell immunoglobulin and mucin domain-containing protein 3 (sTIM-3) and pan-immune-inflammation value (PIV) for acute rejection after kidney transplantation, and to establish a predictive model combined with other independent risk factors for acute rejection after kidney transplantation. **Methods:** The clinical data of 320 patients who underwent kidney transplantation at Shulan (Hangzhou) Hospital from January 2022 to April 2025 were retrospectively collected. Serum sTIM-3, urinary sTIM-3, and peripheral blood routine were measured on postoperative day 7, and PIV was calculated. The patients were divided into a rejection group and a non-rejection group according to the occurrence of acute rejection confirmed by biopsy within 6 months after surgery. Univariate and multivariate logistic regression analyses were used to screen independent risk factors and construct a predictive model. Receiver operating characteristic (ROC) curves, calibration curve, and decision curve analysis were used to evaluate the performance in discrimination, calibration, and clinical utility of the model. **Results:** Multivariate logistic regression analysis showed that donor-recipient age difference ≥25 years (odds ratio [OR] = 7.347, 95% confidence interval [CI]: 2.299–23.482, $p < 0.001$), human leukocyte antigen (HLA) mismatch ≥3 (OR = 4.084, 95% CI: 1.313–12.703, $p = 0.015$), PIV (per 100, OR = 2.121, 95% CI: 1.221–3.685, $p = 0.008$), and urinary sTIM-3 (per 10-unit increase, OR = 1.808, 95% CI: 1.484–2.204, $p < 0.001$) were independent risk factors for acute rejection after kidney transplantation. The area under the curve (AUC), sensitivity, and specificity of the predictive model constructed by combining the above-mentioned indicators in the training set were 0.95 (95% CI: 0.92–0.99), 0.93, and 0.90, respectively. The same metrics for the validation cohort were 0.85 (95% CI: 0.77–0.94), 0.59, and 0.85. The Hosmer–Lemeshow test showed that the model was a good fit ($p = 0.69$, $\chi^2 = 5.59$ in the training set and $p = 0.45$, $\chi^2 = 7.81$ in the validation set). Decision curve analysis showed that the model had a positive net benefit within the threshold probability range of 10%–60%, commonly used in clinical practice. **Conclusion:** Postoperative urinary sTIM-3 and PIV are independent predictors of acute rejection after kidney transplantation. The predictive model incorporating the donor-recipient age difference and HLA mismatch number demonstrated good performance in discrimination, calibration, and clinical utility, providing a non-invasive tool for early risk stratification of acute rejection after kidney transplantation.

Keywords: kidney transplantation; graft rejection; TIM-3; PIV; predictive model

1. Introduction

For patients with end-stage renal disease, kidney transplantation remains the optimal therapeutic option, offering substantial improvements in both survival outcomes and quality of life [1]. With the development of surgical techniques, optimization of immunosuppressive regimens, and improvement of perioperative management, the short-term prognosis after kidney transplantation has been significantly improved. However, acute rejection remains a primary complication affecting the survival of transplanted kidneys, and its incidence ranges from 10% to 30% within 12 months after surgery [2]. Acute rejection can not only directly lead to graft function injury, but also induce chronic graft injury and eventually lead to graft failure [3]. Therefore, early identification and prediction of the risk of acute rejection is of great significance for optimizing immunosuppressive regimens and improving the prognosis of patients.

At present, renal allograft biopsy remains the most reliable diagnostic method for confirming acute rejection, but it is an invasive procedure with risks of bleeding and infection [4,5]. Serum creatinine is the most commonly used indicator of renal function in clinical practice; however, its elevation often occurs after pathological changes associated with rejection have developed and is not specific for acute rejection. It is important to highlight that histological evidence of rejection (subclinical rejection) has been detected on graft biopsies in approximately 25% of patients with stable serum creatinine [6,7]. Given the clinical challenges described above, the search for non-invasive, simple, and reproducible biomarkers for the prediction and diagnosis of acute rejection has become a research hotspot in the field of kidney transplantation.

T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is an immunoregulatory receptor that delivers inhibitory signals to T-cells [8]. When TIM-3 binds

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to its ligand galectin-9 (Gal-9), it can negatively regulate T-cell immune response, induce T-cell exhaustion and apoptosis, and play an important role in maintaining immune tolerance [9]. Soluble TIM-3 (sTIM-3) is the extracellular portion of TIM-3 cleaved by a protease and released into the blood and urine. Changes in its level can indirectly reflect the activation state of the TIM-3 signaling pathway [10]. A study has shown that sTIM-3 levels are significantly increased in the urine of patients with acute rejection after kidney transplantation [11]. However, existing studies on sTIM-3 mostly focus on the diagnostic value of sTIM-3 at the time of rejection or during the stable period after transplantation. Whether the early postoperative sTIM-3 level can predict the risk of subsequent acute rejection warrants validation through systematic studies.

Pan-immune-inflammation value (PIV) is a combined inflammatory indicator, which is based on the comprehensive calculation of neutrophils, monocytes, platelets, and lymphocytes in peripheral blood. This index can comprehensively reflect the inflammatory and immune status of the body. Since Fucà et al. [12] first proposed PIV in metastatic colorectal cancer, this indicator has been found to demonstrate good prognostic value in a variety of solid tumors, and high PIV levels are significantly correlated with poor overall survival and progression-free survival in lung cancer patients [13]. In the field of kidney transplantation, studies based on inflammation-immune–related composite indicators have been preliminarily explored. Evidence has shown that neutrophil-to-lymphocyte ratio (NLR) is related to acute rejection and delayed graft function (DGF) after kidney transplantation. Higher preoperative NLR is significantly associated with an increased risk of early postoperative rejection [14]. In addition, the systemic immune-inflammation index (SII) has also shown predictive value in kidney transplantation, and a study has found that preoperative SII is an effective indicator for predicting DGF [15]. However, most of the above-mentioned indicators only integrate two or three components of blood cells. As a composite indicator, PIV may provide a more comprehensive assessment of systemic inflammatory and immune status, and its predictive value for acute rejection after kidney transplantation warrants further investigation.

In the present study, clinical data of 320 renal transplant recipients were retrospectively collected, serum and urinary sTIM-3 levels were detected, and PIV was calculated. The risk factors of acute rejection after kidney transplantation were systematically analyzed, and the predictive value of early postoperative urinary sTIM-3 and PIV for acute rejection was evaluated. A predictive model incorporating other independent risk factors was constructed.

