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An integrated machine learning model enhances delayed graft function prediction in pediatric renal transplantation from deceased donors

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Abstract

Background Kidney transplantation is the optimal renal replacement therapy for children with end-stage renal disease; however, delayed graft function (DGF), a common post-operative complication, may negatively impact the long-term outcomes of both the graft and the pediatric recipient. However, there is limited research on DGF in pediatric kidney transplant recipients. This study aims to develop a predictive model for the risk of DGF occurrence after pediatric kidney transplantation by integrating donor and recipient characteristics and utilizing machine learning algorithms, ultimately providing guidance for clinical decision-making.

Methods This single-center retrospective cohort study includes all recipients under 18 years of age who underwent single-donor kidney transplantation at our hospital between 2016 and 2023, along with their corresponding donors. Demographic, clinical, and laboratory examination data were collected from both donors and recipients. Univariate logistic regression models and differential analysis were employed to identify features associated with DGF. Subsequently, a risk score for predicting DGF occurrence (DGF-RS) was constructed based on machine learning combinations. Model performance was evaluated using the receiver operating characteristic curves, decision curve analysis (DCA), and other methods.

Results The study included a total of 140 pediatric kidney transplant recipients, among whom 37 (26.4%) developed DGF. Univariate analysis revealed that high-density lipoprotein cholesterol (HDLC), donor after circulatory death (DCD), warm ischemia time (WIT), cold ischemia time (CIT), gender match, and donor creatinine were significantly associated with DGF ($P < 0.05$). Based on these six features, the random forest model (mtry = 5, 75%p) exhibited the best predictive performance among 97 machine learning models, with the area under the curve values reaching 0.983, 1, and 0.905 for the entire cohort, training set, and validation set, respectively. This model significantly outperformed single indicators. The DCA curve confirmed the clinical utility of this model.

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Conclusions In this study, we developed a machine learning-based predictive model for DGF following pediatric kidney transplantation, termed DGF-RS, which integrates both donor and recipient characteristics. The model demonstrated excellent predictive accuracy and provides essential guidance for clinical decision-making. These findings contribute to our understanding of the pathogenesis of DGF.

Keywords Pediatric kidney transplantation, Machine learning, Delayed graft function, Predict, DGF

Background

Kidney transplantation (KT) is currently recognized as the optimal treatment for children with end-stage renal disease (ESRD). With the current high success rate of pediatric KT, where over 80% of children survive and grow into adolescents and adults, maintaining a good quality of life and minimizing significant long-term side effects are essential priorities [1]. Delayed graft function (DGF), a common complication after KT with an incidence ranging from 20 to 50% [2], not only potentially increases the risk of post-transplant graft loss [3] and chronic allograft nephropathy in children but also leads to increased medical resource utilization and costs [4–6]. However, there is currently a paucity of studies on pediatric KT, with some DGF studies selectively excluding the pediatric population [7–11]. Therefore, timely identification of high-risk factors for DGF occurrence and implementation of effective preventive and therapeutic measures are crucial for improving the prognosis of pediatric KT.

The occurrence of DGF is closely associated with acute ischemia–reperfusion injury in the donor kidney. Ischemia–reperfusion injury can cause apoptosis and necrosis of renal tubular epithelial cells, inflammatory cell infiltration, and microcirculatory disorders, ultimately resulting in delayed recovery of the transplanted kidney function [12]. Pediatric kidney transplant recipients typically have smaller arterial diameters and lower cardiac output compared to adults. When pediatric kidney transplant recipients receive kidneys from older donors, their cardiovascular system may not provide adequate perfusion to the mature donor kidney, potentially leading to renal hypoperfusion. Furthermore, children have a relatively low blood volume compared to adults. When a large volume of blood rapidly enters the transplanted kidney during the intraoperative restoration of blood flow, it can readily cause hypotension in the pediatric patient, further exacerbating the inadequate perfusion of the transplanted kidney, potentially leading to acute tubular necrosis and inducing DGF [13, 14]. The pathogenesis of DGF remains poorly understood. It is widely accepted that immunological and non-immunological factors, including donor-related factors (ischemia duration, age, terminal serum creatinine (Scr), hypertension history, and cardiopulmonary resuscitation history), recipient-related factors (immune response, ischemia–reperfusion injury, and dialysis duration), and surgical factors, contribute to the onset and progression of DGF [4, 15]. Recently, several novel biomarkers have demonstrated potential for the early diagnosis of DGF. Recent studies have highlighted the potential utility of specific liver enzymes as early biomarkers for DGF in kidney transplantation. For instance, Malyszko et al. demonstrated that alkaline phosphatase (ALP) may offer superior predictive capability for DGF compared to creatinine, exhibiting an earlier elevation (12 to 96 h prior to a detectable increase in serum creatinine) [16]. In a related study, Jochmans et al. established that plasma aspartate transaminase (AST) not only reflected the severity of initial kidney graft injury but also predicted graft dysfunction with greater accuracy and timeliness compared to creatinine clearance and histological assessment [16]. Moreover, studies have shown a correlation between bilirubin levels and intraoperative blood flow measurements, potentially serving as a predictor of early graft function following transplantation [17]. This observed association between liver function markers and kidney graft outcomes highlights the intricate interrelationship among organ systems in the post-transplant milieu. The incorporation of lipid profiles in our investigation was predicated on emerging evidence suggesting their potential prognostic value in kidney transplantation outcomes. In a recent study, Shi et al. reported that serum high-density lipoprotein cholesterol (HDL-C) may function as a predictive biomarker for postoperative DGF following kidney transplantation [18]. This observation suggests that lipid metabolism may exert an influence during the early post-transplant period and potentially impact graft function. Conventionally, the assessment of donor and recipient kidneys has primarily relied on age, gender, body mass index (BMI), Scr, and urea nitrogen; however, these indicators have limited predictive value [19]. Nevertheless, the majority of studies investigating the predictive value of biomarkers for DGF following KT have been performed in adult populations. Studies involving pediatric patients have been limited by small sample sizes or a restricted number of parameters. Thus, identifying biomarkers for the early diagnosis and prediction of DGF following pediatric KT is crucial for guiding clinical management and improving patient outcomes.

