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Long-term outcomes in rapamycin on renal allograft function: a 30-year follow-up from a single-center experience

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Abstract

Objectives To evaluate long-term renal graft prognosis and the role of rapamycin from a single-center in China over a 30-year follow-up.

Methods This study enrolled a total of 654 patients who underwent kidney transplantation between 1989 and 2020. The basic characteristics of the included patients were collected. Graft survival was described and compared using Kaplan-Meier curves (K-M curves). Both continuous and categorical variables were included in a multivariate Cox proportional-hazards model. Patients were divided into rapamycin-based quadruple immunosuppression regimen group (rapa group, $n=41$) and conventional tacrolimus-based triple immunosuppression regimen group (control group, $n=218$). The indication biopsy results of the two groups were further reviewed to compare the incidence of rejection, acute rejection, and banff score.

Results The overall 5, 10, 15, 20-year graft survival rate of our center is 87.5%, 62.4%, 46.4% and 20.9%, respectively. The median survival time after surgery is 14 years. Multiple Cox regression analysis identified BMI ($p=0.035$), dialysis type ($p<0.001$), immunosuppressants ($p<0.01$), urine albumen ($p<0.001$), globulin ($p=0.041$), and blood glucose ($p=0.002$) as risk factors. The 20-year, 10-year and 5-year AUC is 0.78, 0.75 and 0.75. The combination of FK506 and rapamycin was further suggested by the model to effectively improve the graft prognosis ($p<0.01$, HR = 0.763). The K-M curve showed that the long-term survival rate of renal grafts in the rapa group was significantly better than that in the conventional group ($p<0.001$). In addition, indication biopsy records revealed a lower possibility of immune rejection in the rapa group than that in the conventional group ($p<0.001$). Banff score indicated that rapa group had less vascular inflammation in the transplanted kidney.

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Conclusions In this study, a 30-year follow-up was performed in a single center, and a total graft 20-year survival rate of 20.9% was reported. The prognostic model and subgroup analysis suggested that FK506 combined with rapamycin could effectively improve the prognosis of renal transplantation, which could be explained by reduced acute rejection and less vascular inflammation.

Keywords Graft survival, Rapamycin, Prediction model, Kidney transplantation

Introduction

Chronic kidney disease (CKD) has gradually become a significant global health problem. In China, The incidence of CKD has reached 10.8%, affecting approximately 130 million people, with 1–2% of them eventually progressing to end stage of renal disease (ESRD) [1, 2]. Currently, ESRD mainly relies on replacement therapy, including hemodialysis, peritoneal dialysis, and allograft kidney transplantation (KTx). Compared with hemodialysis and peritoneal dialysis, KTx has significantly lower patient mortality, less complication rate and higher quality of life [3], which is considered to be the most ideal treatment for ESRD at present.

The world's first kidney transplant took place in 1950 [4, 5]. The development of surgical techniques and perioperative nursing has also improved the prognosis of kidney transplant recipients. Despite remarkable improvement over the past few decades, patients are still experiencing late allograft failure. In recent years, numerous factors affecting the prognosis of renal transplant recipients have been extensively reported worldwide, encompassing baseline data of recipients, surgical conditions, immunosuppressive regimens, and others. Postoperative acute rejection and perioperative vascular complications were found as risk factors for the survival of kidney graft by Zhu's work [6]. Notably, Dr. Domínguez-Gil and Jose M Morales also observed lower long-term patient- and graft-survival rates in hepatitis C virus (HCV) positive patients, with elevated mortality primarily attributed to liver disease and infections [7]. Moreover, there have been some findings on that the new brain death followed by circulatory death (DBCD) policy of donation produced acceptable results similar or even better than the death cardiac death (DCD) practice recently, as illustrated by Fang's team [8]. However, in any case what we can't deny the most is that immunosuppressive drugs such as glucocorticoids, cytotoxic drugs including cyclophosphamide have been applied in clinical practice, greatly reducing the incidence of postoperative immune rejection [9]. The flexibility of postoperative immunosuppressive regimens has brought more possibilities for changes in the prognosis of kidney transplant patients, and various types of immunosuppressive agents such as calcineurin inhibitors (CNIs), mammalian target of rapamycin inhibitors, Immunosuppressive drugs such as mTOR inhibitors and cytokine receptor antibodies have been introduced in the past century [3]. Although clinical trials have verified their safety, there is no unified conclusion on their long-term effect on the prognosis of kidney transplantation. Therefore, long-term follow-up records and analysis are necessary to evaluate the cost-effectiveness of these immunosuppressants.

