Development and internal validation of a predictive nomogram for early postoperative bacterial infections following liver transplantation in patients with hepatocellular carcinoma

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Background: Early postoperative bacterial infections (EPBIs) represent a significant complication following liver transplantation (LT) in individuals with hepatocellular carcinoma (HCC). However, existing predictive tools derived from general LT populations fail to account for HCC-specific risk factors, including cirrhosis-associated immune dysfunction compounded by tumor-induced immunosuppression, frequent healthcare exposures from bridging therapies, and surgical complexities unique to HCC patients. This study aimed to develop and internally validate HCC-specific predictive models for EPBI risk stratification.

Methods: A retrospective cohort study was conducted on 549 consecutive HCC patients undergoing LT between 2015 and 2025. EPBI was defined as any bacterial infection occurring within 30 days postoperatively. Consecutive patients who met the inclusion criteria were enrolled. Data collectors responsible for assessing preoperative and intraoperative predictors were blinded to postoperative infection outcomes to minimize ascertainment bias, particularly for outcomes that require clinical judgment such as infection classification. Three predictive models were constructed: a conventional logistic regression model (Model 1), a stepwise regression model optimized using the Akaike information criterion (AIC; Model 2), and a least absolute shrinkage and selection operator (LASSO)-Ridge regression model (Model 3). Model performance was evaluated based on discrimination [area under the curve (AUC)], calibration, clinical utility, and internal validation using 10-fold cross-validation and bootstrapping.

Results: The cohort had a median age of 55 years [interquartile range (IQR), 49–60 years], with 85.1% male patients. EPBI occurred in 250 patients (45.5%), mainly pulmonary (51.2%) and intra-abdominal (43.3%). Among 468 isolates, Gram-negative (51.7%) and Gram-positive (48.3%) bacteria were similarly distributed. Multivariate analysis identified Child-Pugh class B, prolonged operative time, extended intensive care unit (ICU) stay, and decreased postoperative estimated glomerular filtration rate (eGFR) as independent predictors. Model 2 showed fair-to-good discrimination [AUC 0.784, 95% confidence interval (CI): 0.746–0.822]. At the optimal cutoff, sensitivity was 72.4% (95% CI: 68.2–76.6%), specificity 71.2% (95% CI: 67.1–75.3%), positive predictive value (PPV) 69.8% (95% CI: 65.4–74.2%), and negative predictive value (NPV) 73.1% (95% CI: 69.0–77.2%). Decision curve analysis (DCA) demonstrated greater net benefit than treat-all or treat-none strategies at a 6.3% risk threshold.

Conclusions: This study developed and internally validated a nomogram for EPBI in HCC patients undergoing LT. The model demonstrates fair discriminative ability and potential clinical utility, supporting

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its potential for early risk stratification and targeted prevention strategies in clinical practice. External validation is required before widespread clinical implementation.

Keywords: Early postoperative bacterial infections (EPBIs); hepatocellular carcinoma (HCC); liver transplantation (LT); predictive nomogram

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Introduction

Liver transplantation (LT) is considered the gold-standard curative intervention for individuals with hepatocellular carcinoma (HCC) who meet either the Milan or Hangzhou criteria, with long-term survival outcomes remaining favorable in appropriately selected cases (1). Despite advancements in surgical techniques and immunosuppressive management, early postoperative bacterial infections (EPBI) represent a major and potentially fatal complication following LT (2). Recent studies have reported EPBI incidence rates ranging from 20% to 60%, with associated mortality reaching up to 30% in specific patient subgroups (3-6). While EPBI represents a major complication in HCC patients undergoing LT, current prediction tools remain inadequate for this specific population.

Highlight box

Key findings

- An hepatocellular carcinoma (HCC)-specific nomogram incorporating perioperative factors effectively predicts early postoperative bacterial infections (EPBIs) after liver transplantation (LT).

What is known and what is new?

- EPBIs are a frequent complication after LT, but existing prediction models are based on general transplant populations.
- This study introduces and internally validates a prediction model specifically tailored to HCC patients, accounting for tumor- and procedure-related risks.

What is the implication, and what should change now?

- The nomogram enables early risk stratification to support targeted prevention and optimized postoperative management in HCC transplant recipients.
- External validation and prospective studies are needed before widespread clinical adoption.

Current EPBI prediction in LT primarily relies on models derived from general transplant populations. The Model for End-Stage Liver Disease (MELD)-based infection risk scores (e.g., MELD >20–30 thresholds) demonstrate reduced accuracy in HCC recipients due to the discordance between oncologic transplantation timing and hepatic dysfunction severity. Similarly, general surgical site infection models neglect HCC-specific immunosuppressive states, while inflammation-based scores [e.g., neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP)] fail to account for the unique immune dysregulation of concurrent cirrhosis and cancer. This performance gap necessitates HCC-specific risk stratification that integrates tumor-related immunosuppression, prior treatment exposures, and HCC-specific surgical factors.

This predictive inadequacy is further compounded by the distinct infection susceptibility profile of HCC patients, which stems from the convergence of three high-risk conditions: (I) the presence of cirrhosis-associated immune dysfunction compounded by immunosuppressive effects of the tumor microenvironment; (II) frequent exposure to healthcare settings resulting from pre-transplant bridging therapies such as transarterial chemoembolization (TACE) and ablation, which increase the risk of colonization with multidrug-resistant (MDR) organisms; and (III) intraoperative challenges, including portal vein reconstruction and extended operative durations, that facilitate bacterial translocation. Although current research in LT primarily emphasizes long-term oncological outcomes such as adherence to the Milan criteria and recurrence of HCC, early postoperative infections remain insufficiently explored, despite being a leading cause of preventable mortality in this population (7).

The prognostic superiority of composite inflammatory indices over traditional markers like leukocyte count lies in their ability to capture the multifaceted immune

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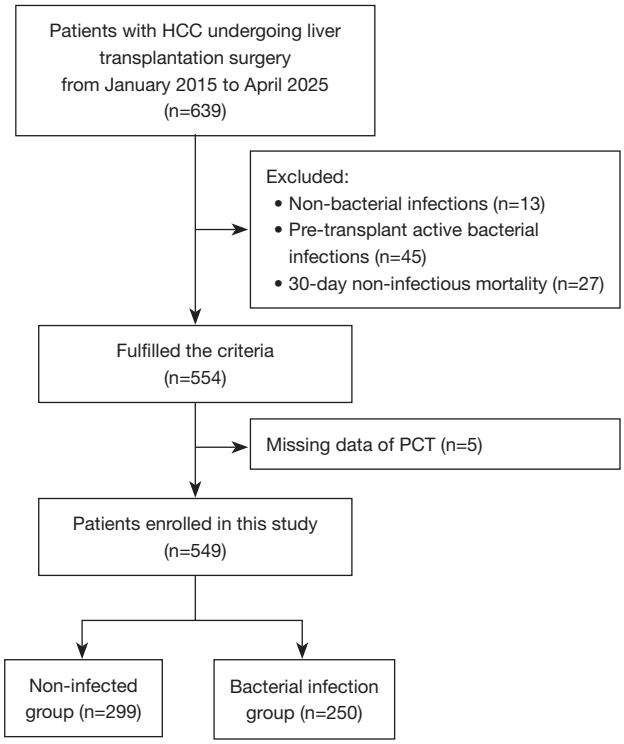

Figure 1 Flowchart of study subject selection process. HCC, hepatocellular carcinoma; PCT, procalcitonin.

dysregulation characteristic of HCC patients. The NLR reflects the critical balance between neutrophil-mediated innate inflammatory activation and lymphocyte-dependent adaptive immune competence. Similarly, the pan-immune-inflammation value (PIV) and systemic immune-inflammation index (SII) extend this assessment by incorporating monocytes (essential for pathogen recognition and antigen presentation) and platelets, which contribute to thrombosis-mediated immunomodulation. These composite indices thus provide a more integrated evaluation of net immune status in the context of combined cirrhosis and cancer-related immunosuppression.

Although current research in LT primarily emphasizes long-term oncological outcomes such as adherence to the Milan criteria and recurrence of HCC, early postoperative infections remain insufficiently explored, despite being a leading cause of preventable mortality in this population.

In this study, we developed the first infection risk stratification model specifically tailored for individuals with HCC undergoing LT. A unique feature of this study is the comparative evaluation of three modeling strategies [i.e., conventional logistic regression, stepwise Akaike information criterion (AIC) optimization, and least absolute shrinkage and selection operator (LASSO)-Ridge regularization] to identify the optimal balance between statistical performance and clinical applicability for this specific patient population. Table S1 compares variables used in existing prediction models versus our proposed HCC-specific approach, highlighting the novel integration of tumor-related factors often omitted from conventional models.

The study has three specific objectives: first, to determine the incidence and microbiological characteristics of EPBI following LT; second, to identify HCC-specific risk factors for EPBI through comprehensive analysis of preoperative, intraoperative, and postoperative variables; and third, to construct and validate a clinically applicable nomogram for EPBI risk stratification to support timely and targeted clinical interventions. This work aims to advance precision antimicrobial strategies for transplant recipients with HCC and reduce infection-related graft loss and mortality. We present this article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-786/rc).