With the rapid advancement of artificial intelligence technology, machine learning (ML) has found increasing applications in the medical field. ML is a computational approach that predicts outcomes through data mining and algorithmic analysis [20]. In recent years, ML has demonstrated promising potential in predicting complications following KT [21]. For instance, multiple logistic regression (LR)-based models have been constructed to predict the occurrence of DGF in kidney transplant recipients [22–25]. Moreover, decision tree (DT) algorithms have demonstrated satisfactory predictive performance in the context of DGF [26]. Nevertheless, the aforementioned studies merely utilize a single ML model for the prediction and evaluation of DGF. Research has indicated that the integration of multiple ML models can substantially enhance the prediction of outcomes [27]. Consequently, there is a pressing necessity to develop a model that can accurately predict the incidence of DGF following KT by leveraging a combination of multiple ML techniques.

Given the paucity of research on predicting DGF following pediatric KT, this study aims to develop a predictive model for DGF risk in pediatric kidney transplant recipients by integrating clinical characteristics and diagnostic indicators of both donors and recipients with multiple ML algorithms. Analyzing the associations between DGF occurrence and various factors, including donor and recipient age, primary disease, dialysis duration, cold ischemia time (CIT), preoperative immunosuppressive regimen, human leukocyte antigen (HLA) typing and compatibility, and retransplantation, as well as comprehensively evaluating DGF risk in pediatric patients, can further enhance the accuracy of DGF risk prediction. This approach offers novel insights into the early detection and prevention of DGF following pediatric KT, ultimately leading to improved prognosis and quality of life for pediatric patients. This study is anticipated to provide a crucial theoretical basis and practical guidance for advancing the field of pediatric KT.

Methods

Study population and data collection

This study employed a retrospective cohort study design and collected clinical data of all recipients and their corresponding donors who underwent single-donor KT in the Department of Kidney Transplantation at Zhujiang Hospital, Southern Medical University, from January 2016 to December 2023. The study was approved by the hospital's ethics committee, and written informed consent was obtained from all participants. Inclusion criteria were as follows: (1) first-time kidney transplant recipients; (2) recipients of single-donor KT; (3) recipients aged 18 years or younger at the time of surgery; (4) complete preoperative and postoperative follow-up data; and (5) grafts obtained from deceased donors (DD). Exclusion criteria included (1) recipients of multi-organ transplantation; (2) incomplete preoperative and postoperative follow-up data; and (3) death within one year after surgery. From an initial cohort of 153 pediatric kidney transplant recipients, we excluded (1) 3 patients with a history of kidney transplantation; (2) 10 patients with incomplete follow-up data. In this study, a total of 140 kidney transplant recipients were ultimately included, of which 78 (55.7%) were male and 62 (44.3%) were female. Among the donors, 87 (62.1%) were male and 53 (37.9%) were female. We retrospectively collected (1) recipient characteristics: high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), P, total cholesterol, triglyceride (TG), HLA-A mismatch, HLA-B mismatch, HLA-DRB1 mismatch, HLA-ABDR mismatch, direct bilirubin, albumin (Alb), aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, alkaline phosphatase (ALP), dialysis before KT, peritoneal dialysis Before KT, hemodialysis before KT, kidney transplant recipients (KTR) age, KTR height, KTR weight, KTR BMI, KTR gender, panel-reactive antibody (PRA), white blood cell (WBC), neutrophil, lymphocyte, platelet, K, Scr, blood urea nitrogen (BUN), Total CO_2, glucose (Glu), and DGF; (2) Donor characteristics: donor after circulatory death (DCD), donor gender, donor age, donor height, donor weight, donor creatinine; warm ischemia time (WIT) in minutes and CIT in hours; (3) Donor-recipient matching characteristics: age gap between donor and recipients, absolute age gap between donor and recipients, gender match. We gathered various clinical indicators, including the recipient's HDLC. It should be noted that while HDLC is not routinely measured in pediatric recipients at many transplant centers, it was incorporated into our center's comprehensive pretransplant evaluation protocol. In our study, donor creatinine refers to the final serum creatinine measurement obtained prior to organ procurement. It is crucial to emphasize that these kidneys did not have known suboptimal function or chronic kidney disease. Instead, the elevated creatinine levels observed in some cases were likely attributable to acute kidney injury associated with critical illness or the dying process in deceased donors. All kidneys were considered suitable for pediatric transplantation based on a comprehensive evaluation, including kidney biopsy when clinically indicated. All kidneys were stored by static cold storage alone. DGF was defined as requiring at least one

dialysis treatment within one week after kidney transplant surgery [28, 29].

Correlation analysis of clinical characteristics with DGF

First, normality tests were performed on all continuous variables, revealing that the data followed a non-normal distribution ($P<0.05$). Non-normally distributed data were presented as median (interquartile range), and comparisons between groups were conducted using the Mann–Whitney U test. Categorical variables were presented as number (percentage), and comparisons between groups were conducted using the chi-square test or Fisher's exact test. Subsequently, univariate LR analysis was employed to investigate the associations between various clinical indicators of kidney transplant recipients and donors and the incidence of DGF. Variables with $P<0.05$ in the univariate LR analysis and differential analysis were included in the subsequent analysis. The results demonstrated that HDLC, DCD, WIT, CIT, gender match, and donor creatinine were risk factors for DGF (all $P<0.05$) and were utilized for the development of subsequent predictive models.

Construction of a DGF-Risk Score (DGF-RS) predictive model using ML algorithms

Based on the results of the multivariate analysis, we selected six indicators: HDLC, DCD, WIT, CIT, gender match, and donor creatinine as independent variables, with the occurrence of DGF as the dependent variable (1 = yes, 0 = no). We then constructed DGF predictive models based on classical ML algorithms, including LR, linear discriminant analysis (LDA), K-nearest neighbor (KNN), DT, random forest (RF), XGBoost, support vector machine (SVM), gradient boosting machine (GBM), and naive Bayes [27]. Additionally, we explored several regularized regression methods, such as Lasso regression, Ridge regression, and ElasticNet, to address potential overfitting issues. Considering the limited sample size, we randomly partitioned the dataset into a training set and a validation set using a 7:3 ratio. In our RF model, we optimized the mtry parameter, which represents the number of variables randomly sampled as candidates at each split. This optimization helped improve the model's predictive performance. To identify the best-performing model for subsequent analysis, we compared various evaluation metrics, including area under the curve (AUC), specificity, sensitivity, accuracy, precision, recall, and F1 score, across all constructed models.