2. Methods

2.1 Subjects

Patients who underwent kidney transplantation at the Shulan (Hangzhou) Hospital from January 2022 to April 2025 were selected as the research subjects. The inclusion criteria of this study are: (1) first or second renal allograft transplantation; (2) age ≥18 years; and (3) regular postoperative follow-up with complete clinical data. The exclusion criteria of this study include: (1) multiple organ transplantation; (2) DGF within 1 week after transplantation that affected the judgment of rejection, to avoid the confounding effect of ischemia-reperfusion injury on early post-transplant inflammatory markers; (3) preoperative active infection or malignant tumor; (4) presence of severe cardiovascular and cerebrovascular diseases or immunodeficiency diseases; (5) long-term use of immunosuppressive agents before surgery; and (6) loss to follow-up or missing key variables after surgery.

2.2 Collection of Clinical Data

All data were extracted from the electronic medical record system and examined independently by two investigators to ensure data accuracy. Discrepancies were resolved through discussion, and a third senior investigator was consulted when consensus could not be reached. Different categories of data were collected, as follows: (i) general information, including recipient age, sex, body mass index (BMI), duration and type of preoperative dialysis (hemodialysis/peritoneal dialysis), number of transplantations (first/second), and primary disease (chronic glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, interstitial nephritis, polycystic kidney, and others); (ii) donor data, including donor age, sex, donor-recipient age difference (≥25 years/<25 years), and cold ischemia time (≥12 hours) [16]; and (iii) immunological data, including number of human leukocyte antigen (HLA) mismatches (<3/≥3), preoperative panel reactive antibody (PRA), and donor-specific antibody (DSA) status (positive/negative). PRA was detected using the Luminex-based single-antigen bead assay, and positivity was defined as PRA ≥10% [17]. DSA was detected using the Luminex-based single-antigen bead assay, and positivity was defined as mean fluorescence intensity (MFI) ≥1000 [18]. Details of induction therapy and maintenance immunosuppressive regimens were also recorded. Peripheral venous blood and morning urine samples were collected on the 7th day after kidney transplantation. This time point was selected because TIM-3 expression surges from day 7 onward [19], and day 7 is a routine lab assessment time point in our center. Serum sTIM-3 level, urinary sTIM-3 level, and urine creatinine were detected, and PIV was calculated. PIV was calculated using the following formula: PIV = (neutrophil count × monocyte count × platelet count)/lymphocyte count. Serum and urinary sTIM-3 levels were measured using enzyme-linked immunosorbent assay (ELISA) (Human TIM-3 ELISA Kit, MA1104; Meilunbio, Dalian, China), and the detection procedures were strictly performed according to the manufacturer's instructions. Urinary sTIM-3 levels were corrected by urine creatinine (Cr) ratio, with serum sTIM-3 units in pg/mL and urinary sTIM-3 units in pg/μmol Cr. The cut-off

of 25 years for donor-recipient age difference was selected based on previous reports that indicate that an age gap exceeding 25 years significantly increases the risk of rejection after kidney transplantation [20,21]. The HLA mismatch count was dichotomized as ≥3 vs. <3, which is a widely adopted stratification in the literature to define high immunologic risk [22,23].

2.3 Surgical Procedure

All donor kidneys were obtained from donation after circulatory death (DCD) or living donors. Donor kidneys were retrieved and preserved using low-temperature lavage with hypothermic perfusion with either histidine-tryptophan-ketoglutarate (HTK) (Custodiol®; Dr. Franz Köhler Chemie GmbH, Bensheim, Germany) or University of Wisconsin (UW) solution (Belzer UW®; Preservation Solutions, Inc., Elkhorn, WI, USA). Kidney transplantation was performed using a standard procedure: an arc-shaped incision (Gibson incision) was made in the lower abdomen of the affected side, the external or internal iliac arteries and veins were dissected, and the donor renal vein was anastomosed end-to-side to the external iliac vein. The donor renal artery was preferentially anastomosed end-to-end to the internal iliac artery; when the internal iliac artery was unsuitable due to disease or small caliber, end-to-side anastomosis to the external iliac artery was performed instead. Ureter and bladder submucosal tunnel anastomosis was performed. A ureteral stent (double J tube) was routinely placed after operation and removed under cystoscopy 4 weeks postoperatively.

2.4 Immunosuppressive Regimen

All patients received induction therapy according to immunological risk stratification. The induction protocols are as follows: Protocol A: basiliximab (Simulect; Novartis Pharma Schweiz AG, Switzerland) 20 mg on day 0 and day 4 post-transplant combined with methylprednisolone (Solu-Medrol; Pfizer Inc., New York, NY, USA) and prednisone (Shanghai General Pharmaceutical Co., Ltd., Shanghai, China); Protocol B: rabbit anti-human thymocyte globulin (ATG) (Thymoglobulin; Sanofi S.A., Paris, France) combined with methylprednisolone and prednisone. The choice between Protocol A and Protocol B was made based on individual patient characteristics and immunological risk.

For maintenance immunosuppression, all patients received a calcineurin inhibitor (CNI)-based triple regimen consisting of tacrolimus or cyclosporine, mycophenolate mofetil, and corticosteroids. The specific maintenance protocols are as follows: Regimen A: cyclosporine (Neoral; Novartis Pharma AG, Basel, Switzerland) at an initial dose of 6–8 mg/kg/day (orally, twice daily) + mycophenolate mofetil at 0.5–1.0 g per dose, twice daily (1.0–2.0 g/day) + prednisone at an initial dose of 0.5 mg/kg/day, tapered to a maintenance dose of 5–10 mg/day. Regimen B: tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) at an initial dose of 0.1–0.2 mg/kg/day (orally, twice daily) + mycophenolate mofetil (CellCept; Roche Pharmaceuticals, Basel, Switzerland) at 0.5–1.0 g per dose, twice daily (1.0–2.0 g/day) + prednisone at an initial dose of 0.5 mg/kg/day, tapered to a maintenance dose of 5–10 mg/day. Subsequent dose adjustments were guided by therapeutic drug monitoring and renal function.