Methods

This study was approved by the Institutional Review Board of Beijing Youan Hospital of Capital Medical University (No. LL-2024-127-K), in accordance with national transplantation regulations and the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants following the required 24-hour reflection period, with voluntariness independently verified. Organ allocation and data management adhered to national regulatory standards.

Patient selection

A total of 639 consecutive patients with HCC who underwent orthotopic LT at the hospital between January 2015 and April 2025 were initially screened for this retrospective observational cohort study. The following exclusion criteria were applied: (I) presence of non-bacterial infections (n=13); (II) active infections prior to transplantation (n=45); (III) mortality within 30 days post-transplantation due to non-infectious complications (n=27); and (IV) incomplete key clinical or laboratory data (n=5). Following these exclusions, 549 individuals were included in the final analysis (*Figure 1*).

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Definition and diagnostic criteria for infection

EPBI was defined as any bacterial infection occurring within 30 days following LT. Diagnoses were established through a systematic review of electronic medical records, microbiological culture results, and transplant registry data, in accordance with the standardized surveillance criteria established by the Centers for Disease Control (8). To minimize ascertainment bias, a structured blinding protocol was implemented: data collectors assessing preoperative and intraoperative predictor variables were blinded to postoperative infection outcomes, while the outcome adjudication team determined EPBI diagnoses using standardized Centers for Disease Control and Prevention (CDC) criteria without access to predictor data. Infections were classified into the following categories: Pulmonary infections, intra-abdominal infections, urinary tract infections, surgical site infections, and bloodstream infections.

Colonization was rigorously distinguished from infection using CDC criteria: pulmonary infections: required clinical symptoms + radiographic evidence + significant pathogen; urinary tract infections**: mandated symptoms + pyuria + $\geq 10^5$ colony-forming unit (CFU)/mL; all diagnoses** underwent independent adjudication by infectious disease specialists.

Patient management

All patients included in the study underwent standard LT using either the conventional or piggyback technique followed by uniform postoperative management protocols. Immunosuppressive therapy consisted of tacrolimus/cyclosporine, mycophenolate mofetil, and tapered corticosteroids. Routine antibacterial prophylaxis was administered to all recipients. For patients positive for hepatitis B virus (HBV) infection, combination prophylaxis with hepatitis B immunoglobulin and nucleos(t)ide analogs were provided. Postoperative care included comprehensive monitoring through daily laboratory testing, systematic surveillance for infectious complications, and protocol-driven assessment for rejection when clinically indicated.

Data collection

Data extracted from electronic medical records encompassed the following categories: (I) Baseline characteristics, including age, sex, ABO blood type, presence of hypertension or diabetes mellitus, hepatic encephalopathy, ascites, cirrhosis, history of interventional ablation, MELD score, and Child-Pugh classification; (II) laboratory parameters: preoperative (day –1) measurements denoted with suffix "_0" included white blood cell count (WBC_0), lymphocyte count (L_0), platelet count (PLT_0), monocyte count (M_0), neutrophil count (N_0), hemoglobin (Hb_0), prothrombin activity (PTA_0), alanine aminotransferase (ALT_0), aspartate aminotransferase (AST_0), albumin (ALB_0), estimated glomerular filtration rate (eGFR_0), prognostic nutritional index (PNI_0), platelet-to-lymphocyte ratio (PLR_0), NLR_0, lymphocyte-to-monocyte ratio (LMR_0), SII_0, PIV_0, platelet-to-albumin ratio (PAR_0), neutrophil-to-platelet ratio (NPR_0). Postoperative (day +1) measurements denoted with suffix "_1" included corresponding parameters (WBC_1, L_1, PLT_1, M_1, N_1, Hb_1, PTA_1, ALT_1, AST_1, ALB_1, eGFR_1, PNI_1, PLR_1, NLR_1, LMR_1, SII_1, PIV_1, PAR_1, NPR_1), with the addition of procalcitonin (PCT_1). (III) Intraoperative variables, including operation time, intraoperative blood loss, volume of blood transfusion, and cold ischemic time. (IV) Postoperative outcomes, including initial tacrolimus concentration, length of hospital stay, length of intensive care unit (ICU) stay. (V) Infection-specific data, including pathogen spectrum and anatomical distribution of infections.

PNI, PLR, NLR, LMR, SII, PIV, PAR and NPR were calculated as follows: PNI = ALB + 5 × L; PLR = PLT/L; NLR = N/L; LMR = L/M; SII = PLT × N/L; PIV = N × M × PLT/L; PAR = PLT/ALB; NPR = N/PLT.

Sample size justification and overfitting prevention

The final cohort size of 549 patients was determined by consecutive enrollment of all eligible HCC patients undergoing LT between January 2015 and April 2025. Post-hoc power analysis demonstrated that this sample provides >90% statistical power to detect an AUC of 0.75 with alpha =0.05, adequate for the objectives of this predictive modeling study. Although the initial variable pool contained 32 candidate predictors, rigorous variable selection procedures were employed to mitigate overfitting risk. The final models utilized 6–8 predictors against 250 EPBI events, yielding events-per-variable (EPV) ratios ranging from 31.3:1 to 41.7:1, which exceed the recommended minimum threshold of 10:1 for logistic regression. Additional safeguards against overfitting included regularization techniques (LASSO-Ridge), internal validation with 10-fold cross-validation, and bootstrap

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validation with 1,000 iterations.

Blinding protocol

Data collectors extracting predictor variables were blinded to infection outcomes. Outcome assessors determining EPBI diagnoses were blinded to predictor data. Infection classification followed standardized CDC criteria with independent adjudication.

Prediction model development

Three distinct logistic regression models were developed to predict the risk of EPBI following LT, using complementary approaches to variable selection. The comparative modeling approach was designed to balance statistical performance with clinical applicability, hypothesizing that regularized regression would better handle potential multicollinearity while stepwise selection might yield more parsimonious models.

- Model 1: variable selection was based on a sequential statistical filtering process employing a dual-threshold approach to address methodological limitations of traditional univariate screening. Clinically plausible variables were initially screened through univariate logistic regression using an inclusive threshold of $P<0.20$ to identify potential predictor candidates. This relaxed criterion aimed to reduce the risk of omitting variables that might exhibit significance only in multivariate contexts (suppressor effects) or function as important confounders. Variables meeting this initial threshold were then included in a multivariate logistic regression model, with final model inclusion requiring a conventional threshold of $P<0.05$ to ensure statistical rigor and clinical interpretability. Predictors exhibiting marginal significance ($P>0.1$) in the final multivariate model were excluded. This dual-threshold approach emphasized clinical interpretability while maintaining statistical robustness against Type I error inflation.
- Model 2: automated variable selection was conducted using bidirectional stepwise regression based on minimization of the AIC. The process commenced with all variables significant in univariate analysis ($P<0.05$) and proceeded through iterative forward inclusion and backward elimination. Variables demonstrating multicollinearity, defined as variance inflation factors >5 were excluded to enhance model stability.
- Model 3: a regularized regression approach was applied using the LASSO (L1 penalty) for feature selection and Ridge regression (L2 penalty) for coefficient stabilization. Feature selection was performed using LASSO regularization with 20-fold cross-validation. This method inherently excluded non-contributory predictors while retaining clinically relevant variables.

Final model construction and visualization

Each model was constructed using its respective optimized predictor set. Final outputs were visualized as nomograms to facilitate clinical interpretation and application in patient risk stratification.

Prediction model evaluation

Model performance was rigorously evaluated using a tripartite analytical framework encompassing discrimination, calibration, and clinical utility. Discriminative performance was assessed using receiver operating characteristic (ROC) curves and quantified by the area under the curve (AUC). Calibration was determined by comparing predicted versus observed infection rates via calibration curves, supplemented by the Hosmer-Lemeshow goodness-of-fit test. Clinical utility was assessed through decision curve analysis (DCA), which quantified the net benefit of model-guided interventions when compared to default clinical strategies across a range of risk thresholds. To ensure robust generalizability, internal validation was conducted using dual resampling methods. Ten-fold cross-validation was used to estimate out-of-sample stability based on mean AUC. In addition, bootstrap validation (1,000-iterations) was performed to obtain optimism-corrected performance estimates.

Statistical analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution were expressed as mean ± standard deviation (SD) and compared using Student's *t*-test. Non-normally distributed variables are expressed as median with interquartile range (IQR) and analyzed using the Mann-Whitney *U* test for two group comparisons or Kruskal-Wallis test for comparisons involving multiple groups. Categorical variables are presented as frequencies and percentages, and were analyzed

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using Pearson's chi-squared (χ^2) test or Fisher's exact test. To compare the discriminative performance of different predictive models, DeLong test was used to analyze the differences between ROC curves, with a two-tailed P<0.05 considered statistically significant. The optimal threshold for each model was determined using the Youden index (sensitivity + specificity – 1), and corresponding diagnostic metrics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) [with 95% confidence intervals (CIs)] were calculated at this threshold. All statistical analyses were conducted using R software (version 4.2.2).