Statistical analysis

We employed the receiver operating characteristic (ROC) curve to assess the predictive capability of the model for DGF and computed the AUC along with its 95% confidence interval (CI) [30]. The optimal diagnostic cutoff point was ascertained by maximizing the Youden index, and the corresponding sensitivity and specificity were derived. Furthermore, decision curve analysis (DCA) was employed to assess the clinical utility of the predictive model, specifically the net benefit under the guidance of the predictive model at various threshold probabilities [31]. The statistical analyses and graphical plotting pertaining to this study were conducted in the R software environment (Version: 4.1). The visualization in this study was carried out utilizing the ggplot2 package [32, 33]. All hypothesis tests were two-sided, and a P-value less than 0.05 was deemed statistically significant.

Results

Basic clinical characteristics of pediatric kidney transplant recipients and donors

This study included a total of 140 pediatric patients who underwent KT. The patients were divided into two groups: the DGF group (37 cases) and the non-DGF group (103 cases), based on the occurrence of DGF after surgery. The kidney transplant recipients were followed up until December 31, 2023, with a median follow-up duration of 21.80 months (interquartile range [IQR] 10.09–31.90 months). The demographic and clinical characteristics of the donor and recipients are summarized in Tables 1, 2, and 3. No significant differences were observed between the two groups in terms of donor and recipient age, height, and weight. The distribution of pre-transplantation dialysis modality (peritoneal dialysis or hemodialysis) was similar between the two groups. However, the CIT was significantly longer in the DGF group compared to the non-DGF group, with median CITs of 10 and 6 h, respectively ($P<0.001$). Furthermore, donors in the DGF group had significantly higher Scr levels compared to those in the non-DGF group ($P<0.001$), suggesting worse renal function. Furthermore, a significantly higher proportion of donor kidneys in the DGF group (29.7%) were from DCD donors compared to the non-DGF group (4.9%) ($P<0.001$). Regarding laboratory indicators, the preoperative HDLC level was significantly lower in the DGF group compared to the non-DGF group ($P<0.001$). However, no significant differences were observed in other blood lipid indicators, including total cholesterol, LDLC, and TGs. Similarly, other indicators, including blood routine, liver function, and kidney function, showed no statistically significant differences between the two groups. Moreover, immunological indicators, such as HLA mismatch degree and PRA positive rate, were comparable between the two patient groups. In conclusion, the pediatric kidney transplant patients in the DGF and non-DGF groups included in this study were well-matched in terms of baseline characteristics, such as

Table 1 Donor characteristics stratified by delayed graft function (DGF)

	Level	Overall	DGF (No)	DGF (Yes)	*P*-value
Patient number		140	103	37	
Donor age (median [IQR])		8.50 [4.00, 13.00]	8.00 [4.00, 12.50]	9.00 [5.00, 14.00]	0.391
Donor height (median [IQR])		130.00 [107.00, 155.50]	128.00 [107.00, 158.00]	140.00 [110.00, 155.00]	0.857
Donor weight (median [IQR])		26.00 [16.00, 44.25]	25.00 [16.00, 43.50]	35.00 [17.00, 48.00]	0.638
Donor creatinine (median [IQR])		65.30 [30.50, 110.25]	54.30 [27.05, 88.55]	111.10 [68.00, 135.10]	< 0.001
Donor DCD (%)	No	124 (88.6)	98 (95.1)	26 (70.3)	< 0.001
	Yes	16 (11.4)	5 (4.9)	11 (29.7)	
Donor gender (%)	Female	53 (37.9)	39 (37.9)	14 (37.8)	1.000
	Male	87 (62.1)	64 (62.1)	23 (62.2)	
WIT/min (median [IQR])		0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 15.00]	< 0.001
CIT/h (median [IQR])		6.00 [4.00, 9.25]	6.00 [4.00, 8.00]	10.00 [6.00, 14.00]	< 0.001

Abbreviations: DGF Delayed graft function, *DCD* Donor after circulatory death, *WIT* warm ischemia time, *CIT* Cold ischemia time

age and dialysis modality. However, the DGF group had a higher proportion of transplanted kidneys from DCD donors, longer CIT, and poorer donor kidney function, which may contribute to the development of DGF in the transplanted kidney. Additionally, the decreased preoperative HDLC level observed in patients of the DGF group warrants further investigation to determine its clinical significance.

Screening and performance comparison of DGF Risk Stratification Models

In this study, we developed a model (DGF-RS) to predict the risk of DGF in pediatric kidney transplant recipients post-transplantation. As illustrated in Fig. 1, the process of constructing DGF-RS involves several steps, including data collection, data preprocessing, feature selection, ML model training, and validation. We initially performed univariate LR analysis on the clinical data of pediatric kidney transplant recipients and donors in the training set, which consisted of 70% of the total sample size. The results demonstrated that HDLC, DCD, WIT, CIT, gender match, and donor creatinine were significantly associated with the occurrence of post-transplantation DGF ($P < 0.05$, Fig. 2A). Additional differential analysis further confirmed significant differences between the DGF and non-DGF groups in the aforementioned indicators ($P < 0.05$, Fig. 2B). Based on these findings, we incorporated the six identified variables into the subsequent ML model training to develop a reliable DGF prediction tool. The novelty of this study lies in identifying specific risk factors that influence the occurrence of DGF in the pediatric kidney transplant population, thereby providing new insights for clinical practice.

Evaluation of the predictive performance of the DGF-RS model

To identify the optimal ML model for predicting DGF, we compared 97 different model combinations using the training and validation datasets. Figure 3A illustrates the top 10 models ranked by their predictive performance. The results demonstrated that the RF model consistently exhibited superior performance under various parameter settings. When the mtry parameter was set to 5 and 75% of the features were retained, the average area under the AUC value on the training and validation datasets reached 0.951, ranking first among all models (Fig. 3B). Furthermore, we assessed several other widely used binary classification metrics, including Recall, F1-score, Precision, and Accuracy. Our findings revealed that the RF model (with mtry = 5 and 75% of features retained) significantly outperformed other models on these metrics (Fig. 3C–E; Additional file 1: Fig. S1-4), validating its predictive capability for DGF. In contrast, despite the XGBoost model being proven to yield favorable classification results in certain studies, its performance on the dataset in the present study was not noteworthy. In summary, through extensive model comparisons, this study identified the optimal ML model for predicting the risk of DGF occurrence in pediatric kidney transplant recipients, which bears considerable significance in guiding clinical decision-making and improving prognosis.