2.5 Diagnosis of Acute Rejection

The diagnosis of acute rejection was based on Banff 2017 criteria [24], combined with clinical manifestations (such as fever, pain in the renal allograft area, and decreased urine output), changes in serum creatinine level (≥20% higher than the baseline value), and pathological results of renal biopsy. For patients with clinically suspected acute rejection, renal allograft biopsy was performed under the guidance of ultrasound. The biopsy tissue was fixed in formaldehyde, embedded in paraffin, and sectioned for staining. The patients were divided into the rejection group and the non-rejection group according to the occurrence of acute rejection confirmed by biopsy within 6 months after surgery. A total of 320 patients were finally included and divided into a training set (224 cases) and a validation set (96 cases) according to the ratio of 7:3 using a simple random sampling method.

2.6 Statistical Methods

SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) software were used for statistical analysis. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared between groups using the independent samples t-test. Continuous variables that did not conform to a normal distribution were expressed as median and interquartile range [M (Q_1, Q_3)] and analyzed using the Mann–Whitney U test. Categorical variables were expressed as count and percentage [n (%)], and the chi-square test was used for between-group comparisons. Yates' continuity correction was applied when any expected cell count was <5, and Fisher's exact test was used when the expected frequency was <1. Given that urinary sTIM-3 exhibited a significantly skewed distribution (Shapiro–Wilk $p < 0.001$) and violated the linearity assumption in the Box-Tidwell test ($p = 0.036$), it was natural log-transformed (ln) prior to inclusion in the logistic regression models. The Box-Tidwell test confirmed that the linearity assumption was satisfied after log-transformation ($p = 0.373$). Therefore, ln(urinary sTIM-3) was used as a continuous predictor in all subsequent logistic regression analyses. All patients were randomly divided into a training set and a validation set at a 7:3 ratio. Standardized mean difference (SMD) was used to assess the balance of baseline covariates between the training and validation sets. SMD was calculated as the difference in means or proportions between the two groups divided by the pooled standard deviation. An SMD of <0.2 was considered to indicate good

balance. Variable selection and model construction were performed exclusively in the training set, and model performance was subsequently evaluated in the validation set. Candidate variables for univariate analysis were prespecified based on prior literature and clinical knowledge. With the occurrence of acute rejection as the dependent variable, variables with $p < 0.05$ in the univariate analysis were included in the multivariate logistic regression model, and the variables were screened using the backward stepwise regression method with a removal criterion of $p > 0.10$. The events-per-variable (EPV) ratio in the training set was 10.25 (41 events for 4 candidate variables), exceeding the recommended minimum of 10. The odds ratio (OR) and 95% confidence interval (CI) of each variable were calculated. The variance inflation factor (VIF) was used to evaluate the diagnosis of collinearity, and VIF >5 suggests potential or substantial multicollinearity. A predictive model was constructed incorporating the statistically significant independent factors identified in the multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve was used to evaluate the discriminative ability of the model, and the area under the curve (AUC), the best cut-off value (determined by the Youden index, i.e., maximum sensitivity + specificity – 1), sensitivity, and specificity were calculated. The Hosmer–Lemeshow goodness-of-fit test and calibration curve were used to evaluate the calibration ability of the model. Decision curve analysis (DCA) was used to evaluate the net clinical benefit of the model. Two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison Between Training Set and Validation Set

A total of 320 renal transplant recipients were included in this study, including 224 in the training set and 96 in the validation set. Except for recipient age, none of the other variables differed significantly between the two groups (all $p > 0.05$). The difference in recipient age approached the threshold for statistical significance ($p = 0.05$). Except for recipient age (SMD = 0.239), the standardized mean differences for all covariates were below 0.2, indicating that the two groups were generally well balanced. The incidence of acute rejection was 18.3% (41/224) in the training set and 17.7% (17/96) in the validation set, with no significant difference between the two sets ($p > 0.05$), suggesting that the training and validation sets were comparable (Table 1).

3.2 Comparison Between Rejection Group and Non-Rejection Group

Among the 320 patients, 58 (18.13%) developed biopsy-proven acute rejection within 6 months after transplantation. Baseline characteristics of patients with and without acute rejection are presented in Table 2. Compared with the non-rejection group, the rejection group had significantly higher proportions of patients with a donor-recipient age difference ≥25 years ($p < 0.001$), HLA mismatch ≥3 ($p = 0.007$), and a cold ischemia time ≥12 hours ($p = 0.006$). In addition, the rejection group had significantly higher levels of PIV ($p < 0.001$), serum sTIM-3 ($p < 0.001$), and urinary sTIM-3 ($p < 0.001$). No significant differences were observed between the two groups in terms of recipient age, sex, BMI, donor age, donor sex, dialysis type, preoperative dialysis time, primary disease, transplant number, DSA status, PRA status, induction therapy, or maintenance immunosuppressive regimen (all $p > 0.05$).

3.3 Univariate Logistic Regression Analysis

Univariate logistic regression analysis showed that donor-recipient age difference ≥25 years ($p < 0.001$), HLA mismatch ≥3 ($p = 0.018$), cold ischemia time ≥12 hours ($p = 0.027$), PIV ($p < 0.001$), DSA positivity ($p = 0.048$), serum sTIM-3 ($p < 0.001$), and urinary sTIM-3 ($p < 0.001$) were significantly associated with acute rejection following kidney transplantation. Donor sex, recipient sex, dialysis type, PRA status, transplant number, recipient age, donor age, BMI, primary disease, preoperative dialysis time, induction therapy, and maintenance immunosuppressive regimen were not significantly associated with acute rejection (all $p > 0.05$) (Table 3).

3.4 Multivariate Logistic Regression Analysis

The variables with $p < 0.05$ in the univariate analysis, namely donor-recipient age difference ≥25 years, HLA mismatch ≥3, cold ischemia time ≥12 hours, DSA status, PIV, serum sTIM-3, and urinary sTIM-3, were included in a multivariate logistic regression analysis, and the independent predictors were screened using backward stepwise regression. Collinearity diagnosis showed that there was a certain collinearity between serum sTIM-3 and urinary sTIM-3 (VIF = 8.000 and 7.899, respectively), and the VIFs of other variables were less than 2 (donor-recipient age difference ≥25 years: 1.063, HLA mismatch class: 1.008, cold ischemia time ≥12 hours: 1.070, PIV: 1.057, DSA status: 1.067). Cold ischemia time ≥12 hours and serum sTIM-3 were excluded in the stepwise regression process, and the final retained variables were donor-recipient age difference ≥25 years, HLA mismatch ≥3, PIV, and urinary sTIM-3. The results showed that donor-recipient age difference ≥25 years ($p < 0.001$), HLA mismatch ≥3 ($p = 0.015$), PIV ($p = 0.008$), and urinary sTIM-3 ($p < 0.001$) were independent risk factors for acute rejection after kidney transplantation (Table 4).