Results

Baseline characteristics of the study population

A total of 549 patients who underwent LT for HCC were included in this study. Among them, 250 patients (45.5%) developed EPBI within 30 days following LT, while 299 patients (54.5%) did not experience any infections (*Table 1*).

Demographic and clinical characteristics

The median age of the cohort was 55 years (IQR, 49.00–60.00 years), with patients in the infected group being slightly older than those without infection (56 *vs.* 54 years, P=0.005). Most patients were male (85.1%), with no sex difference between groups (P=0.99). ABO blood type distribution was comparable across groups (P=0.97).

Higher rates of hepatic encephalopathy (26.0% *vs.* 15.1%, P=0.002), ascites (58.4% *vs.* 43.8%, P=0.001), and cirrhosis (94.4% *vs.* 89.3%, P=0.046) were observed among patients who developed infections. In addition, this group exhibited more severe hepatic dysfunction, with significantly higher proportions classified as Child-Pugh class B (56.4%) and C (23.6%) compared to the non-infection group (45.5% B and 8.4% C; P<0.001), and higher MELD scores (14.0 *vs.* 11.0, P<0.001).

Preoperative immune-inflammatory and nutritional profiles

Preoperative evaluation identified significant differences in inflammatory and nutritional markers between the two groups. Patients who developed EPBI demonstrated a more pronounced pro-inflammatory state, as indicated by significantly higher NLR [3.94 (IQR, 2.50–7.31) *vs.* 3.15 (IQR, 2.00–5.16), P<0.001] and lower LMRs [2.20 (IQR, 1.33–3.08) *vs.* 2.75 (IQR, 2.04–3.81), P<0.001], consistent with systemic immune dysregulation. In addition, these patients exhibited significantly lower PNI values [35.73 (IQR, 32.20–40.94) *vs.* 37.44 (IQR, 33.80–43.22), P=0.001], indicating a compromised nutritional status. Collectively, these findings indicate that patients predisposed to post-transplant infections presented with a distinct profile of immune activation and nutritional impairment prior to transplantation.

Furthermore, patients in the infection group exhibited significantly poorer baseline hematologic and biochemical profiles, including lower Hb (101.00 *vs.* 115.00 g/L, P<0.001), ALB (32.15 *vs.* 33.70 μmol/L, P=0.01), and PTA (59.0% *vs.* 68.0%, P<0.001), along with higher AST levels (48.00 *vs.* 41.00 U/L, P=0.002).

Perioperative outcomes and postoperative course

Significant differences in perioperative parameters were observed between the groups. Patients in the EPBI group underwent more complex intraoperative courses, with longer median operative durations (7.50 *vs.* 6.63 hours, P<0.001). This group experienced greater intraoperative blood loss (median 1,000 *vs.* 600 mL, P<0.001) and required approximately double the volume of blood transfusions (800 *vs.* 400 mL, P<0.001). In addition, cold ischemic times were significantly longer in the EPBI group (318.00 *vs.* 300.00 minutes, P=0.004).

Postoperative outcomes were more severe among patients in the EPBI group. Notably, PCT levels were elevated by a factor of 2.9 [7.40 (IQR, 2.33–22.24) *vs.* 2.59 (IQR, 0.64–8.17) ng/mL, P<0.001]. Renal function was significantly reduced, with eGFR values 8.7% lower than in the non-infected group (96.61 *vs.* 105.83 mL/min/1.73 m^2, P<0.001). Furthermore, the median length of ICU stay was longer among patients with infections (5.00 *vs.* 4.00 days, P<0.001).

Microbiological profile of EPBI after LT

Microbiological cultures obtained from the 250 patients with EPBI yielded a total of 468 distinct bacterial isolates (*Table 2*). Gram-negative organisms comprised 51.7% (242/468) of all isolates, with *Klebsiella pneumoniae* (16.7%), *Acinetobacter baumannii* (9.0%), and *Pseudomonas aeruginosa* (6.0%) being the most frequently identified species. Gram-positive organisms accounted for 48.3% (226/468) of isolates, predominantly *Enterococcus faecium* (14.1%) and *Staphylococcus epidermidis* (13.2%) (*Table 1*). The most common sites of infection were the lungs (51.20%),

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Table 1 General baseline information and preoperative and postoperative variables

Variables	Overall (n=549)	Non-infected group (n=299)	Bacterial infection group (n=250)	P
Age (years)	55 [49–60]	54 [48–60]	56 [51–61]	0.005
Gender				0.99
Male	467 (85.1)	254 (84.9)	213 (85.2)	
Female	82 (14.9)	45 (15.1)	37 (14.8)	
ABO				0.97
A	150 (27.3)	81 (27.1)	69 (27.6)	
B	163 (29.7)	88 (29.4)	75 (30.0)	
O	144 (26.2)	81 (27.1)	63 (25.2)	
AB	92 (16.8)	49 (16.4)	43 (17.2)	
Hypertension	108 (19.7)	56 (18.7)	52 (20.8)	0.62
Diabetes	144 (26.2)	69 (23.1)	75 (30.0)	0.08
Hepatic encephalopathy	110 (20.0)	45 (15.1)	65 (26.0)	0.002
Ascites	277 (50.5)	131 (43.8)	146 (58.4)	0.001
Cirrhosis	503 (91.6)	267 (89.3)	236 (94.4)	0.046
Child-Pugh				<0.001
A	188 (34.2)	138 (46.2)	50 (20.0)	
B	277 (50.5)	136 (45.5)	141 (56.4)	
C	84 (15.3)	25 (8.4)	59 (23.6)	
MELD	12 [9–16]	11 [9–14]	14 [10–19]	<0.001
Interventional ablation	222 (40.4)	125 (41.8)	97 (38.8)	0.53
WBC_0 ($\times10^9$/L)	3.70 [2.58–5.48]	3.69 [2.60–5.21]	3.71 [2.45–5.73]	0.32
Monocyte_0 ($\times10^9$/L)	0.29 [0.19–0.42]	0.28 [0.19–0.41]	0.30 [0.20–0.47]	0.29
Neutrophil_0 ($\times10^9$/L)	2.46 [1.64–3.57]	2.33 [1.62–3.33]	2.55 [1.73–4.01]	0.059
Hb_0 (g/L)	111.00 [87.00–128.00]	115.00 [95.50–131.00]	101.00 [80.00–123.00]	<0.001
ALT_0 (U/L)	32.00 [21.00–49.10]	32.00 [23.00–49.05]	32.15 [19.05–49.77]	0.44
AST_0 (U/L)	43.00 [29.20–69.00]	41.00 [28.00–60.75]	48.00 [30.85–82.75]	0.002
ALB_0 (g/L)	33.00 [29.20–37.20]	33.70 [29.95–38.05]	32.15 [28.60–36.62]	0.01
eGFR_0 (mL/min/1.73 m^2)	99.30 [43.80–110.03]	102.00 [78.05–110.22]	95.96 [21.68–109.90]	0.03
PTA_0	64.00 [52.20–77.30]	68.00 [57.00–79.00]	59.00 [46.00–72.75]	<0.001
PNI_0	36.80 [32.81–41.98]	37.44 [33.80–43.22]	35.73 [32.20–40.94]	0.001
PLR_0	104.39 [70.02–164.48]	102.89 [69.60–160.36]	107.16 [71.80–172.65]	0.50
NLR_0	3.59 [2.16–6.23]	3.15 [2.00–5.16]	3.94 [2.50–7.31]	<0.001
LMR_0	2.50 [1.67–3.59]	2.75 [2.04–3.81]	2.20 [1.33–3.08]	<0.001
SII_0	257.16 [128.04–479.49]	256.15 [126.15–446.28]	259.88 [134.87–568.46]	0.13
PIV_0	75.90 [29.57–169.50]	72.43 [27.53–155.14]	85.27 [32.18–191.74]	0.08