In this study, we enrolled a total of 654 patients who underwent kidney transplantation between 1989 and 2020. A multivariate Cox proportional-hazards model was constructed to screen out the potential prognosis-related factors. We focused on the immunosuppressive regimens and further subgroup analysis was performed on the factors that were significantly associated with the prognosis according to the model. The combination of rapamycin to traditional protocol was found to effectively improve the graft prognosis. This research is not only relevant for adding options to a more personalized approach in clinical care after KTx, but also for quality control and optimization of organ transplantation programs, thus further prolonging patients' life.

Patients and methods

Ethical statement

The protocols followed were approved by the local ethics committee of the First Affiliated Hospital of Nanjing Medical University. We obtained written informed consent from all transplant recipients. The procedures followed in our study were in accordance with the ethical standards of the Declarations of Helsinki and Istanbul. The study was strictly limited to living-related transplantation of kidney donors to lineal or collateral relatives not beyond the third degree of kinship or transplantation of kidney donors from deceased allograft donors after cardiac death.

Study design and patient population

A retrospective study was conducted on a cohort comprising 654 patients who underwent kidney transplantation at the First Affiliated Hospital of Nanjing Medical University between January 1989 and April 2020. The follow-up period for the subjects extended from the time of kidney transplantation until the last documented date in March 2021. Clinical data for all patients in this study were extracted from medical records. Variables were included in a multiple Cox model, according to which further subgroup analysis was performed on the factors that were significantly associated with the graft prognosis.

Immunosuppression

Basiliximab or antihuman thymocyte immunoglobulin was employed as induction therapy for kidney transplantation. All participants received CNIs, specifically tacrolimus (FK506) or cyclosporin A (CsA), as part of the immunosuppressive regimens during the maintenance period. The detailed immunosuppression protocols were outlined in one of our previous papers [10]. The dosage of immune suppressants was adjusted according to the serum creatinine level and drug concentration. For conversion therapy, which was carried by reducing the amount of CNIs and adding rapamycin (RAPA) to form a low-dose quadruple regimen, the criteria was when nephrotoxicity (Scr < 2.5 mg/dl; GFR > 40 ml/min; proteinuria < 0.5 g/d) or elevated blood sugar occurred in patients treated with triple therapy, accompanying substandard drug concentrations. The target RAPA concentration required for conversion therapy was 8-10ng/ml. The distribution of the conversion dates in the postoperative days has been concluded in Supplementary Fig. 1, and most of the conversions happened within 5 years after the surgery.

Data collection

The data collected demographic characteristics including gender, age, occupation, marital status, etc. Both preoperational characteristics including blood type, dialysis type, BMI, HBV, donor sex, donor age and whether related donor, and post operation information containing immunosuppressants strategy, immunosuppressants blood concentration, BUN value, Scr value and other lab data were retrieved. In this study, all cases are ABO-compatible. Graft loss was defined as eGFR less than 30 ml/min/1,73m^2, indicating the CKD staging is G4 or G5 according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline published in 2002 for evaluation, classification, and stratification of CKD [11]. Notably, eGFR was calculated based on the Creatinine Equation (CKD-EPI 2,009) for estimating GFR, expressed for specified sex, serum creatinine level [12].