3.5 Assessment of Model Discrimination

The ROC curve showed that the predictive model demonstrated good discriminative ability in both the training and validation sets (Fig. 1). In the training set, the AUC, sensitivity, and specificity of the model for predicting acute rejection were 0.95 (0.92–0.99), 0.93 (0.85–1.00), and 0.90 (0.85–0.94), respectively, and the optimal cut-off value was 0.163. In the validation set, the AUC was 0.85 (0.77–0.94), sensitivity was 0.59 (0.35–0.82), and specificity was 0.85 (0.77–0.93). Considering the lower sensitivity of the model

Table 1. Comparison of baseline characteristics of kidney transplant recipients between training set and validation set.

Variable	Total (n = 320)	Validation set (n = 96)	Training set (n = 224)	Statistic	p	SMD
Donor age (years), M (Q_1, Q_3)	45.00 (37.00, 51.00)	44.00 (38.00, 50.00)	45.00 (37.00, 52.00)	Z = –0.45	0.66	0.031
Donor sex, n (%)				χ^2 = 1.14	0.29	–0.13
Female	131 (40.94)	35 (36.46)	96 (42.86)			
Male	189 (59.06)	61 (63.54)	128 (57.14)			
Donor-recipient age difference ≥25 years, n (%)				χ^2 = 0.71	0.40	0.10
No	247 (77.19)	77 (80.21)	170 (75.89)			
Yes	73 (22.81)	19 (19.79)	54 (24.11)			
Recipient age (years), mean ± SD	45.32 ± 9.93	43.66 ± 9.81	46.03 ± 9.92	t = –1.97	0.05	0.24
Recipient sex, n (%)				χ^2 = 0.68	0.41	–0.10
Female	97 (30.31)	26 (27.08)	71 (31.70)			
Male	223 (69.69)	70 (72.92)	153 (68.30)			
BMI (kg/m^2), M (Q_1, Q_3)	23.20 (21.70, 25.03)	22.85 (21.48, 24.43)	23.30 (21.80, 25.23)	Z = –1.35	0.18	0.113
Preoperative dialysis time (months), M (Q_1, Q_3)	16.35 (11.10, 23.40)	17.60 (10.80, 24.80)	16.00 (11.48, 22.73)	Z = –0.41	0.686	–0.081
Primary disease, n (%)				χ^2 = 1.94	0.858	
Chronic glomerulonephritis	114 (35.63)	33 (34.38)	81 (36.16)			0.037
Diabetic nephropathy	25 (7.81)	7 (7.29)	18 (8.04)			0.027
Hypertensive nephropathy	28 (8.75)	6 (6.25)	22 (9.82)			0.120
Interstitial nephritis	63 (19.69)	19 (19.79)	44 (19.64)			–0.004
Others	52 (16.25)	18 (18.75)	34 (15.18)			–0.100
Polycystic kidney disease	38 (11.88)	13 (13.54)	25 (11.16)			–0.076
PIV, mean ± SD	378.73 ± 88.52	378.98 ± 85.43	378.62 ± 90.00	t = 0.03	0.974	–0.004
Serum sTIM-3 (pg/mL), M (Q_1, Q_3)	6642.00 (5248.00, 8577.25)	7027.50 (5255.50, 8926.50)	6528.00 (5197.75, 8456.00)	Z = –1.09	0.276	–0.103
Urinary sTIM-3 (pg/μmol Cr), M (Q_1, Q_3)	1195.50 (942.75, 1595.50)	1216.00 (954.25, 1676.00)	1184.50 (942.75, 1515.75)	Z = –0.74	0.460	–0.013
Dialysis type, n (%)				χ^2 = 0.50	0.480	–0.088
Hemodialysis	264 (82.50)	77 (80.21)	187 (83.48)			
Peritoneal dialysis	56 (17.50)	19 (19.79)	37 (16.52)			
HLA mismatch number, n (%)				χ^2 = 1.15	0.283	0.131
<3 mismatches	162 (50.63)	53 (55.21)	109 (48.66)			
≥3 mismatches	158 (49.38)	43 (44.79)	115 (51.34)			
PRA status, n (%)				χ^2 = 1.58	0.209	–0.164
Negative	290 (90.63)	84 (87.50)	206 (91.96)			
Positive	30 (9.38)	12 (12.50)	18 (8.04)			
DSA status, n (%)				χ^2 = 0.14	0.711	–0.046
Negative	296 (92.50)	88 (91.67)	208 (92.86)			
Positive	24 (7.50)	8 (8.33)	16 (7.14)			
Cold ischemia time ≥12 hours, n (%)				χ^2 = 0.29	0.593	0.064
No	261 (81.56)	80 (83.33)	181 (80.80)			
Yes	59 (18.44)	16 (16.67)	43 (19.20)			
Transplant number, n (%)				χ^2 = 0.088	0.766	0.036
First transplantation	291 (90.94)	88 (91.67)	203 (90.63)			
Re-transplantation	29 (9.06)	8 (8.33)	21 (9.38)			
Induction type, n (%)				χ^2 = 0.14	0.711	–0.045
Protocol A	185 (57.81)	54 (56.25)	131 (58.48)			
Protocol B	135 (42.19)	42 (43.75)	93 (41.52)			
Immunosuppression, n (%)				χ^2 = 1.10	0.294	0.129
Regimen A	126 (39.38)	42 (43.75)	84 (37.50)			
Regimen B	194 (60.63)	54 (56.25)	140 (62.50)			

BMI, body mass index; DSA, donor-specific antibody; PIV, pan-immune-inflammation value; PRA, panel reactive antibody; HLA, human leukocyte antigen; M, median; SD, standard deviation; SMD, standardized mean difference; sTIM-3, soluble T-cell immunoglobulin and mucin domain-containing protein 3; Cr, creatinine.

Table 2. Comparison between rejection group and non-rejection group.