Table 1 *(continued)*

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Table 1 *(continued)*

Variables	Overall (n=549)	Non-infected group (n=299)	Bacterial infection group (n=250)	P
PAR_0	2.18 [1.33–3.56]	2.33 [1.40–3.60]	2.01 [1.22–3.50]	0.08
NPR_0	0.03 [0.02–0.05]	0.03 [0.02–0.04]	0.04 [0.03–0.06]	<0.001
Operation time (hours)	7.00 [6.00–8.12]	6.63 [5.70–7.67]	7.50 [6.35–8.81]	<0.001
Blood loss (mL)	800 [500–1,300]	600 [400–1,000]	1,000 [600–1,500]	<0.001
Blood transfusion volume (mL)	800 [0–1,200]	400 [0–1,100]	800 [400–1,600]	<0.001
Cold ischemic time (minutes)	309.00 [256.00–385.00]	300.00 [245.00–368.00]	318.00 [268.25–396.50]	0.004
WBC_1 ($\times10^9$/L)	7.80 [5.43–11.26]	7.84 [5.49–10.89]	7.80 [5.27–11.62]	0.93
Monocyte_1 ($\times10^9$/L)	0.30 [0.20–0.45]	0.32 [0.22–0.47]	0.29 [0.19–0.43]	0.058
Neutrophil_1 ($\times10^9$/L)	7.13 [4.80–10.31]	7.30 [4.84–10.05]	6.87 [4.67–10.72]	0.74
Hb_1 (g/L)	84.00 [75.00–96.00]	88.00 [78.00–100.00]	81.00 [72.00–91.00]	<0.001
PCT_1 (ng/mL)	4.33 [1.16–13.48]	2.59 [0.64–8.17]	7.40 [2.33–22.24]	<0.001
PTA_1	78.00 [68.00–89.00]	79.00 [71.00–89.00]	77.50 [63.92–88.50]	0.02
eGFR_1 (mL/min/1.73 m^2)	102.40 [79.60–114.00]	105.83 [93.20–117.10]	96.61 [63.31–108.91]	<0.001
ALT_1 (U/L)	270.00 [157.90–446.00]	247.00 [156.25–414.25]	289.50 [162.00–485.25]	0.11
AST_1 (U/L)	126.00 [73.00–269.00]	121.20 [73.00–240.00]	130.20 [73.00–329.78]	0.34
ALB_1 (g/L)	37.90 [35.00–40.60]	38.10 [34.95–41.00]	37.75 [35.30–40.18]	0.53
PNI_1	39.69 [36.88–42.84]	39.95 [36.60–43.00]	39.43 [37.02–42.31]	0.43
PLR_1	173.24 [111.69–265.44]	175.77 [116.76–276.55]	167.74 [109.38–256.72]	0.35
NLR_1	23.75 [15.47–36.10]	23.52 [15.49–34.96]	23.93 [15.06–36.63]	0.60
LMR_1	0.97 [0.67–1.45]	0.96 [0.65–1.38]	1.00 [0.70–1.51]	0.29
SII_1	1,183.10 [697.15–2,138.78]	1,192.83 [726.56–2,172.01]	1,170.33 [662.09–2115.26]	0.32
PIV_1	372.97 [159.88–854.35]	425.04 [180.01–928.05]	340.20 [152.16–692.63]	0.08
PAR_1	1.24 [0.86–1.93]	1.30 [0.91–2.00]	1.15 [0.80–1.83]	0.058
NPR_1	0.14 [0.10–0.20]	0.14 [0.10–0.18]	0.15 [0.10–0.21]	0.040
Tacrolimus concentration (ng/mL)	2.10 [1.00–3.90]	2.50 [1.20–4.20]	1.60 [0.70–3.60]	<0.001
Length of hospital stay (days)	20.00 [15.00–32.00]	19.00 [14.00–29.00]	21.00 [16.00–35.00]	0.07
Length of ICU stay (days)	4.00 [3.00–6.00]	4.00 [3.00–5.00]	5.00 [3.00–9.00]	<0.001

Data are presented as median [interquartile range] or n (%). Suffix "_0" means preoperative (day –1); suffix "_1" means postoperative (day +1). ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; ICU, intensive care unit; LMR, lymphocyte-to-monocyte ratio; MELD, Model for End-Stage Liver Disease; NPR, neutrophil-to-platelet ratio; NLR, neutrophil-to-lymphocyte ratio; PAR, platelet-to-albumin ratio; PCT, procalcitonin; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PTA, prothrombin activity; SII, systemic immune-inflammation index; WBC, white blood cell count.

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Table 2 Distribution of pathogenic bacteria of EPBI after LT

Classification	Pathogenic bacteria	Number of plants	Composition ratio (%)
Gram-negative bacteria (51.7%)	*Klebsiella pneumoniae*	78	16.7
	Acinetobacter baumannii	42	9.0
	Pseudomonas aeruginosa	28	6.0
	Maltooligomonas maltogenes	27	5.8
	Escherichia coli	16	3.4
	Enterobacter cloacae	10	2.1
	Burkholderia cepacia	6	1.3
	Proteus mirabilis	5	1.1
	Others	30	6.4
Gram-positive bacteria (48.3%)	*Enterococcus faecium*	66	14.1
	Staphylococcus epidermidis	62	13.2
	Staphylococcus hemolyticus	18	3.8
	Enterococcus faecalis	17	3.6
	Staphylococcus hominis	15	3.2
	Staphylococcus aureus	14	3.0
	Staphylococcus cephalus	9	1.9
	Others	25	5.3
Total		468	100

EPBI, early postoperative bacterial infection; LT, liver transplantation.

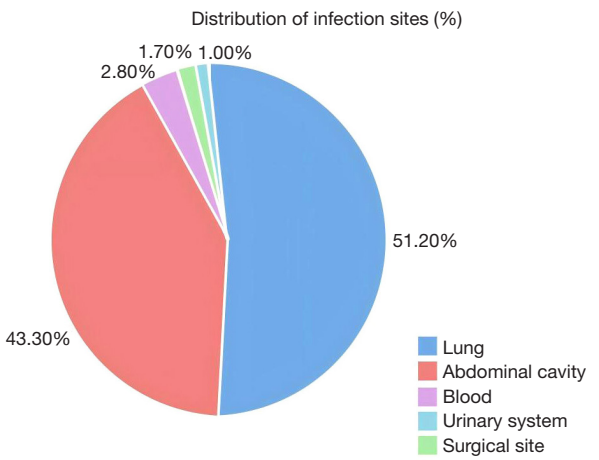

Figure 2 Distribution of infection sites after LT. LT, liver transplantation.

abdominal cavity (43.30%), and bloodstream (2.80%) (*Figure 2*).

Risk factors for EPBI following LT

The results of both univariate and multivariate logistic regression analyses are presented in *Tables 3*,*4*, respectively. In the multivariate analysis, variables with P<0.05 were identified as independent risk factors for the development of EPBI post-LT. Operation time [odds ratio (OR) =1.211, 95% CI: 1.065–1.377, P=0.003] and length of ICU stay (OR =1.040, 95% CI: 1.010–1.071, P=0.008) were significantly associated with an increased risk of infection. Additionally, classification as Child-Pugh B (OR =1.898, 95% CI: 1.071–3.363, P=0.03) was an independent predictor when compared to Child-Pugh A. In contrast, higher postoperative eGFR_1 demonstrated a protective effect (OR =0.992, 95% CI: 0.984–0.999, P=0.04) (*Figure 3*).

Development of the nomogram models

Three distinct predictive models were constructed using complementary analytical approaches to identify risk

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Table 3 Univariate analysis of factors associated with EPBI

Variables	OR (95% CI)	P
Age	1.030 (1.010–1.051)	0.003
Gender		
Female	Reference	
Male	1.020 (0.637–1.641)	0.94
ABO blood type		
A	Reference	
B	1.000 (0.641–1.562)	>0.99
O	0.913 (0.576–1.446)	0.70
AB	1.030 (0.611–1.734)	0.91
Hypertension	1.140 (0.747–1.737)	0.54
Diabetes	1.429 (0.976–2.095)	0.07
Ascites	1.800 (1.283–2.533)	<0.001
Hepatic encephalopathy	1.983 (1.301–3.046)	0.002
Cirrhosis	2.020 (1.073–3.992)	0.04
MELD	1.126 (1.089–1.168)	<0.001
Child-Pugh		
A	Reference	
B	2.861 (1.927–4.295)	<0.001
C	6.514 (3.730–11.667)	<0.001
Interventional ablation	0.883 (0.626–1.243)	0.48
WBC_0	1.095 (1.029–1.170)	0.005
Neutrophil_0	1.159 (1.073–1.261)	<0.001
Monocyte_0	2.412 (1.177–5.316)	0.02
Hb_0	0.984 (0.978–0.990)	<0.001
PTA_0	0.976 (0.966–0.985)	<0.001
ALT_0	1.001 (0.998–1.004)	0.47
AST_0	1.002 (1.001–1.004)	0.01
ALB_0	0.965 (0.937–0.992)	0.01
eGFR_0	0.996 (0.993–1.000)	0.042
PNI_0	0.962 (0.939–0.985)	0.002
PLR_0	1.001 (1.000–1.003)	0.09
NLR_0	1.095 (1.051–1.145)	<0.001
LMR_0	0.813 (0.726–0.903)	<0.001
SII_0	1.001 (1.000–1.001)	<0.001
PIV_0	1.001 (1.001–1.002)	<0.001
PAR_0	0.991 (0.914–1.072)	0.82
Cold ischemic time	1.001 (1.000–1.002)	0.14
Blood loss	1.000 (1.000–1.000)	0.03
Blood transfusion volume	1.000 (1.000–1.001)	<0.001
Operation time	1.260 (1.142–1.396)	<0.001
WBC_1	1.016 (0.981–1.053)	0.38
Neutrophil_1	1.009 (0.972–1.048)	0.64
Monocyte_1	0.614 (0.278–1.318)	0.22
Hb_1	0.971 (0.960–0.982)	<0.001
PTA_1	0.984 (0.973–0.994)	0.002
ALT_1	1.000 (1.000–1.000)	0.06
AST_1	1.000 (1.000–1.000)	0.26
ALB_1	0.990 (0.955–1.026)	0.57
PCT_1	1.020 (1.011–1.030)	<0.001
eGFR_1	0.983 (0.977–0.989)	<0.001
PNI_1	1.004 (0.985–1.025)	0.67
PLR_1	1.000 (0.999–1.001)	0.79
NLR_1	1.004 (0.997–1.012)	0.25
LMR_1	1.191 (0.985–1.468)	0.09
SII_1	1.000 (1.000–1.000)	0.97
PIV_1	1.000 (1.000–1.000)	0.63
PAR_1	0.909 (0.771–1.064)	0.24
Tacrolimus concentration	0.928 (0.872–0.984)	0.01
Length of ICU stay	1.071 (1.042–1.106)	<0.001
Length of hospital stay	1.012 (1.002–1.023)	0.03

Suffix "_0" means preoperative (day −1); suffix "_1" means postoperative (day +1). ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; EPBI, early postoperative bacterial infection; Hb, hemoglobin; ICU, intensive care unit; LMR, lymphocyte-to-monocyte ratio; MELD, Model for End-Stage Liver Disease; NPR, neutrophil-to-platelet ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PAR, platelet-to-albumin ratio; PCT, procalcitonin; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PTA, prothrombin activity; SII, systemic immune-inflammation index; WBC, white blood cell count.