Table 1 Characteristics of the study population

	n=(654)
Male, n(%)	489 (74.8)
Median age at Ktx, years(IQR)	37.5 (29.0-45.3)
Median BMI at KTx, kg/m2(IQR)	21.3 (18.8–23.4)
Transplants, n(%)	
Primary/re-transplant	647 (98.9)/7 (1.1)
Pre-transplant dialysis, n(%)	
Peritoneal dialysis	30 (4.6)
Hemodialysis	598 (91.4)
No dialysis	26 (4.0)
Median durantion of dialysis, months(IQR)	8 (3.0–20.0)
Median durantion of follow up, years (IQR)	2.1 (0.68–5.80)
HBV, n(%)	10 (1.5)
Immunosupressants, n(%)	
Cyclosporin A	482 (73.7)
Tacolimus	259 (39.6)
Rapamycin	41 (6.3)
Drug Side Effects, n(%)	1(0.2)
Infection, n(%)	14 (2.1)
Complication, n(%)	8 (1.2)
Median donor age, years(IQR)	46.5 (33.3–52.0)
Donor sex, male n(%)	329 (50.3)
Living related donor, n(%)	71 (10.9)

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on the normality of the distribution. Categorical variables are presented as percentages. Differences in continuous variables were analyzed using analysis of variance (ANOVA), and chi-square test was applied to analyze the differences in categorical variables. Graft survival was depicted using Kaplan-Meier curves both in the overall and subgroup analysis. We used the general linear regression model to screen out the continuous variables that were significantly correlated with eGFR, and then incorporated them together with the categorical variables the multivariate Cox proportional-hazards model. The final prediction model was obtained through the iterative forward and backward stepwise analysis respectively. For calibration, selected models were trained on a randomly chosen 80% subset of the data, with observed versus predicted 20-year risks calculated on the remaining data, using product-limit estimates for the expected event and groups defined by quantiles of the predicted probabilities. The results were expressed as adjusted hazard ratio (HR) with a 95% confidence interval (CI) in the Cox model. A two-sided $P < 0.05$ was considered statistically significant. The ROC curve was plotted according to the model and the area under the curve (AUC) was calculated to evaluate the predictive ability of the model for the prognosis of KTx. All data analysis in this study was performed using R version 3.6.1.

Results

Population characteristics

The detailed follow-up information is presented in the Table S1 and Table S2. The main population characteristics are summarized in Table 1. KTx were carried out in 654 patients, and 7 patients underwent re-transplantation. The median age was 37.5 years, and the median duration of follow-up is 2.1 years. A total of 26 recipients (4.0%) underwent preemptive KTx, and the remaining 628 recipients were on dialysis at the time of KTx. The median duration of dialysis before KTx was 8 months.

The median age of the donors was 46.5 years, among which 71 (10.9%) were living related donor. In immunosuppressive protocols, both steroids and mycophenolate mofetil were routinely used combined with calcineurin inhibitors or mTOR inhibitors. CsA was used the most in 73.7% patients, followed by Tacrolimus (39.6%) in 259 patients, and rapamycin (6.3%) in 41 patients.

Graft survival and characteristics after KTx

The overall 20-year graft Kaplan-Meier survival curve of our center is illustrated in Fig. 1. The survival rates at 20, 15, 10, and 5 years after KTx were determined to be 20.9% (95% CI 9.0-48.2), 46.4% (40.6–52.9), 62.4% (58.8–66.2), and 87.5% (86.0–89.0), respectively. The median survival time for grafts after KTx is approximately 14 years after surgery. We also closely monitored the BUN level and serum creatinine (Scr) of the patients throughout different postoperative periods along with the calculated eGFR to assess the graft function at the corresponding time (Table S3). On average, patients exhibited a BUN level of 6.01 mmol/L at the first year post-KTx, which increased to 6.46 mmol/L at the 5-year mark and further rose to 9.38 mmol/L after a 20-year follow-up period, indicating a progressive upward trend. Similarly, the Scr values demonstrated an upward trajectory, with an initial level of 99.0 μmol/L in the first year post-surgery and a subsequent increase to 149.0 μmol/L after a 20-year duration. The eGFR of patients was calculated based on their postoperative Scr value, sexuality, and age, which were 62.35, 54.09, 44.94, 45.30, 39.17 ml/min/1.73m^2 at 1, 5, 10, 15 and 20 years after surgery, respectively. Remarkably, there was an overall decline of 23.18 ml/min/1.73 m^2 observed over the 20-year duration.