Variables	Rejection group (n = 58)	Non-rejection group (n = 262)	Statistic	p
Donor age (years), mean ± SD	45.60 ± 11.80	44.14 ± 10.07	t = 0.97	0.33
Donor sex, n (%)			χ^2 = 0.27	0.61
Female	22 (37.93)	109 (41.60)		
Male	36 (62.07)	153 (58.40)		
Donor-recipient age difference ≥25 years, n (%)			χ^2 = 19.50	<0.01
No	32 (55.17)	215 (82.06)		
Yes	26 (44.83)	47 (17.94)		
Recipient age (years), mean ± SD	46.97 ± 10.71	44.95 ± 9.73	t = 1.40	0.16
Recipient sex, n (%)			χ^2 = 0.20	0.65
Female	19 (32.76)	78 (29.77)		
Male	39 (67.24)	184 (70.23)		
BMI (kg/m^2), mean ± SD	23.78 ± 2.66	23.35 ± 2.36	t = 1.24	0.22
Preoperative dialysis time (months), M (Q_1, Q_3)	15.65 (10.58, 20.40)	16.55 (11.30, 23.83)	Z = –0.97	0.33
Primary disease, n (%)			χ^2 = 7.38	0.19
Chronic glomerulonephritis	19 (32.76)	95 (36.26)		
Diabetic nephropathy	7 (12.07)	18 (6.87)		
Hypertensive nephropathy	3 (5.17)	25 (9.54)		
Interstitial nephritis	7 (12.07)	56 (21.37)		
Others	13 (22.41)	39 (14.89)		
Polycystic kidney disease	9 (15.52)	29 (11.07)		
PIV, mean ± SD	436.58 ± 78.27	365.92 ± 85.62	t = 5.77	<0.01
Serum sTIM-3, M (Q_1, Q_3)	9594.50 (7898.25, 11588.00)	6227.50 (4856.50, 7630.00)	Z = –8.83	<0.01
Urinary sTIM-3, M (Q_1, Q_3)	1989.00 (1554.50, 2439.50)	1094.00 (897.25, 1393.50)	Z = –9.12	<0.01
Dialysis type, n (%)			χ^2 = 1.45	0.23
Hemodialysis	51 (87.93)	213 (81.30)		
Peritoneal dialysis	7 (12.07)	49 (18.70)		
HLA mismatch number, n (%)			χ^2 = 7.39	0.01
<3 mismatches	20 (34.48)	142 (54.20)		
≥3 mismatches	38 (65.52)	120 (45.80)		
PRA status, n (%)			χ^2 = 3.15	0.08
Negative	49 (84.48)	241 (91.99)		
Positive	9 (15.52)	21 (8.02)		
DSA status, n (%)			χ^2 = 3.01	0.08
Negative	50 (86.21)	246 (93.89)		
Positive	8 (13.79)	16 (6.11)		
Cold ischemia time ≥12 hours, n (%)			χ^2 = 7.48	0.01
No	40 (68.97)	221 (84.35)		
Yes	18 (31.03)	41 (15.65)		
Transplant number, n (%)			χ^2 = 0.78	0.38
First transplantation	51 (87.93)	240 (91.60)		
Re-transplantation	7 (12.07)	22 (8.40)		
Induction type, n (%)			χ^2 = 0.20	0.65
Protocol A	32 (55.17)	153 (58.40)		
Protocol B	26 (44.83)	109 (41.60)		
Immunosuppression, n (%)			χ^2 = 0.71	0.40
Regimen A	20 (34.48)	106 (40.46)		
Regimen B	38 (65.52)	156 (59.54)		

in the validation set, we explored threshold adjustment as a potential optimization strategy. When the cut-off was lowered to 0.080, sensitivity increased to 0.88 (0.64–0.99), with a specificity of 0.64 (0.57–0.78); at a cut-off of 0.100, sensitivity was 0.71 (0.44–0.90) and specificity was 0.73 (0.62–0.83); at a cut-off of 0.200, sensitivity was 0.59 (0.33–0.82) and specificity was 0.85 (0.75–0.92). Thus, the optimal cut-off should be selected according to the clinical context.

Table 3. Univariate logistic regression analysis of the influencing factors of acute rejection after kidney transplantation.

Variables	β	SE	Z	*p*	OR (95% CI)
Donor age (years)	0.020	0.017	1.174	0.240	1.020 (0.987–1.054)
Donor sex					
Female					1.000 (Reference)
Male	0.070	0.350	0.199	0.842	1.072 (0.540–2.131)
Donor-recipient age difference ≥25 years					
No					1.000 (Reference)
Yes	1.563	0.367	4.260	<0.001	4.773 (2.325–9.796)
Recipient age (years)	0.007	0.018	0.400	0.689	1.007 (0.973–1.042)
Recipient sex					
Female					1.000 (Reference)
Male	–0.001	0.371	–0.002	0.999	0.999 (0.483–2.069)
BMI (kg/m^2)	0.108	0.071	1.533	0.125	1.115 (0.970–1.280)
Preoperative dialysis time (months)	–0.031	0.022	–1.408	0.159	0.970 (0.929–1.012)
Primary disease					
Chronic glomerulonephritis					1.000 (Reference)
Diabetic nephropathy	0.610	0.603	1.012	0.311	1.841 (0.565–5.998)
Hypertensive nephropathy	–0.280	0.687	–0.408	0.683	0.756 (0.196–2.906)
Interstitial nephritis	–0.280	0.529	–0.530	0.596	0.756 (0.268–2.129)
Others	–0.192	0.566	–0.339	0.734	0.825 (0.272–2.504)
Polycystic kidney disease	0.812	0.520	1.562	0.118	2.252 (0.813–6.238)
PIV (per 100)	0.969	0.222	4.355	<0.001	2.635 (1.704–4.074)
Serum sTIM-3 (per 100 pg/mL)	0.078	0.012	6.496	<0.001	1.081 (1.056–1.106)
ln(urinary sTIM-3) (per 10-unit increase)	0.525	0.079	6.683	<0.001	1.691 (1.449–1.972)
Dialysis type					
Hemodialysis					1.000 (Reference)
Peritoneal dialysis	–0.423	0.515	–0.820	0.412	0.655 (0.239–1.800)
HLA mismatch number					
<3 mismatches					1.000 (Reference)
≥3 mismatches	0.866	0.367	2.360	0.018	2.377 (1.158–4.877)
PRA status					
Negative					1.000 (Reference)
Positive	0.893	0.533	1.675	0.094	2.443 (0.859–6.948)
DSA status					
Negative					1.000 (Reference)
Positive	1.087	0.549	1.981	0.048	2.966 (1.012–8.692)
Cold ischemia time ≥12 hours					
No					1.000 (Reference)
Yes	0.862	0.391	2.207	0.027	2.368 (1.101–5.091)
Transplant number					
First transplantation					1.000 (Reference)
Re-transplantation	0.371	0.544	0.682	0.495	1.450 (0.499–4.213)
Induction type					
Protocol A					1.000 (Reference)
Protocol B	–0.127	0.353	–0.358	0.720	0.881 (0.441–1.761)
Immunosuppression					
Regimen A					1.000 (Reference)
Regimen B	0.450	0.375	1.198	0.231	1.568 (0.751–3.270)