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Table 4 Logistic multivariate analysis of related factors affecting EPBI

Variable	β	SE	Wald	P	OR	95% CI
Child-Pugh class B *vs.* A	0.641	0.292	2.194	0.03	1.898	1.071–3.363
eGFR_1	−0.008	0.004	−2.002	0.043	0.992	0.984–0.999
Operation time	0.191	0.065	2.921	0.003	1.211	1.065–1.377
Length of ICU stay	0.039	0.015	2.623	0.008	1.040	1.010–1.071

Suffix "_1" means postoperative (day +1). CI, confidence interval; eGFR, estimated glomerular filtration rate; EPBI, early postoperative bacterial infection; ICU, intensive care unit; OR, odds ratio; SE, standard error.

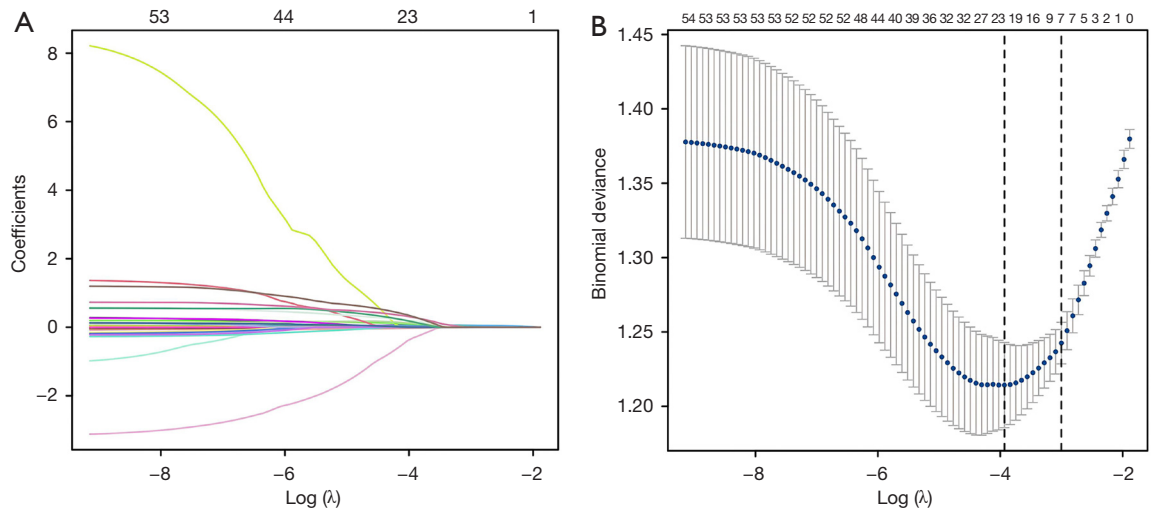

Figure 3 Regularization path (A) and cross-validation (B) for LASSO and Ridge regression models. LASSO, least absolute shrinkage and selection operator.

factors for EPBI (*Figure 4*). Model 1 utilized a threshold of P<0.1 for inclusion in multivariate logistic regression. This approach identified six significant predictors across three clinical domains: procedural factors (operation time, length of ICU stay), liver and renal function (Child-Pugh classification, eGFR_1), and systemic inflammation markers (NLR_0, PCT_1) (*Table 5*). Model 1 demonstrated good discriminative performance while preserving clinical interpretability, making it well-suited for application by transplant specialists.

Sensitivity analysis confirmed that using a more liberal univariate threshold (P<0.20) did not alter the core predictor set identified through our rigorous multivariate modeling process, supporting the robustness of our findings.

Model 2 utilized stepwise regression based on the minimization of the AIC, resulting in an optimized model with eight predictors. In addition to the core variables retained from Model 1, Model 2 incorporated additional clinically relevant factors, including tacrolimus concentration and novel inflammatory indices (PIV_0, M_1) (*Table 6*). Collinearity diagnostics confirmed the robustness of the model, with all variance inflation factors remaining below 2, indicating minimal multicollinearity among the selected predictors.

For Model 3, an advanced penalized regression framework was implemented, combining LASSO, L1 penalty and Ridge regression (L2 penalty) techniques (*Figure 2*). Using 10-fold cross-validation (optimal λ.1se =0.045), LASSO regression identified six non-redundant predictors, including MELD score and SII_0, while reaffirming three consensus variables from the previous models: operation time, length of ICU stays, and eGFR_1 (*Table 7*).

Model validation and performance assessment

Three distinct predictive models were developed and

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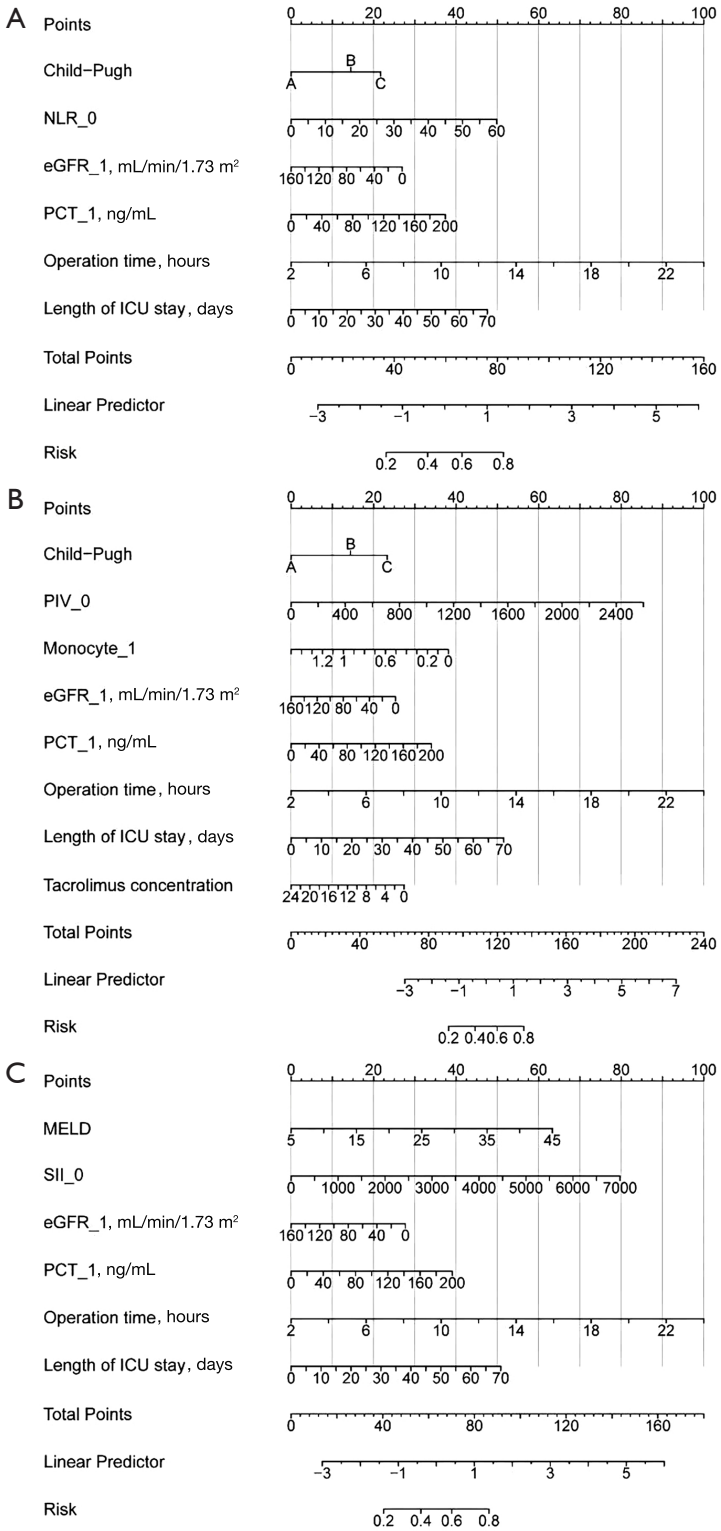

Figure 4 Nomogram of EPBI after LT. (A) Model 1; (B) Model 2; (C) Model 3. Suffix "_0" means preoperative (day −1); suffix "_1" means postoperative (day +1). Model 1, a conventional logistic regression model; Model 2, a stepwise regression model optimized using the Akaike information criterion; Model 3, a least absolute shrinkage and selection operator-Ridge regression model. eGFR, estimated glomerular filtration rate; EPBI, early postoperative bacterial infection; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-

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Stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.