Evaluation of the predictive performance of the DGF-RS Model

To comprehensively evaluate the predictive performance of the DGF-RS developed based on the RF (mtry = 5, 75%p) model, we plotted the ROC curve and calculated the AUC. The results showed that in the entire study cohort, the AUC of DGF-RS was 0.983 (95% CI

Table 2 Recipient characteristics stratified by delayed graft function (DGF)

	Level	Overall	DGF (No)	DGF (Yes)	*P*-value
Patient number		140	103	37	
HDLC (median [IQR])		1.32 [1.06, 1.32]	1.32 [1.28, 1.36]	1.06 [1.00, 1.15]	< 0.001
LDLC (median [IQR])		2.32 [2.14, 2.50]	2.32 [2.14, 2.49]	2.29 [2.15, 2.49]	0.211
P (median [IQR])		2.01 [1.76, 2.19]	2.01 [1.79, 2.20]	2.04 [1.74, 2.17]	0.437
Total cholesterol (median [IQR])		4.34 [3.67, 5.00]	4.34 [3.63, 5.13]	4.23 [3.78, 4.91]	0.768
TG (median [IQR])		1.52 [1.08, 1.94]	1.52 [1.10, 1.85]	1.69 [1.03, 2.37]	0.215
HLA-A mismatch (median [IQR])		1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	0.427
HLA-B mismatch (median [IQR])		2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.429
HLA-DRB1 mismatch (median [IQR])		1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.288
HLA-ABDR mismatch (median [IQR])		4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.884
Direct bilirubin (median [IQR])		3.10 [2.40, 3.92]	3.20 [2.40, 3.95]	2.90 [2.50, 3.80]	0.471
Alb (median [IQR])		41.25 [36.90, 45.92]	40.90 [36.90, 45.55]	41.85 [37.40, 46.00]	0.6
AST (median [IQR])		17.50 [13.00, 25.00]	18.00 [13.00, 26.00]	16.00 [14.00, 20.00]	0.442
ALT (median [IQR])		10.00 [7.00, 17.00]	10.00 [7.00, 18.50]	11.50 [8.00, 16.00]	0.617
Total Bilirubin (median [IQR])		7.35 [5.40, 10.70]	7.10 [5.35, 10.70]	8.25 [5.90, 10.60]	0.537
ALP (median [IQR])		187.00 [116.50, 288.00]	186.50 [109.50, 278.50]	202.00 [122.00, 291.00]	0.686
KTR age (median [IQR])		13.00 [9.00, 15.00]	12.00 [9.00, 15.00]	13.00 [10.00, 16.00]	0.113
KTR height (median [IQR])		145.00 [125.50, 160.25]	145.00 [123.00, 159.00]	150.00 [137.00, 163.00]	0.082
KTR weight (median [IQR])		35.25 [23.50, 45.23]	33.30 [21.85, 44.25]	37.70 [27.00, 50.00]	0.054
KTR BMI (median [IQR])		16.05 [14.70, 18.14]	15.80 [14.70, 17.85]	16.30 [14.95, 18.70]	0.392
WBC (median [IQR])		6.16 [4.90, 7.15]	6.16 [4.73, 7.07]	6.16 [5.51, 7.28]	0.501
Neutrophil (median [IQR])		3.42 [2.56, 4.38]	3.29 [2.50, 4.40]	3.50 [2.99, 4.35]	0.303
Lymphocyte (median [IQR])		1.79 [1.44, 2.33]	1.76 [1.33, 2.31]	1.88 [1.51, 2.33]	0.437
Platelet (median [IQR])		219.50 [175.75, 276.00]	225.00 [178.50, 282.00]	202.00 [175.00, 252.00]	0.239
K (median [IQR])		4.42 [3.85, 4.91]	4.40 [3.78, 4.88]	4.67 [3.96, 4.99]	0.378
Scr (median [IQR])		816.00 [649.00, 990.25]	840.00 [640.50, 968.00]	778.00 [656.00, 1048.00]	0.671
BUN (median [IQR])		24.17 [17.32, 30.29]	24.49 [17.72, 30.55]	22.83 [16.98, 28.49]	0.653
Total CO_2 (median [IQR])		22.20 [20.30, 24.63]	22.20 [20.25, 25.15]	22.20 [20.60, 24.00]	0.889
Glu (median [IQR])		5.00 [4.52, 5.41]	5.01 [4.54, 5.44]	4.96 [4.51, 5.36]	0.821
Dialysis BeforeKT (%)	No	11 (7.9)	8 (7.8)	3 (8.1)	1.000
	Yes	129 (92.1)	95 (92.2)	34 (91.9)	
Peritoneal dialysis BeforeKT (%)	No	68 (48.6)	50 (48.5)	18 (48.6)	1.000
	Yes	72 (51.4)	53 (51.5)	19 (51.4)	
Hemodialysis BeforeKT (%)	No	82 (58.6)	60 (58.3)	22 (59.5)	1.000
	Yes	58 (41.4)	43 (41.7)	15 (40.5)	
KTR Gender (%)	Female	62 (44.3)	45 (43.7)	17 (45.9)	0.965
	Male	78 (55.7)	58 (56.3)	20 (54.1)	
PRA (%)	Negative	133 (95.0)	97 (94.2)	36 (97.3)	0.758
	Positive	7 (5.0)	6 (5.8)	1 (2.7)	

Abbreviations: DGF Delayed graft function, *HDLC* High-density lipoprotein cholesterol, *IQR* Interquartile range, *LDLC* Low-density lipoprotein cholesterol, *TG* Triglyceride, *HLA* Human leukocyte antigen, *Alb* Albumin, *AST* Aspartate transaminase, *ALT* Alanine transaminase, *ALP* Alkaline phosphatase, *KTR* Kidney transplant recipients, *WBC* White blood cell, *Scr* Serum creatinine, *BUN* Blood urea nitrogen, *Glu* Glucose, *KT* Kidney transplantation, *DCD* Donor after circulatory death, *PRA* Panel-reactive antibody