Prediction model for graft loss

Separate linear regression analyses with Scr considered as the outcome variable were conducted for 20-year prognosis (Table S4). BMI, donor age, leukocyte count, platelet count, ALT, globulin, blood urea nitrogen, urine volume, cholesterol, triglycerides, serum urine acid and blood glucose were screened out to be combined with all categorical variables, taking graft loss as outcome variable, to carry on with the multiple Cox regression. Eventually, a total of six factors, including BMI, dialysis type, drug strategy, urine albumin, plasma globulin, and blood glucose, were incorporated into the model based on the nomogram (Fig. 2-**A**, Table 2). Elevated urine albumin, globulin and blood glucose levels were considered as risk factors for graft loss while hemodialysis and BMI were on the contrary. Most interestingly, our model found that the addition of rapamycin to the postoperative immunotherapy regimen significantly improved graft outcomes (HR=1.31, $p<0.01$). ROC curve of the Cox regression

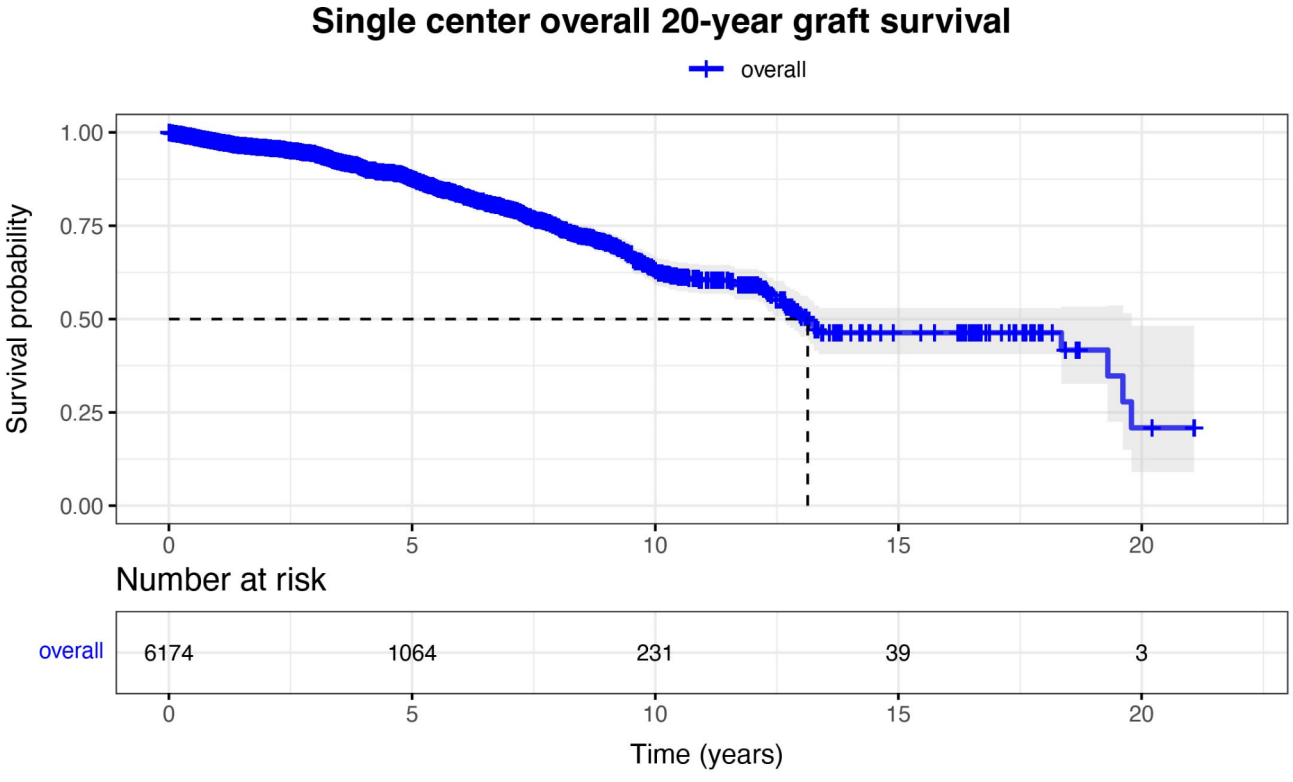
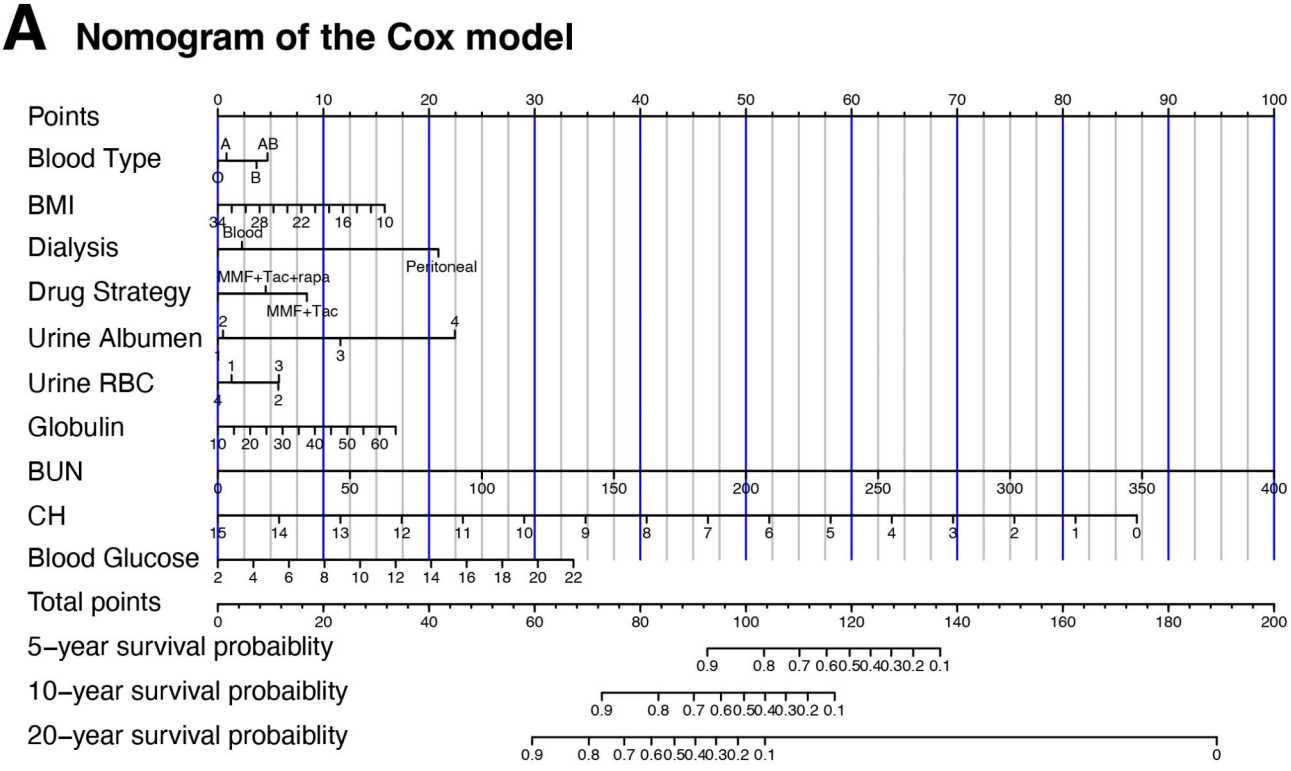