Table 5 Logistic multivariate analysis of related factors affecting early postoperative bacterial infection (Model 1)

Variable	β	SE	Wald	P	OR	95% CI
Child-Pugh class B *vs.* A	0.872	0.218	3.395	<0.001	2.393	1.560–3.671
Child-Pugh class C *vs.* A	1.328	0.319	4.164	<0.001	3.778	2.021–7.063
NLR_0	0.052	0.021	2.444	0.02	1.053	1.010–1.098
eGFR_1	–0.010	0.003	–3.063	0.002	0.990	0.983–0.996
PCT_1	0.010	0.005	2.190	0.03	1.010	1.001–1.019
Operation time	0.189	0.056	3.368	0.001	1.208	1.082–1.349
Length of ICU stay	0.042	0.014	2.949	0.003	1.043	1.014–1.072

Suffix "_0" means preoperative (day –1); suffix "_1" means postoperative (day +1). CI, confidence interval; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PCT, procalcitonin; SE, standard error.

Table 6 Logistic multivariate analysis of related factors affecting early postoperative bacterial infection (Model 2)

Variables	β	SE	Wald	P	OR	95% CI
Child-Pugh class B *vs.* A	0.903	0.225	4.012	<0.001	2.468	1.587–3.836
Child-Pugh class C *vs.* A	1.486	0.326	4.556	<0.001	4.419	2.232–8.373
PIV_0	0.002	0.001	3.916	<0.001	1.002	1.001–1.003
Monocyte_1	–1.680	0.537	–3.127	<0.001	0.186	0.065–0.534
eGFR_1	–0.010	0.003	–2.937	0.003	0.990	0.983–0.997
PCT_1	0.009	0.005	2.028	0.04	1.009	1.000–1.019
Operation time	0.199	0.057	3.495	<0.001	1.220	1.091–1.365
Length of ICU stay	0.047	0.015	3.157	0.002	1.048	1.018–1.079
Tacrolimus concentration	–0.069	0.034	–2.047	0.04	0.933	0.873–0.997

Suffix "_0" means preoperative (day –1); suffix "_1" means postoperative (day +1). CI, confidence interval; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin; PIV, pan-immune-inflammation value; SE, standard error.

Table 7 Logistic multivariate analysis of related factors affecting early postoperative bacterial infection (Model 3)

Variables	β	SE	Wald	P	OR	95% CI
MELD	0.095	0.020	4.771	<0.001	1.099	1.057–1.143
SII_0	0.001	0.001	3.169	0.002	1.001	1.000–1.001
eGFR_1	–0.010	0.003	–3.081	0.002	0.990	0.983–0.996
PCT_1	0.010	0.005	2.270	0.02	1.010	1.001–1.020
Operation time	0.187	0.056	3.310	0.001	1.205	1.079–1.346
Length of ICU stay	0.044	0.015	3.061	0.002	1.045	1.016–1.075

Suffix "_0" means preoperative (day –1); suffix "_1" means postoperative (day +1). CI, confidence interval; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PCT, procalcitonin; SE, standard error; SII, systemic immune-inflammation index.

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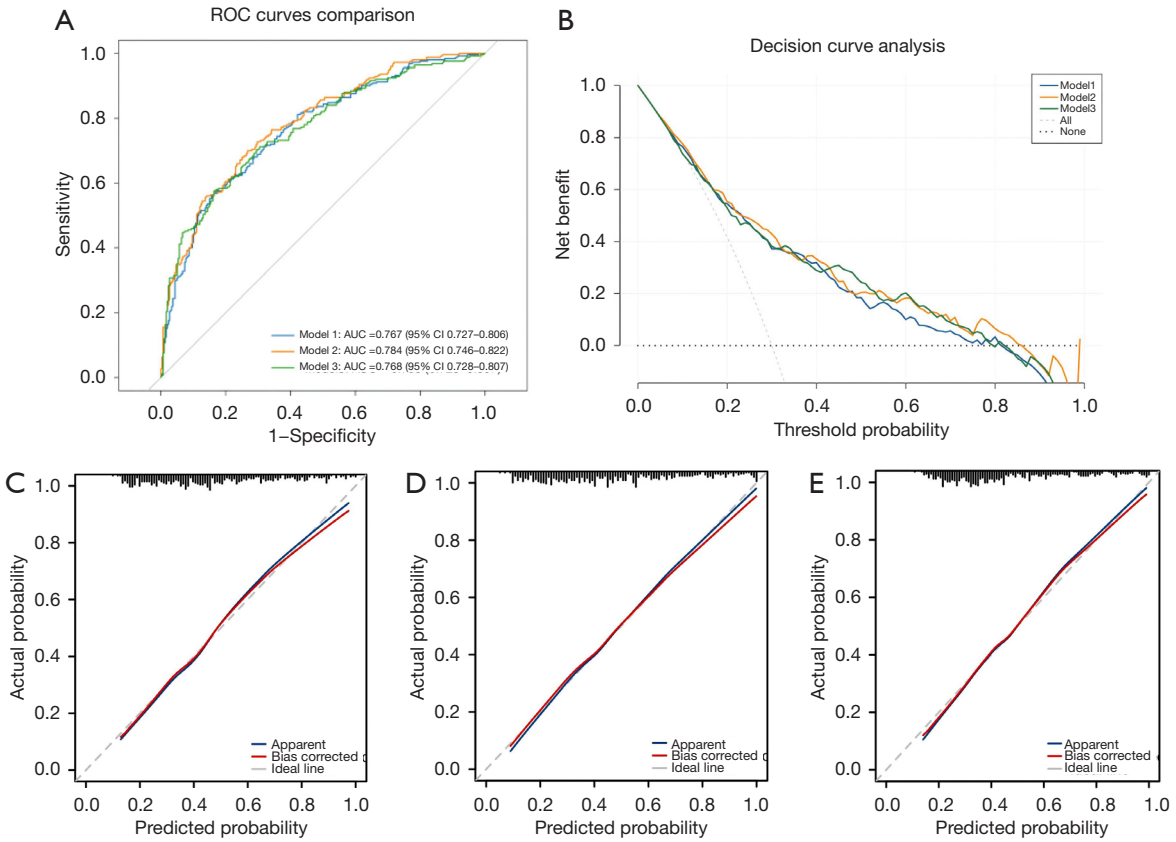

Figure 5 Performance evaluation of predictive models for EPBI. (A) ROC curves (DeLong test: Model 2 *vs.* Model 3, P=0.63); (B) decision curve analysis; (C) calibration curves of Model 1; (D) calibration curves of Model 2 (no high-risk decile underestimation; MAE =0.008 validated by cross-validation); (E) calibration curves of Model 3. Model 1, a conventional logistic regression model; Model 2, a stepwise regression model optimized using the Akaike information criterion; Model 3, a least absolute shrinkage and selection operator-Ridge regression model. AUC, area under the curve; CI, confidence interval; EPBI, early postoperative bacterial infection; MAE, mean absolute error; ROC, receiver operating characteristic.

rigorously validated to stratify the risk of EPBI following LT. Among them, Model 2 achieved the highest discriminative performance, achieving an AUC of 0.784 and achieving an AUC of 0.784 (falling into the 'Fair to Good' range) and showing no statistically significant difference compared to Model 3 (AUC =0.768) and Model 1 (AUC =0.767) in pairwise DeLong tests (Model 2 *vs.* Model 3, P=0.63; Model 2 *vs.* Model 1, P=0.58) (*Figure 5*).

In terms of calibration accuracy, all models indicated excellent agreement between predicted probabilities and observed outcomes, as indicated by non-significant results in the Hosmer-Lemeshow goodness-of-fit tests (Model 1: χ^2=10.83, P=0.21; Model 2: χ^2=6.86, P=0.55; Model 3: χ^2=3.95, P=0.86). Notably, Model 2 exhibited the most precise calibration (mean absolute error =0.008, mean squared error =0.00015), confirmed by 10-fold cross-validation and bootstrap resampling (1,000 iterations) to rule out training set overfitting artifacts. Scrutiny of its calibration curve (*Figure 5D*) showed no high-risk decile underestimation, with predicted and observed infection rates closely aligning across all risk strata.

DCA was subsequently conducted to assess clinical utility. Model 2 demonstrated the highest net benefit, with meaningful clinical utility beginning at thresholds exceeding 6.28% [i.e., if a clinician is willing to treat (prophylactically) a patient with a probability of infection as low as 6.3%, using this nomogram provides a greater net benefit than treating all patients or treating none], compared to higher thresholds required by Model 1 (>10.90%) and Model 3 (>13.27%).