SE, standard error; OR, odds ratio; CI, confidence interval; ln, natural logarithm. Continuous variables were scaled per 100 (PIV), per 100 pg/mL (serum sTIM-3), and per 10-unit increase in ln(urinary sTIM-3) to facilitate interpretation of odds ratios.

Table 4. Multivariate logistic regression analysis of independent influencing factors of acute rejection after kidney transplantation.

Variables	β	SE	Z	*p*	OR (95% CI)
Donor-recipient age difference ≥25 years					
No					1.000 (Reference)
Yes	1.994	0.593	3.364	<0.001	7.347 (2.299–23.482)
HLA mismatch category					
<3 mismatches					1.000 (Reference)
≥3 mismatches	1.407	0.579	2.430	0.015	4.084 (1.313–12.703)
PIV (per 100)	0.752	0.282	2.669	0.008	2.121 (1.221–3.685)
ln(urinary sTIM-3) (per 10-unit increase)	0.592	0.101	5.869	<0.001	1.808 (1.484–2.204)

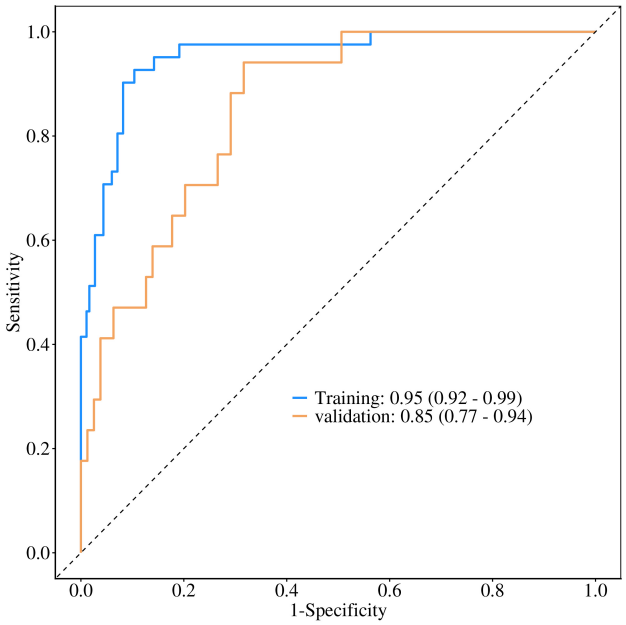


Fig. 1. Receiver operating characteristic (ROC) curves of the training and validation sets for predicting acute rejection after kidney transplantation.

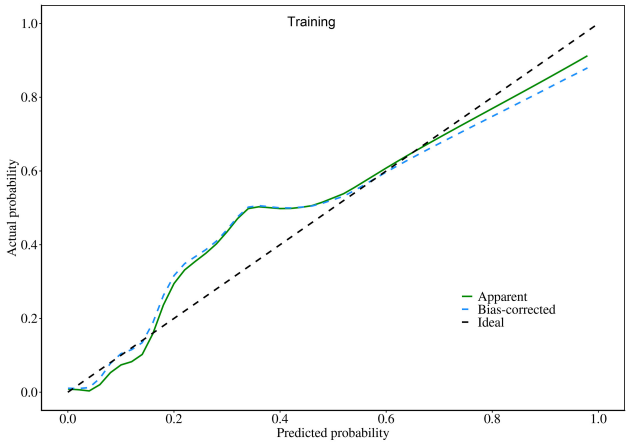


Fig. 2. Calibration curves for the training set.

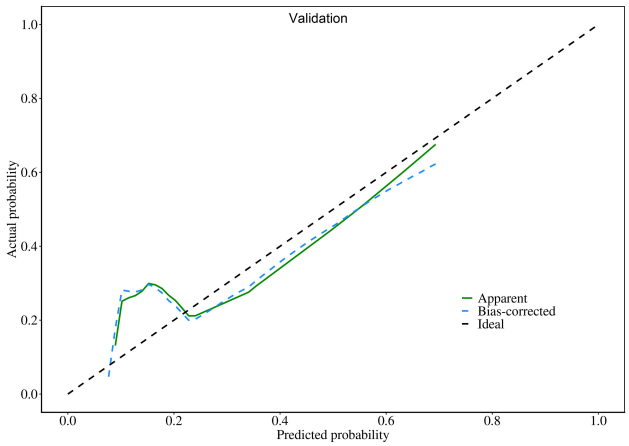


Fig. 3. Calibration curve of the validation set.

3.6 Calibration Curves and Clinical Utility

The calibration curve for the training set showed acceptable agreement between the predicted and observed probabilities, although some deviation was observed in the mid-range probability region. In the validation set, the calibration curve exhibited greater fluctuations, likely due to the smaller sample size (Figs. 2,3). Overall, the Hosmer–Lemeshow test confirmed good calibration in both sets (training: $\chi^2 = 5.59$, df = 8, $p = 0.69$; validation: $\chi^2 = 7.81$, df = 8, $p = 0.45$). DCA showed that the model demonstrated a positive net benefit within the threshold probability range of 10% to 60%, suggesting good clinical utility (Figs. 4,5).