Fig. 1 Overall 20-year graft survival as time going



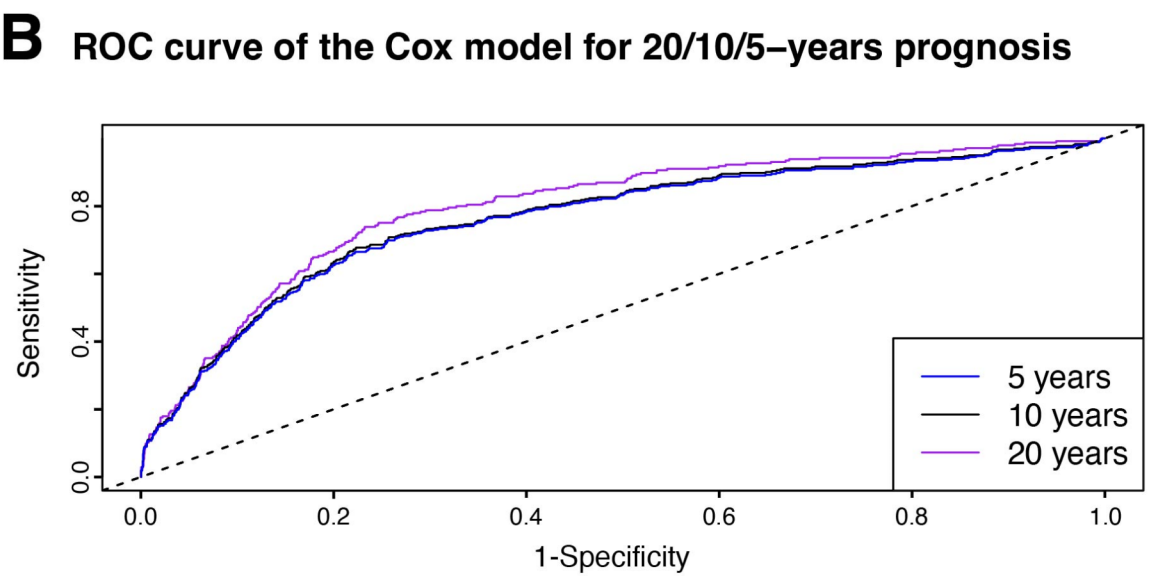


Fig. 2 Cox regression outcomes for 20-year graft survival. **A**: Nomogram of the Cox model. **B**: ROC curve of the Cox model for 20/10/5-years prognosis

model (Fig. 2-**B**) was plotted, with its 20-year, 10-year and 5-year AUC being 0.78, 0.75 and 0.75.

Subgroup analysis for the graft survival of two groups with different medication regimens

Among all the prognostic factors, we focused on the immunosuppressive factors with more controllable space, and divided the patients treated with tacrolimus into the traditional triple immunosuppressive regimen group and rapamycin-based quadruple immunosuppressive regimen group. The population characteristics of the two groups are shown in Table 3. The distribution of each population characteristic and donor characteristics in two groups were uniform, with no confounding factors

Table 2 Cox model for 20 year graft survival

Characteristics	Hazard.Ratio	CI95	*P*.Value	
BMI	0.97	0.94-1	0.035	*
Dialysis Type				
Peritoneal	0.18	0.13–0.26	< 0.001	***
Blood	0.14	0.08–0.26	< 0.001	***
Drug Strategy				
Steroid + MMF + Tac	1.35	1-1.81	0.047	*
Steroid + MMF + Tac + rapa	1.03	1.01–1.18	< 0.001	***
Urine Albumen				
++	1.01	0.78–1.3	0.952	
+++	1.78	1.26–2.52	0.001	**
>+++	2.95	1.81–4.79	< 0.001	***
Globulin	1.03	1-1.05	0.041	*
Blood Glucose	1.14	1.02–1.26	0.002	**

found. Based on this, we plotted the survival curves of the two groups of patients (Fig. 3), and found that the long-term prognosis of patients with the addition of rapamycin was significantly better than that of traditional FK506-based triple immunosuppressive protocol ($p<0.001$), and the median survival time was 17 years in the rapa group while only 10 years in the control group.

We further analyzed the incidence of delayed graft function (DGF) and rejection in the two groups during follow-up (Table 3). In our center we observed that the overall DGF incidence was 3.5% within 20 years after the surgery, and the rapa group shared a lower portion (2.4%) than those in the conventional group (3.6%, $p=0.0498$). On the other hand, 21.2% of all patients received an indication biopsy, among all the findings of which, 74.5% were diagnosed with rejection, and the rejection rate in the rapa group (31.7%) was much lower than that in the control group (77.8%, $p<0.001$). In terms of the rejection type, more than 60% of the rejection diagnosis were antibody-mediated rejection, and approximately another 7% cases were T-cell-mediated, and the distribution of this feature did not differ between the groups ($p=0.782$). Both results support that rapa can improve graft outcomes in the long term.