All three modeling approaches consistently identified operation time, ICU stay duration, and eGFR_1 as

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core predictors, underscoring their established clinical significance. At the optimal Youden index threshold, Model 2 achieved a sensitivity of 72.4% (95% CI: 68.2–76.6%), specificity of 71.2% (95% CI: 67.1–75.3%), PPV of 69.8% (95% CI: 65.4–74.2%), and NPV of 73.1% (95% CI: 69.0–77.2%), which clarifies its practical diagnostic performance at the key clinical decision point. Although Model 3 achieved predictive performance equivalent to that of Model 2 with a more parsimonious variable set (6 *vs.* 8 predictors), Model 2 retains value for its balanced performance and clinical interpretability. Model 3, with its regularization-derived stability, may be preferred in scenarios requiring robust generalization to external populations. Internal validation using 10-fold cross-validation confirmed robust model stability, yielding mean AUCs of 0.766±0.061, 0.759±0.055, and 0.759±0.056 for Models 2, 3, and 1, respectively. Additionally, bootstrap validation (n=1,000 iterations) demonstrated minimal performance degradation, with bias-corrected AUCs deviating by less than 2% from their original estimates. Collectively, these validation results support the clinical applicability of all three models, particularly Model 2, for postoperative risk stratification.

Discussion

In this rigorously controlled single-center cohort of 549 patients undergoing LT for HCC, the incidence of EPBI was 45.5%. This clinically significant rate supports the classification of HCC recipients as a distinct high-risk group and provides a key epidemiological basis for interpreting associated microbiological patterns. The use of standardized protocols across all cases contributed to consistent and reliable infection estimates, minimizing the diagnostic variability often encountered in multicenter studies. The microbiological analysis yielded important observations that both corroborate and extend existing knowledge regarding infectious complications following LT. The near equal distribution of Gram-negative (51.7%) and Gram-positive (48.3%) pathogens differs from the predominance of Gram-negative organisms typically reported in general LT populations (9,10). This distribution may be attributable to several HCC-specific risk factors. First, frequent pre-transplant healthcare exposures, including repeated hospitalizations for bridging therapies and surveillance imaging, likely increase the risk of colonization by both Gram-negative and Gram-positive nosocomial organisms. Second, individuals with HCC commonly exhibit an altered immune profile characterized by cirrhosis-related immune dysfunction and tumor-mediated myeloid cell impairment, both of which may impair host defense mechanisms against a broad spectrum of bacterial pathogens (11,12). Third, the complexity of the surgical procedures in this population introduces multiple potential infection pathways, with biliary and abdominal sources favoring Gram-negative infections, and catheter- or wound-related sources predisposing to Gram-positive infections.

Among the Gram-negative isolates, *K. pneumoniae* (16.7%) was the most frequently identified pathogen, followed by *A. baumannii* (9.0%) and *P. aeruginosa* (6.0%). This distribution diverges from the *Escherichia coli*-dominant profiles commonly reported in Western LT groups, which may reflect regional variations in antibiotic stewardship practices or patient population characteristics (13). Notably, these predominant Gram-negative pathogens exhibited a significant pulmonary tropism, potentially contributing to the high incidence of pulmonary infections (51.2%) observed in this cohort. *K. pneumoniae* employs capsular polysaccharides to evade host immune responses, while *A. baumannii* utilizes adhesive fimbriae to facilitate adherence to bronchial epithelium, virulence mechanisms that promote respiratory colonization, particularly among ventilated patients with HCC (14,15).

The relatively high proportion of *A. baumannii* (accounting for nearly 10% of all isolates) is of particular concern, given its multidrug resistance potential and its association with adverse outcomes in immunocompromised populations (16-18). Among Gram-positive pathogens, coagulase-negative staphylococci and enterococci remain the predominant organisms implicated in bloodstream infections in LT recipients (19). In the present study, *E. faecium* (14.1%) and *S. epidermidis* (13.2%) were the most frequently isolated Gram-positive organisms. This distribution likely reflects established transplant-related risk factors, including prolonged ICU stay and exposure to invasive devices such as central venous catheters and drainage tubes (20,21). This near-equal distribution of Gram-negative and Gram-positive pathogens (51.7% *vs.* 48.3%) represents a key epidemiological contribution of the present study, distinct from the traditional paradigm of Gram-negative dominance in abdominal surgical infections. Notably, Gram-positive pathogens such as *Enterococcus faecium* (14.1%) and *Staphylococcus epidermidis* (13.2%) were among the most prevalent isolates, highlighting that standard empiric antibiotic protocols overly focused on Gram-negatives may be insufficient for HCC-LT

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patients. More aggressive coverage of Gram-positives (e.g., incorporating enterococcal-active agents) should be considered in clinical practice to optimize infection control in this high-risk population.

The Child-Pugh classification remains an essential clinical tool for assessing hepatic functional reserve. Current evidence indicates that its predictive value for post-transplant infections is highly context dependent. In general cirrhotic populations, Class C has been identified as an independent predictor of post-transplant bacteremia and mortality, in cases of spontaneous bacterial peritonitis (P=0.003) (22,23), and has been associated with an increased risk of pulmonary infections (24).

In contrast, the present study indicated a distinct threshold effect among HCC recipients: Child-Pugh Class B (OR =1.898, P=0.03), rather than Class C, was independently associated with EPBI. This finding suggests that even moderate hepatic dysfunction (i.e., Class B) may be sufficient to confer significantly elevated infection risk in this population. Such a deviation from the traditional risk paradigm, centered on Class C in non-HCC populations, highlights the importance of disease-specific monitoring strategies in HCC transplant recipients.

The MELD score is a widely accepted metric for assessing liver disease severity prior to LT (25). Although previous studies have proposed various MELD thresholds for predicting infection risk such as MELD >30 in Italian cohorts and >20 in French reports (2,26), this HCC-specific analysis identified significant infection risk differentiation at considerably lower MELD scores (median 14 in infected patients *vs.* 11 in non-infected, P<0.001).

This notable distinction is likely attributable to several HCC-specific pathophysiological factors. First, in HCC populations, transplantation timing is typically guided by oncologic rather than hepatic dysfunction criteria, such as those outlined in the Milan criteria. As a result, transplantation often occurs at earlier stages of liver disease, yielding lower baseline MELD scores. Second, the immunosuppressive tumor microenvironment associated with HCC may exacerbate susceptibility to infections independent of MELD-defined hepatic dysfunction, likely via dysregulation of myeloid and lymphoid cell populations. Third, prior liver-directed therapies such as TACE, may alter both hepatic parenchyma and systemic physiology, further modulating the relationship between MELD score and infection risk.

Overall, while the MELD score continues to offer prognostic value for infection risk among LT recipients with HCC, its interpretation should be adapted to the unique clinical context of this population. Consideration should be given to initiating early interventions in patients with MELD scores exceeding the median threshold observed within the local cohort.

Consistent with findings from prior LT studies, the present analysis identified prolonged operative time as an independent risk factor for EPBI. Prior studies by Liu *et al.* and Zhang *et al.* have delineated key operative duration thresholds exceeding 400 and ≥480 minutes (27,28), respectively, beyond which the risk of infection increases substantially.

Mechanistic explanations for this association include the dual impact of extended surgical duration: direct compromise of sterile operative barriers and disruption of intestinal mucosal integrity, the latter of which facilitates translocation of Gram-negative bacteria (29,30). The temporal relationship appears to follow a dose-response pattern, wherein each additional minute of operative time increases the likelihood of prolonged ICU stay by approximately 0.4%, thereby extending the period of exposure to nosocomial pathogens (31).

Prolonged operative time may lead to subtherapeutic concentrations of prophylactic antibiotics in both serum and tissues due to redistribution and metabolic clearance during extended procedures (32). In the context of HCC, these risks are further compounded by several synergistic mechanisms.

(I) Transfusion-related immunomodulation, often accompanying extensive intraoperative blood loss, can suppress immune function by impairing granulocyte and macrophage activity, thereby impairing bacterial clearance capacity (33);
(II) Volume overload contributes to pulmonary edema, creating a favorable environment for bacterial colonization of the respiratory tract (34);
(III) Prolonged cold ischemia time exacerbates ischemia–reperfusion injury and further compromises host immune defenses.

The clinical data from the present cohort support this multifactorial pathogenesis. Patients who developed EPBI exhibited significantly poorer intraoperative profiles across all major parameters. These findings reinforce the need for targeted quality improvement measures, including operative time reduction, intraoperative blood conservation strategies, minimization of cold ischemia, and enhanced postoperative surveillance protocols for high-risk recipients.

Admission to the ICU following LT is an inherent

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component of postoperative care but also introduces a heightened risk of nosocomial infections due to prolonged exposure to hospital-acquired pathogens. Logistic regression analysis in this study identified ICU stay duration as an independent risk factor for EPBI (OR =1.040, P=0.008). This finding is consistent with findings from previous meta-analyses involving 1,624 LT recipients (24). However, center-specific variations in ICU stay duration (range, 7–14 days) have been reported (10,35,36), likely reflecting institutional differences in patient management protocols.