0.959–1.000), indicating its excellent discriminative ability for DGF (Fig. 4A). Further analysis revealed that the risk score performed equally well in the training and validation sets, with AUC values of 1.000 (95% CI 1.000–1.000) and 0.905 (95% CI 0.781–1.000), respectively. Additionally, we compared the predictive performance of DGF-RS with individual clinical indicators such as HDLC, DCD, WIT, CIT, gender match, and donor creatinine. In both the training and validation sets, the predictive ability of DGF-RS was significantly superior to these single indicators (Additional file 1: Fig. S5), demonstrating the advantage of a combined multi-indicator

Table 3 Donor-recipient matching characteristics stratified by delayed graft function (DGF)

	Level	Overall	DGF (No)	DGF (Yes)	*P*-value
Patient number		140	103	37	
Age gap between donor and recipients (median [IQR])		−4.00 [−8.00, 1.00]	−5.00 [−8.50, 2.00]	−3.00 [−7.00, 0.00]	0.883
Absolute age gap between donor and recipients (median [IQR])		5.00 [3.00, 8.00]	5.00 [3.00, 9.00]	4.00 [2.00, 7.00]	0.122
Gender match (%)	No	67 (47.9)	44 (42.7)	23 (62.2)	0.066
	Yes	73 (52.1)	59 (57.3)	14 (37.8)	

Abbreviations: DGF Delayed graft function

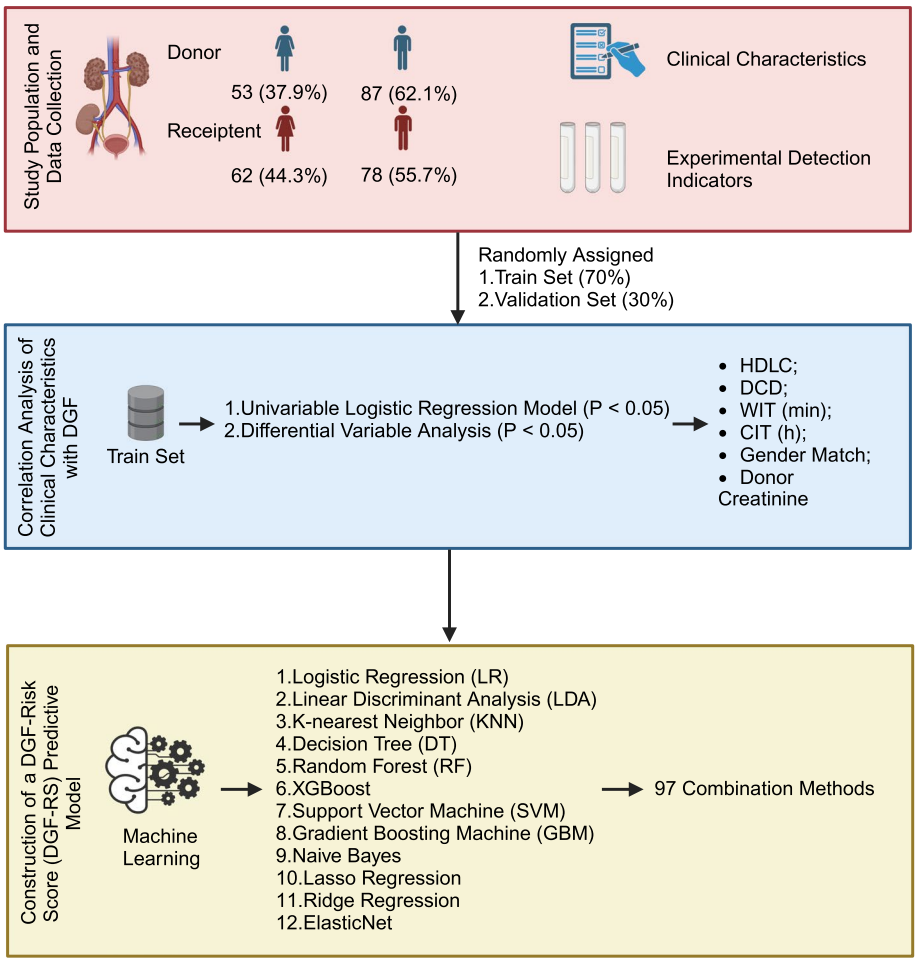

Fig. 1 Schematic overview of the development and validation of the DGF-RS model for predicting DGF in pediatric kidney transplant recipients. The process involves data collection, preprocessing, feature selection using univariate LR and comparative analysis, and training and evaluation of various machine learning models. The best-performing model, a RF with an mtry value of 5 and 75% of features retained, was selected as the final DGF-RS model. Abbreviations: DGF, delayed graft function; DGF-RS, DGF-Risk Score; HDLC, high-density lipoprotein cholesterol; DCD, donor after circulatory death; WIT, warm ischemia time; CIT, cold ischemia time

assessment. The DCA intuitively displayed the net benefit obtained by applying DGF-RS for clinical decision-making at different thresholds (Fig. 4B, C), providing strong evidence for the utility of this model in practical applications. In summary, this study developed and validated a ML-based DGF risk assessment tool for pediatric