Lastly, the banff score was further reviewed and analyzed according to the Banff 2019 Classification of Renal Allograft Pathology. The highest banff index of all pathological results did not exceed 2 points. Results of the difference analysis suggested that rapa group had lower glomerulitis (g), total cortical inflammation (ti), peritubular capillary (ptc) and interstitial inflammation (i)

Table 3 Characteristics of two drug regimen groups

	all Tac users	without rapa	with rapa		
	n = 259	*n* = 218	*n* = 41	p	
Male, n(%)	194(74.9)	163(74.8)	31(75.6)	0.909	
Median age at Ktx, years(IQR)	37(28,44)	37(28,44)	34(28,44)	0.779	
Median BMI at KTx, kg/m^2(IQR)	20.95(18.53,23.24)	20.53(18.51,23,64)	21.45(19.67,22.02)	0.823	
Retransplants, n(%)	3(1.2)	2(1.0)	1(2.4)	0.824	
Pre-transplant dialysis, n(%)				0.723	
Peritoneal dialysis	22(8.5)	18(8.3)	4(9.8)		
Hemodialysis	229(88.4)	194(89.0)	35(85.4)		
No dialysis	8(3.1)	6(2.7)	2(4.8)		
Median durantion of dialysis, months(IQR)	13(6,24)	13(6,24.75)	14(6,21)	0.725	
Median donor age, years(IQR)	46(34.5,53)	46(34.5,53)	45(32,55)	0.861	
Donor sex, male n(%)	197(76.1)	163(74.8)	34(82.9)	0.115	
Living related donor, n(%)	48(18.5)	44(20.2)	4(9.8)	0.199	
Average renal function (eGFR) post surgery, mean (SD)					
5th year	56.81(20.41)	59.97 (20.25)	50.77 (19.35)	< 0.001	***
10th year	46.85(24.60)	50.77 (23.44)	43.89 (25.07)	0.002	***
15th year	44.58(21.33)	38.29 (16.47)	46.58 (23.12)	0.004	***
Average blood FK506 concentration, ng/ml, mean (SD)					
5th year	4.93(2.59)	5.75 (2.39)	3.34 (2.97)	< 0.001	***
10th year	3.80(1.54)	4.51 (2.13)	3.24 (1.47)	< 0.001	***
15th year	4.35(2.13)	4.25 (1.85)	4.65 (3.95)	0.465	
DGF	9(3.5)	8(3.6)	1(2.4)	0.0498	***
Indication biopsies	55(21.2)	36(16.5)	19(46.3)	0.082	
Rejection cases	41(74.5)	28(77.8)	13(31.7)	0.0001	***
ABMR	25(61.0)	16(57.1)	9(69.2)	0.782	
TCMR	3(7.3)	2(7.1)	1(7.7)		
Mixed	13(31.7)	10(35.8)	3(23.1)		