The association between infection and ICU stay is bidirectional. First, preexisting conditions such as elevated MELD scores (>24 or ≥28) have been associated with prolonged hospitalization (37,38), increased antibiotic exposure, and higher susceptibility to colonization by MDR organisms. Second, established infections, particularly bloodstream infections (39,40), approximately double ICU and hospital stay durations, as well as mortality rates, when compared to uninfected patients. This cycle is further exacerbated by prior hospitalization, which contributes to the selection pressure for antimicrobial resistance.

Collectively, these findings highlight the need for institution-specific optimization of ICU discharge protocols and robust antimicrobial stewardship strategies to disrupt this self-perpetuating cycle of infection and prolonged critical care.

Emerging evidence indicates a clinically significant bidirectional association between renal function and infection risk in patients with HCC undergoing LT. In this study, early postoperative renal dysfunction, as measured by eGFR on postoperative day 1, was independently associated with infection risk (OR =0.992 per 1 mL/min/1.73 m^2, 95% CI: 0.984–0.999, P=0.04). This finding aligns with prior observations indicating that pre-transplant renal impairment (eGFR <90 mL/min/1.73 m^2) is associated with increased susceptibility to sepsis (P=0.07) (41).

This bidirectional relationship is further supported by evidence demonstrating that post-transplant infections, particularly pneumonia, contribute to progressive renal dysfunction. Specifically, such infections have been associated with a 40% decline in eGFR [hazard ratio (HR) =3.32, 95% CI: 2.13–5.16] and with adverse composite renal outcomes (HR =3.41, 95% CI: 2.40–5.24) (42). These findings delineate a self-perpetuating cycle between infection and renal impairment, highlighting the necessity for vigilant postoperative monitoring and integrated management strategies.

The diagnostic and prognostic value of PCT in infection detection has been well established across various clinical contexts (43,44). Large-scale studies have demonstrated the strong discriminative ability of PCT for identifying bacteremia, with significantly higher levels observed in confirmed cases (3.2 *vs.* 0.4 ng/mL, P<0.001) (43). Transplant-specific meta-analyses further support these findings, reporting pooled sensitivity and specificity of 85% and 81%, respectively, with improved diagnostic performance in LT recipients (90% sensitivity, 85% specificity) (44).

The current study extends this body of evidence by characterizing the temporal kinetics of PCT in patients with HCC following LT. PCT levels on postoperative day 1 were identified as an independent predictor of infection (OR =1.020, 95% CI: 1.011–1.030, P<0.001), consistent with previously described kinetic patterns presenting sustained elevation in infected patients across postoperative days 1, 3, and 5 (45). The early predictive capacity of PCT is particularly relevant in the HCC population, where infection risk is shaped by the combined effects of cirrhosis-associated immune dysfunction and tumor-related immunosuppressive mechanisms.

The host inflammatory response to infection induces broad activation of hematopoietic cell lineages, resulting in marked changes in cellular counts, functional status, receptor expression patterns, and secretion of signaling molecules. Compared to individual markers, composite inflammatory indices provide a more integrated and representative assessment of the systemic inflammatory state. In this study, NLR on postoperative day 1 was significantly associated with EPBI, consistent with findings by Park *et al.*, who reported a link between preoperative NLR and post-transplant bacteremia and mortality (39). NLR has demonstrated superior predictive performance compared to conventional inflammatory markers due to its ability to simultaneously reflect neutrophil-mediated innate immune activation and lymphocyte-dependent adaptive immune competence (46,47). Furthermore, the current findings support the observation by Tu *et al.* that NLR elevation precedes positive graft preservation cultures, providing a potential time window for early clinical intervention (48).

Another robust index, the SII, which incorporates neutrophil, lymphocyte, and PLTs, also demonstrated significant predictive value for infection risk. Mechanistically, activated platelets facilitate neutrophil recruitment and interact with monocytes and lymphocytes to amplify the proinflammatory cascade (49). Clinically,

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elevated SII values signify a critical imbalance in immune-inflammatory homeostasis, predisposing patients to adverse outcomes. The predictive utility of SII demonstrates a clear dose-response relationship: values ≥270 are associated with increased risk of postoperative infection (36), while levels exceeding 870 identify patients with particularly poor prognoses, including a reported sepsis incidence of 59.1% and mortality rate of 76.9% among transplant recipients (50). The consistency of these findings across studies supports the reliability of SII as a clinically relevant biomarker.

PIV has emerged as a promising marker of systemic immune-inflammatory dysregulation. In the present study, elevated PIV levels were significantly associated with an increased risk of infection (OR =1.001, 95% CI: 1.001–1.002, P<0.001), consistent with prior evidence supporting the prognostic relevance of PIV in infection-related outcomes. In individuals with sepsis-associated acute kidney injury, higher PIV levels have been shown to correlate with increased mortality in a dose-dependent manner, with 30-day OR mortality odds ratios reaching up to 1.62. Additionally, threshold effects have been reported, including a $\log_2$PIV >6.72 associated with a 28-day mortality OR of 1.057 (51,52). The current findings extend these observations by demonstrating that incremental increases in PIV are also associated with elevated postoperative infection risk among LT recipients with HCC. PIV may serve as a clinically meaningful biomarker for early identification of high-risk patients in the post-transplant period.

Overall, the routine clinical application of inflammatory indices such as NLR, SII, and PIV may substantially enhance infection risk assessment, these markers can be calculated from standard complete blood count parameters without requiring additional testing. In this study, a paradoxical relationship was observed between initial postoperative tacrolimus levels and EPBI risk in LT recipients. Patients who developed infections had significantly lower tacrolimus levels than those without infections (1.60 *vs.* 2.50 ng/mL, P<0.001), with higher levels indicating a marginal protective effect (OR =0.933). Notably, both groups exhibited values well below the recommended therapeutic range (10–20 ng/mL), indicating these subtherapeutic concentrations may be insufficient for meaningful immunosuppression (53). The observed differences are more likely attributable to interindividual variability in drug metabolism or adherence-related issues, rather than by direct immunomodulatory effects.

Clinically, tacrolimus levels below 3 ng/mL in the early postoperative period should prompt evaluation for potential complications prior to dose adjustment. Further investigation of longitudinal tacrolimus concentration profiles is warranted to better elucidate the relationship between drug exposure and infection risk. It is important to emphasize that all predictors identified in our nomogram represent risk factors (associative markers) rather than direct causal factors. This distinction is exemplified by the counterintuitive finding of lower tacrolimus concentrations in infected patients—these concentrations serve as surrogates for metabolic variability or adherence, not causal agents of infection. The model's value lies in risk stratification, not establishing causal relationships between variables and EPBI. This innovative multi-model study established a comprehensive framework for stratifying EPBI risk among LT recipients. Each modeling approach demonstrated complementary strengths.

The first model provided immediate clinical applicability through streamlined variable selection based on a P<0.1 threshold, yielding a practical bedside tool that incorporated six key predictors spanning procedural, functional, and inflammatory domains.

The second model achieved a fair to good discriminative performance (AUC =0.784, falling into the "Fair to Good" range per standard AUC classification (70≤ AUC <80) by integrating dynamic immunosuppressive parameters, such as tacrolimus concentration, with novel inflammatory indices such as PIV. This integration supports a more individualized approach to post-transplant care, while acknowledging the model's performance leaves room for further optimization.

The third model applied regularized regression techniques, identifying six non-redundant predictors while maintaining predictive performance equivalent to Model 2 (AUC =0.768; DeLong test P=0.63). Notably, Model 3's regularization-derived stability confers advantages for potential external validation, while Model 2's interpretability facilitates clinical application in the current single-center context.

Notably, the concordance of core predictors across all models reinforces their underlying pathophysiological relevance and strengthens the clinical validity of the proposed stratification framework.

The clinical translation of these predictive models holds particular significance in the context of the unique immunological challenges faced by LT recipients and the rising prevalence of MDR infections. The nomogram derived from these models provides a practical tool for applying predictive analytics in clinical practice, facilitating:

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(I) individualized risk assessment; (II) implementation of targeted preventive measures; and (III) informed decision-making regarding antimicrobial prophylaxis. The inclusion of novel inflammatory indices such as NLR, SII, and PIV is especially noteworthy, as these markers reflect the dynamic interplay between immunosuppression and infection susceptibility, providing clinicians real-time insights into the immunological status of transplant recipients.

Several limitations must be acknowledged. Foremost, the absence of external validation limits generalizability beyond our single-center cohort. While internal validation demonstrated robustness, findings require confirmation in multicenter settings before clinical application. Additionally, future incorporation of emerging biomarkers may enhance predictive accuracy (54,55).

Conclusions

This study provides an internally validated predictive tool for EPBI risk stratification in HCC transplant recipients. The tool exhibits fair discriminative ability and potential clinical utility, but the single-center design and lack of external validation necessitate further verification before widespread clinical implementation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of Beijing Youan Hospital of Capital Medical University (No. LL-2024-127-K), in accordance with national transplantation regulations and the Declaration of Helsinki and its subsequent amendments. The participants provided their written informed consent to participate in this study.

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