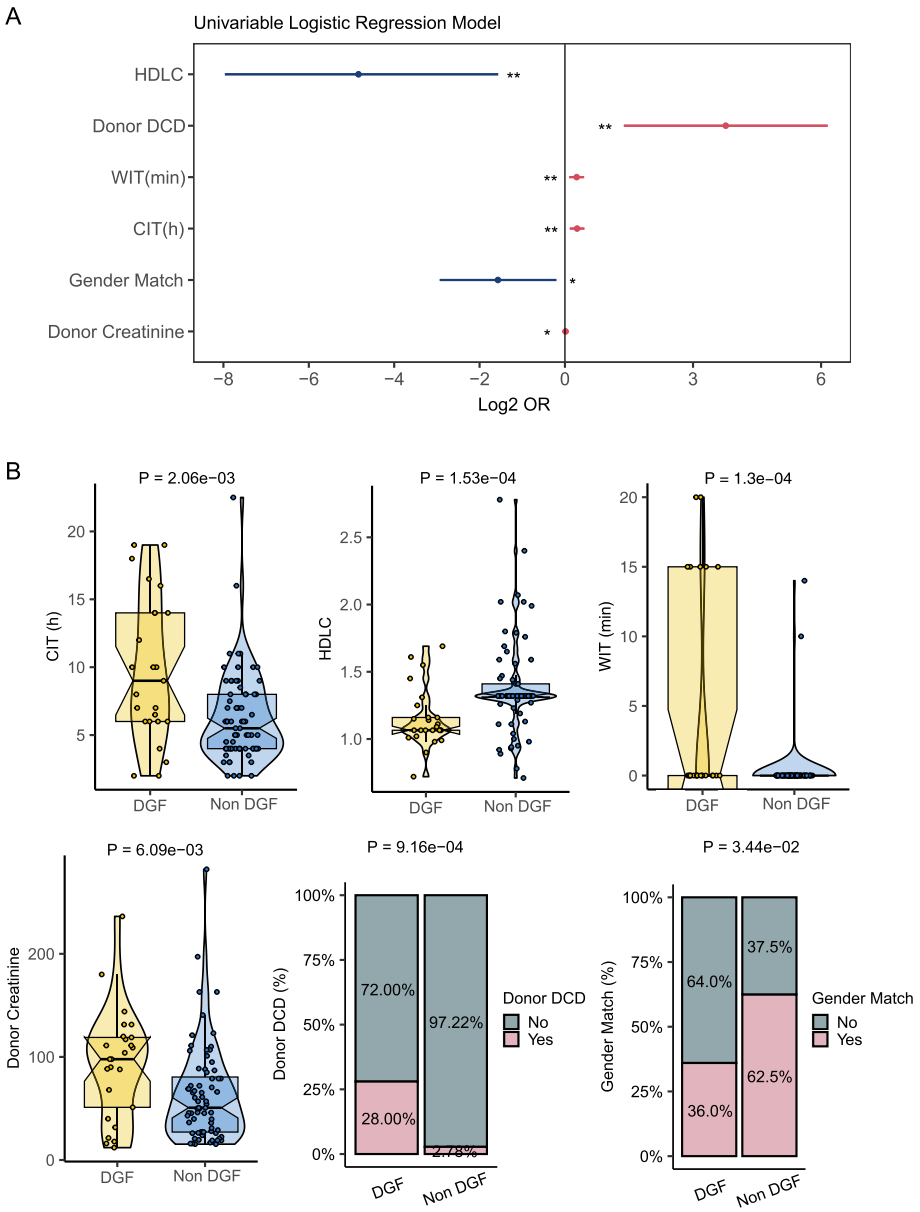

Fig. 2 Identification of key features associated with DGF in pediatric KT. **A** Forest plot depicting the odds ratios and 95% CIs of variables significantly associated with DGF in univariate LR analysis ($P < 0.05$). **B** Comparative analysis of the distribution of these significant features between the DGF and non-DGF groups, revealing notable differences ($P < 0.05$). Abbreviations: DGF, delayed graft function; KT, kidney transplantation; LR, logistic regression; HDLC, high-density lipoprotein cholesterol; DCD, donor after circulatory death; WIT, warm ischemia time; CIT, cold ischemia time

kidney transplant recipients, demonstrating its excellent predictive performance and potential clinical utility in this patient population.

Discussion

KT is a critical treatment option for children (aged < 18 years) with ESRD. DGF is a prevalent complication following KT, with its occurrence being strongly associated with graft and patient outcomes. Consequently, accurate prediction of DGF occurrence is crucial for prompt intervention and improved prognosis. In this study, we concentrated on the field of pediatric KT and developed a risk scoring model (DGF-RS) for predicting DGF occurrence utilizing clinical characteristics and detection indicators of kidney transplant donors and recipients, in conjunction with multiple ML algorithms. By comparing the predictive performance of different ML models, we discovered that the RF model (mtry = 5,

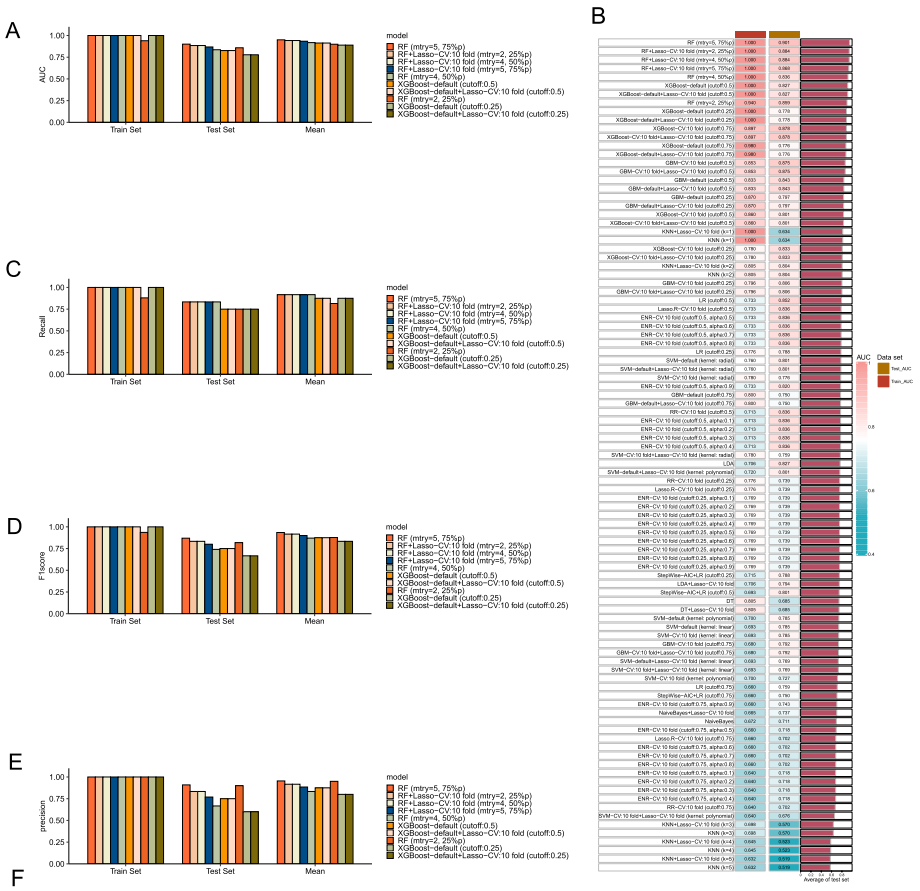

Fig. 3 Comprehensive evaluation and comparison of machine learning models for the prediction of DGF. **A** The top 10 best-performing models ranked by their average area under the AUC values on the training and validation sets. **B** Detailed AUC values of the top 10 models, with the RF model (mtry = 5, 75%p) achieving the highest average AUC of 0.951. **C**–**E** Comparison of other commonly used binary classification metrics, including recall, F1-score, precision, and accuracy, among the top models, confirming the superior performance of the RF (mtry = 5, 75%p) model. Abbreviations: DGF, delayed graft function; AUC, area under the curve; RF, random forest