4. Discussion

Acute rejection after kidney transplantation remains a major factor hampering the long-term survival of the transplanted kidney. Despite the continuous optimization of immunosuppressive regimens such as calcineurin inhibitors, the incidence of postoperative acute rejection remains at approximately 10% to 30%. Traditional serum creatinine monitoring is not particularly useful because any detectable changes in its levels are non-specific and typically happen after pathological changes related to acute rejection have occurred. Renal transplant biopsy is the gold-standard strategy for detection, but this method is not suitable for repeated use owing to its invasiveness. Therefore, it is of great clinical significance to develop non-invasive, reproducible biomarkers and predictive models for early de-

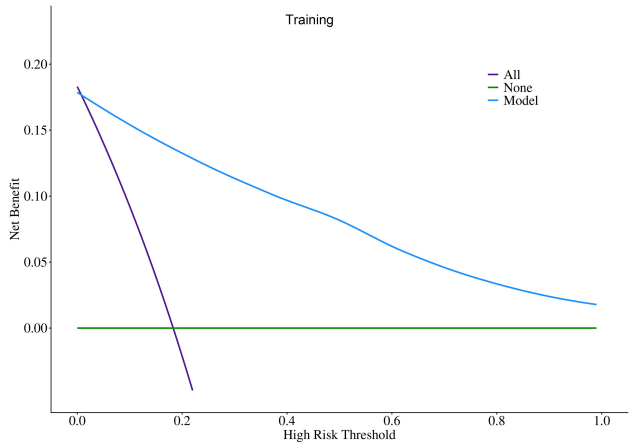


Fig. 4. Decision curve analysis (DCA) of the training set.

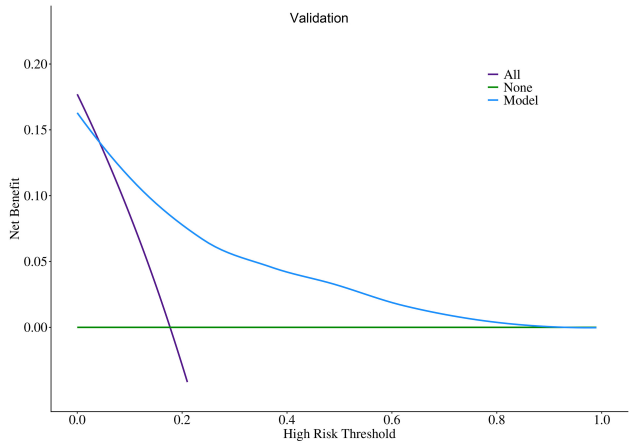


Fig. 5. Decision curve analysis of the validation set.

tection of acute rejection following kidney transplantation. Based on a retrospective cohort of 320 renal transplant recipients, we systematically analyzed the predictive efficacy of urinary sTIM-3, a marker of TIM-3 signaling pathway activation, and PIV, a novel inflammatory composite index, for acute rejection after renal transplantation. We also established a predictive model integrating donor-recipient age difference and HLA mismatch number. The model provides a new non-invasive tool for enabling early risk stratification of acute rejection after kidney transplantation.

This study identified postoperative urinary sTIM-3 level as an independent risk factor for acute rejection. In the multivariate analysis, serum sTIM-3 was excluded from stepwise regression because of collinearity with urine sTIM-3; this suggests that urinary sTIM-3 may be superior in reflecting local immune activation. This compartmental difference between serum and urinary sTIM-3 has important immunological implications. Mechanistically, membrane-bound TIM-3, as a negative costimulatory molecule, is mainly expressed on the surface of T-cells. Under physiological conditions, TIM-3 can negatively regulate T-cell immune response when bound to its ligand galectin-9. T-cell exhaustion and apoptosis are induced to maintain immune tolerance [25,26]. However, in the early stage of acute rejection, a large number of activated effector T-cells (especially T helper 1 [Th1] and T helper 17 [Th17] cells) in the graft microenvironment upregulate the expression of TIM-3, which is actually a compensatory response of the body to stop the negative feedback regulation. At the same time, the activity of inflammatory factors (such as a disintegrin and metalloproteinase 10 [ADAM10]/a disintegrin and metalloproteinase 17 [ADAM17]) in the microenvironment is significantly enhanced, and the highly expressed membrane TIM-3 is cleaved and released into circulation and urine to form soluble sTIM-3 [10]. Therefore, the marked increase in urinary sTIM-3 levels may not simply reflect systemic immune activation, but more precisely reveal an enhanced local effector T-cell immune response that exceeds the negative feedback regulatory capacity of the TIM-3/Gal-9 pathway. Given the relationship of urinary sTIM-3 levels with immune response, sTIM-3 immunosuppression monitoring for patients with elevated urinary sTIM-3 levels after surgery should be strengthened, and the follow-up interval should be shortened. Our findings are consistent with previous studies on urinary sTIM-3 in acute rejection. Chen et al. [11] reported an AUC of 0.88, and Shahbaz et al. [27] further confirmed the diagnostic value of urinary TIM-3. However, these studies focused on diagnosis at the time of rejection rather than early prediction. To our knowledge, this is the first study to demonstrate that urinary sTIM-3 measured on postoperative day 7 can predict subsequent acute rejection.

Another finding of the present study was that PIV on postoperative day 7 was an independent predictor of acute rejection. PIV integrates four blood cell components, including neutrophils, monocytes, platelets, and lymphocytes, which can more comprehensively reflect systemic inflammation and immune balance [28]. The increased number of neutrophils, monocytes, and platelets, and the decreased number of lymphocytes, represented by elevated PIV, coincide with the innate immune activation and adaptive immune homing characteristic of acute rejection. The elevation of neutrophils reflects the rapid mobilization of innate immunity. Recent studies have shown that extracellular traps released by neutrophils can directly activate alloreactive T-cells and amplify adaptive immune responses [29]. The increase in monocytes reflects the mobilization of antigen-presenting cell precursors, and their differentiated macrophages promote the differentiation of Th1/Th17 cells by secreting interleukin-12 (IL-12)/interleukin-23 (IL-23), providing costimulatory signals for T-cell activation [30]. The increase in platelets reveals their immunomodulatory bridge role: activated platelets can stimulate the activation of T-cells and promote the extravasation of neutrophils into grafts [31]. The relative reduction of lymphocytes is not immunosuppression, but a manifestation of excessive homing of T-cells to the transplanted kidney. A large number of donor-specific T-cells are recruited to the graft site, leading to peripheral blood lymphopenia [32]. In sum-

mary, PIV is a potential immune rejection signature before acute rejection, characterized by a synergistic state of innate immune activation (increased neutrophils, monocytes, and platelets) and adaptive immune homing (decreased lymphocytes). Using a single indicator is difficult to predict immune rejection. With four blood cell components captured in an index, PIV can accurately reflect the immune status before acute rejection. Previous studies have explored other inflammation-immune composite indices in kidney transplantation, such as NLR [14] and SII [15], but these integrate only two or three blood cell components. To our knowledge, this is the first study to demonstrate that PIV, which integrates four blood cell components, is an independent predictor of acute rejection after kidney transplantation, extending its application from oncology to organ transplantation.