75%p) demonstrated the highest predictive accuracy. DGF-RS exhibited remarkably high accuracy and sensitivity in both the training set and validation set (training set: AUC = 1; validation set: AUC = 0.905). This result indicates that ML models integrating donor and recipient characteristics can effectively predict the risk of DGF occurrence, offering valuable insights for clinical decision-making. Additionally, our study further validated the application potential of ML in the field of pediatric KT. Compared to traditional statistical methods, ML possesses the ability to uncover intricate patterns in data and enhance the accuracy of predictions. We anticipate that this study will foster the further application of ML in pediatric KT, ultimately benefiting a greater number of children afflicted with the disease.

During the development of the DGF-RS, we identified several features that significantly influence the occurrence of DGF, including HDLC, DCD, WIT, CIT, gender match, and donor creatinine levels [34]. These findings are consistent with previous research. Studies have demonstrated that DCD and prolonged CIT are risk factors for DGF [4, 35]. Similarly, prolonged WIT has been associated with an increased incidence of DGF [4]. Furthermore, gender mismatch between the donor and recipient may elicit an immune response, thereby increasing the risk of DGF [14, 36]. Donor renal dysfunction, as indicated by elevated creatinine levels, has also been associated with recipient DGF [34]. However, the relationship between HDLC and DGF has not been systematically investigated. Considering the anti-inflammatory and endothelial function-improving effects of HDLC [37], we hypothesize that it may influence the occurrence of DGF by regulating the inflammatory response of the graft. Further research is needed to elucidate the role of HDLC in the mechanism of DGF occurrence. In summary, our DGF prediction model integrates demographic, clinical, and biochemical indicators of both donors and recipients, thereby reflecting the risk of DGF occurrence from

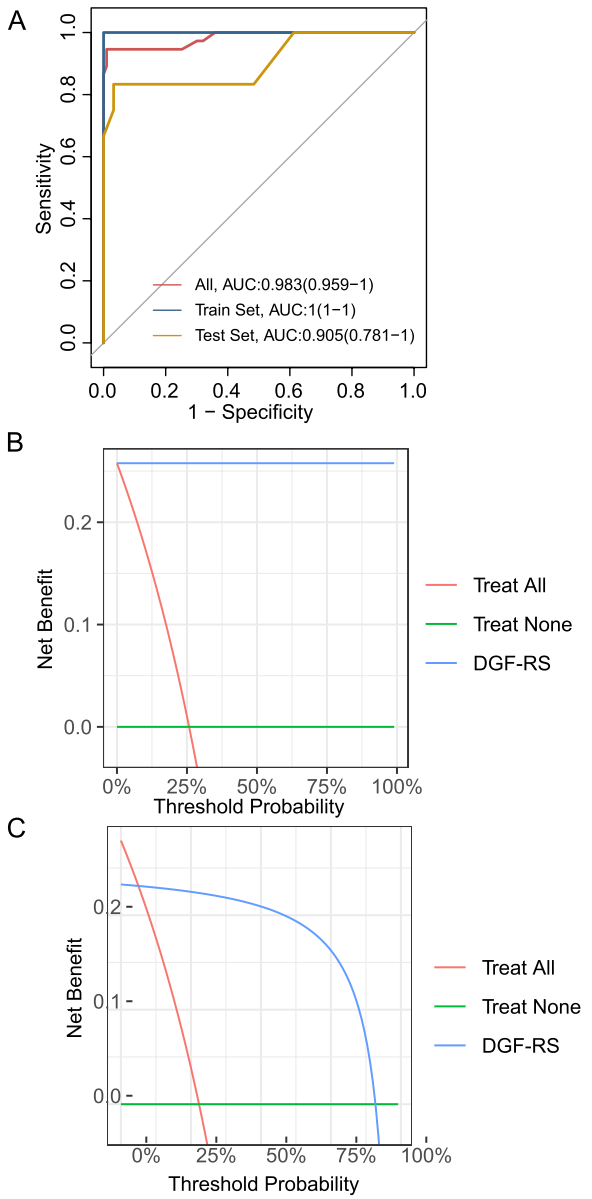

Fig. 4 Comprehensive assessment of the predictive performance of the delayed graft function risk score (DGF-RS) model based on the RF (mtry = 5, 75%p) algorithm. **A** ROC curves and AUC values of the DGF-RS in the entire cohort, training set, and validation set, demonstrating excellent discriminative ability (AUC: 0.983, 1.000, and 0.905, respectively). **B**,**C** DCA illustrating the net benefit of using the DGF-RS for clinical decision-making at different threshold probabilities, providing strong evidence of its potential clinical utility. Abbreviations: RF, random forest; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis

multiple dimensions and providing significant clinical utility.

Long-term graft survival and function are also crucial indicators for evaluating prognosis. Future studies should further explore the association between delayed graft function (DGF) and long-term graft survival, and develop a comprehensive predictive model integrating DGF and long-term prognosis to provide a foundation for personalized diagnostic and treatment strategies. We acknowledge that our single-center retrospective study primarily focused on the incidence of DGF in pediatric kidney transplant recipients without incorporating short-term risk indicators such as incomplete renal function recovery (defined as achieving less than 50% of the donor's estimated glomerular filtration rate [eGFR]) and recipient's 90-day eGFR below 30 [38]. In light of Sandal et al.'s findings that DGF does not invariably correlate with poor long-term graft outcomes [38], we acknowledge the need for further investigation into the relationship between DGF and long-term prognosis through systematic collection of renal function data at 100 days and 1 year post-transplantation. In future prospective studies, we aim to collect comprehensive data from a larger cohort of pediatric kidney transplant recipients, including short-term risk indicators and renal function assessments at 100 days and 1 year post-transplantation. This approach will facilitate a more robust investigation into the association between DGF incidence and long-term outcomes in pediatric kidney transplant recipients, potentially yielding insights for improved post-transplant management strategies. We believe our study contributes valuable insights to the field of pediatric kidney transplantation. Our innovative approach leverages artificial intelligence to integrate multiple potential biomarkers with machine learning algorithms, constructing a risk score for predicting DGF. Although DGF has limitations as a predictor, it remains a crucial short-term measure for determining graft prognosis, guiding organ utilization decisions, and serving as a primary endpoint in clinical trials [39, 40]. Given the paucity of research on DGF prediction in pediatric kidney transplantation, our study aims to address this gap by developing a predictive model based on clinical characteristics and diagnostic indicators of both donors and recipients, incorporating multiple machine learning algorithms. The DGF-RS model developed in this study offers several potential clinical applications. Firstly, it can assist clinicians in identifying patients at high risk for DGF prior to transplantation, enabling the implementation of personalized management strategies and more intensive post-operative monitoring. Secondly, the model can inform decision-making in organ allocation, potentially prioritizing kidneys with lower DGF risk for pediatric recipients. Thirdly, it can serve as a valuable tool for patient and family counseling, providing more accurate risk assessments and facilitating the establishment of realistic expectations. Finally, the model's insights into risk factors can guide future research directions and inform the development of targeted

interventions aimed at reducing DGF incidence in pediatric kidney transplantation.

Despite the favorable outcomes of our study, several issues remain that urgently need to be addressed. First, the relatively small sample size of this study may limit the generalization performance of the model to some extent. Future studies should aim to expand the sample size and incorporate multicenter data to further validate and optimize our predictive model. Second, our model primarily relies on pre-transplantation donor and recipient characteristics, while factors related to the transplantation surgery itself (e.g., operation time, blood loss) may also influence the occurrence of DGF [15]. Integrating multidimensional data from pre- and post-transplantation to construct a dynamic predictive model may further enhance the accuracy of prediction. Third, the model did not incorporate several emerging predictive biomarkers, including peripheral vascular disease and chronic obstructive pulmonary disease for recipients, as well as diabetes history, hypertension history, smoking history, and HCV status for both recipients and donors. Our study enhances the current understanding of DGF risk prediction in pediatric kidney transplantation, surpassing existing risk assessment tools such as the Kidney Donor Risk Index (KDRI) and the recently developed Pediatric KDRI [41]. Although these indices offer valuable insights, our DGF-RS model exhibits superior predictive performance in our cohort, demonstrating an AUC of 0.983 (95% CI 0.959–1.000) compared to the highest reported AUC of 0.6273 for the Pediatric KDRI. It is crucial to acknowledge, however, that our model incorporates several distinct variables compared to the Pediatric KDRI, which may contribute to its enhanced predictive capability. Future investigations should aim to integrate the comprehensive set of variables utilized in the Pediatric KDRI to further refine and validate our DGF-RS model across diverse pediatric populations. Forth, although our model incorporates factors (such as CIT and WIT), it maintains significant value. It can be utilized immediately post-transplant to identify high-risk patients who may benefit from more intensive monitoring and therapeutic interventions. Moreover, the model can be modified for pre-transplant risk assessment by incorporating estimated values for post-transplant factors, facilitating improved preparation and resource allocation. While our study found a significant difference in CIT between DGF and non-DGF groups, we recognize the practical challenges in substantially reducing CIT given the realities of resource constraints, surgeon availability, and personnel logistics. The clinical application of this finding should be interpreted with caution. Our study incorporated HDLC as a predictor, a parameter which is not routinely measured in pediatric recipients at many transplant centers. Although this may limit the immediate generalizability of our model, it simultaneously highlights a potential area for further investigation in pediatric kidney transplantation. Despite these limitations, this study provides significant innovation and academic value by offering novel insights and methods for predicting DGF risk in pediatric kidney transplant recipients.

Conclusions

This study validated the significant value of various ML methods in predicting DGF, with the RF (mtry = 5, 75%p) model exhibiting the highest accuracy and sensitivity. We identified several important predictive factors, including HDLC, DCD, WIT, CIT, gender match, and donor creatinine. These findings provide new insights into the pathogenesis of DGF in pediatric kidney transplant recipients. Future studies should aim to expand the sample size, integrate multi-omics data, improve model interpretability, and explore strategies for clinical translation. In conclusion, we propose that ML-based DGF prediction models have the potential to facilitate clinical practice in pediatric KT, optimize patient management, and improve transplantation outcomes.

Abbreviations

Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CIT	Cold ischemia time
DCA	Decision curve analysis
DCD	Donor after circulatory death
DD	Deceased donors
DGF	Delayed graft function
DGF-RS	DGF-Risk Score
DT	Decision tree
ESRD	End-stage renal disease
GBM	Gradient boosting machine
Glu	Glucose
HDLC	High-density lipoprotein cholesterol
HLA	Human leukocyte antigen
IQR	Interquartile range
KNN	K-nearest neighbor
KT	Kidney transplantation
KTR	Kidney transplant recipients
LDA	Linear discriminant analysis
LDLC	Low-density lipoprotein cholesterol
LR	Logistic regression
ML	Machine learning
Mtry	Number of variables randomly sampled as candidates at each split in random forest models
PRA	Panel-reactive antibody
RF	Random forest
ROC	Receiver operating characteristic
Scr	Serum creatinine
SVM	Support vector machine
TG	Triglyceride
WBC	White blood cell
WIT	Warm ischemia time

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Additional file 5.

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Not applicable.

Authors' contributions
Y-GL, X-YL, R-TF, W-XF, and W-WJ contributed to the study design. J-AC, G-LZ, C-WC, Z-JL, J-DZ, DL, SZ, J-MH, G-RL, and JL collection of data. Z-FG, Y-ZL, S-QY, S-CL, HC, YG, and ML analysis of data. Y-GL, X-YL, R-TF, L-PF, H-YY, J-RC, and L-YL wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
This study strictly complied with relevant international and domestic ethical guidelines and legal regulations and was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University (ID: 2024-KY-114–01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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