This study is the first to apply urinary sTIM-3 combined with PIV in the early prediction of acute rejection after kidney transplantation, and the synergistic mechanism behind it is worth exploring. Elevated urinary sTIM-3 reflects graft local immune activation, characterized by effector T-cell overactivation and impaired negative regulation, while elevated PIV reflects systemic inflammatory microenvironment formation that is conducive to T-cell activation through coordinated involvement of innate immune cells and platelets. Thus, from complementary local and systemic perspectives, urinary sTIM-3 and PIV may together provide a more comprehensive representation of the immune state before acute rejection.

In addition to the novel biomarkers mentioned above, this model also included two classic immunological risk factors: donor-recipient age difference ≥25 years and HLA mismatch ≥3, both of which are strong independent predictors of acute rejection. The large age difference between donors and recipients may reflect changes in the immunogenicity of donor kidneys and differences in the immune response of recipients [33]. High HLA mismatch load directly increases the probability that donor antigens are recognized by recipient T-cells [34]. Our finding is consistent with Gao et al. [35], who reported HLA B eplet mismatch as an independent risk factor for acute rejection, supporting the well-established role of HLA mismatch in defining high immunological risk. This model, combining urinary sTIM-3, PIV, and two easily obtainable clinical factors, showed good discrimination (AUC 0.95), satisfactory calibration, and a favorable net benefit in DCA over the 10%–60% risk threshold, suggesting promising applicability in clinical practice.

The sensitivity of the predictive model in the validation set (0.59) was lower than that in the training set (0.93). Several factors may account for this discrepancy. First, the sample size of the validation set was relatively small (n = 96), which may have limited the statistical power. Second, as the model was developed based on the training set, some degree of overfitting is inevitable, leading to reduced performance when applied to an independent validation cohort. Third, differences in the distribution of baseline characteristics between the two sets may have also contributed to the lower sensitivity, although no significant differences were observed in most variables. Future external validation in larger, multicenter cohorts is needed to further evaluate the generalizability of the model.

Limitation

Our study has several limitations that should be interpreted within the following broader categories. First, regarding study design, this was a retrospective, single-center study with a relatively small sample size. Although the model demonstrated good performance in internal validation, selection bias may still be present, and prospective multicenter external validation is needed to evaluate its generalizability. In addition, due to the limited sample size, we were unable to perform subgroup analyses by donor type (deceased vs. living), rejection subtype (T-cell-mediated vs. antibody-mediated), transplant number, or sensitization status. The predictive performance of the model may differ across these subgroups, and future studies with larger cohorts are needed to validate our findings. Furthermore, although all patients were clinically stable at the time of sample collection on postoperative day 7 and most rejection episodes were diagnosed thereafter, the possibility of subclinical rejection already present at day 7 cannot be completely excluded; therefore, the distinction between predictive and response markers should be interpreted with caution. Second, regarding measurement and follow-up, urinary sTIM-3 and PIV were detected only at a single time point on the 7th day after surgery, and their changes were not dynamically monitored. Future studies should explore whether continuous monitoring at multiple time points (such as postoperative days 1, 3, 7, and 14) can further improve predictive sensitivity. In addition, the model predicted the overall risk of acute rejection within 6 months after transplantation and did not distinguish between different timings of rejection, such as early versus late rejection. Third, regarding statistical considerations and generalizability, patients with DGF within 1 week post-transplant were excluded because early DGF may interfere with the diagnosis and timing of acute rejection, as well as affect the reliability of urinary sTIM-3 and PIV levels; consequently, the applicability of this model to patients with early DGF remains uncertain. We also acknowledge that using a $p < 0.05$ threshold for multivariate inclusion may have excluded some clinically relevant factors, although candidate variables were prespecified based on literature and clinical experience. Future studies with larger sample sizes are needed to further validate the findings regarding TIM-3 and sTIM-3.

5. Conclusion

In conclusion, this study evaluated the combined value of urinary sTIM-3 and PIV for the early prediction of acute rejection after kidney transplantation, and found that both

biomarkers measured on postoperative day 7 were independently associated with the risk of acute rejection. Mechanistically, elevated urinary sTIM-3 may reflect enhanced local effector T-cell activation and impaired negative regulation within the graft, whereas elevated PIV offers an immune rejection signature that allows for early warning of acute rejection following kidney transplantation. The predictive model incorporating donor-recipient age difference and HLA mismatch number demonstrated good performance in discrimination, calibration, and clinical utility, providing a non-invasive tool for individualized risk stratification and immunosuppressive regimen optimization in renal transplant recipients. These findings require further validation in larger prospective multicenter cohorts.

Key Points

• Elevated urinary sTIM-3 on postoperative day 7 reflects local immune activation and is an independent predictor of subsequent acute rejection.

• Elevated PIV on postoperative day 7, reflecting systemic inflammation and immune dysregulation, is also independently associated with an increased risk of acute rejection.

• A predictive model combining urinary sTIM-3, PIV, donor-recipient age difference ≥25 years, and HLA mismatch ≥3 demonstrated good performance in discrimination and calibration, providing a practical non-invasive tool for early risk stratification after kidney transplantation.

• This model may facilitate early identification of high-risk patients and guide individualized immunosuppressive management.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MZ and ZFS designed the research study. MZ and RL performed the research. ZFS and JL analyzed the data. MZ drafted the article. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was a retrospective analysis, and the data were anonymized and approved by the Medical Ethics Committee of Shulan (Hangzhou) Hospital (approval number: KY2026091). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Due to the retrospective nature of the study and the anonymization of the data, the Medical Ethics Committee of Shulan (Hangzhou) Hospital waived the patient's informed consent.

Acknowledgment

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Conflicts of Interest

The authors declare no conflicts of interest.

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