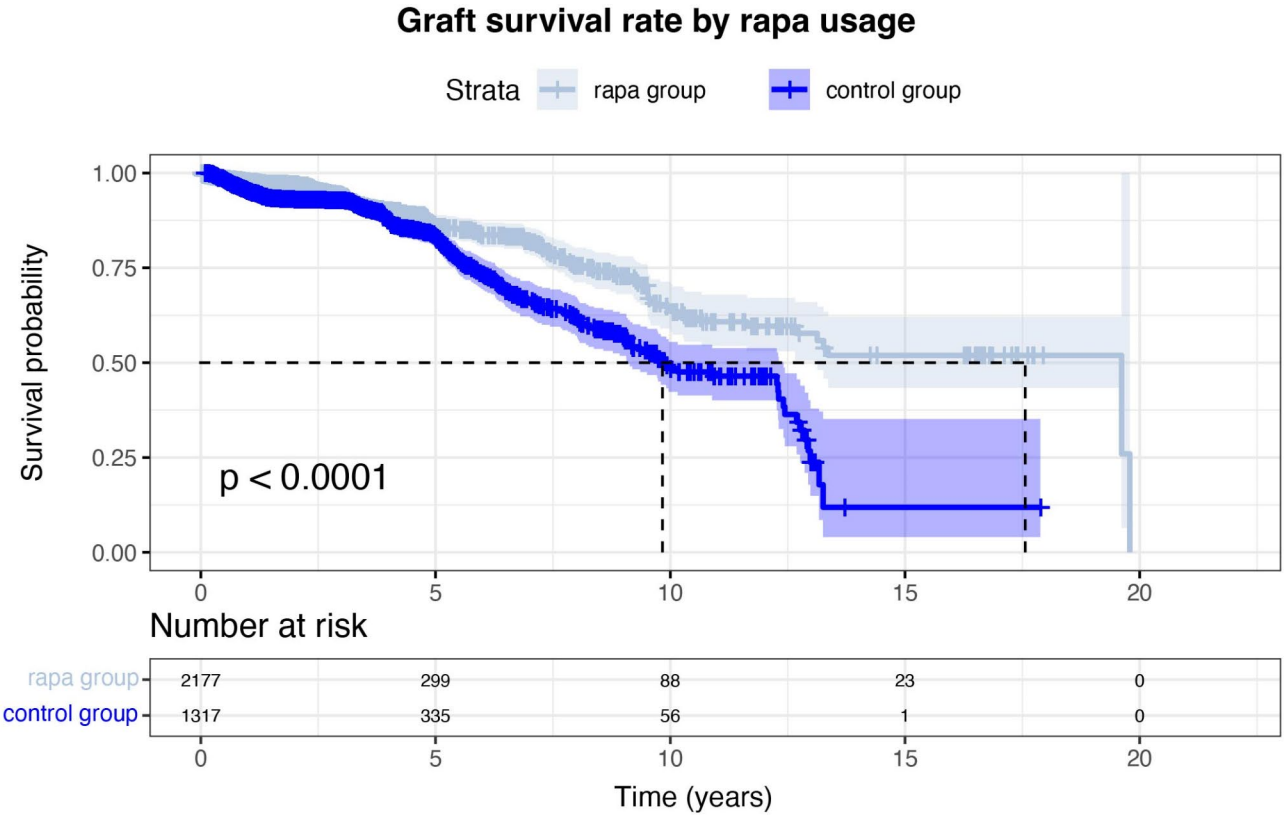


Fig. 3 Graft survival rate by rapa usage

scores. Among above, the difference for the g score was the greatest and the rapa group was estimated over 1 point lower than the control group. While the remaining indicators showed no significant differences between the two groups. Through comparing the pathological scores, we deduce that rapa may reduced the perivascular inflammation and interstitial fibrosis of the transplanted kidney (Fig. 4).

Discussion

In this study, we reviewed the graft survival of 654 patients who underwent kidney transplantation at Jiangsu Province People's Hospital within 30 years after surgery, and established two models based on preoperative and postoperative factors by statistical methods to provide a possible prediction for graft prognosis. The overall graft survival rate of our center is 20.9%. A multivariate Cox proportional-hazards model was constructed to screen out the potential prognosis-related factors. We focused on the immunosuppressive regimens and further subgroup analysis was performed on the factors that were significantly associated with the prognosis according to the model. The combination of rapamycin to traditional protocol was found to effectively improve the graft prognosis.

For nearly a century, patients with end-stage renal disease have had a relatively good long-term survival due to kidney transplantation. However, this outcome does not appear to have a further progress over the past 10 years from worldwide view [20]. In addition, thanks to the influence of modern medicine and globalization, the difference of survival rate of kidney grafts after kidney transplantation has decreased among different regions and races in the world [13–16], including the difference between China and the Western world. Most existing studies mainly focus on postoperative immune rejection [26], while the age of donors and patients, recurrence of glomerular disease, duration of dialysis, pre-existing cardiovascular burden, drug side effects, and traditional risk factors such as hypertension, albuminuria, anemia, dyslipidemia, diabetes, and bone mineral disorders may ultimately lead to severe endothelial cell disorders as well as graft loss and death [17, 18]. These traditional risk factors common in these patients are generally considered minor in comparison to allogenic immunity and immunosuppression problems. Carminatti M's team indicated in a review that they found relatively fewer studies have considered the clinical impact of multidisciplinary interventions on traditional CKD-related risk factors for CKD progression in kidney recipients, which is clearly an attractive field waiting more research [19]. Although

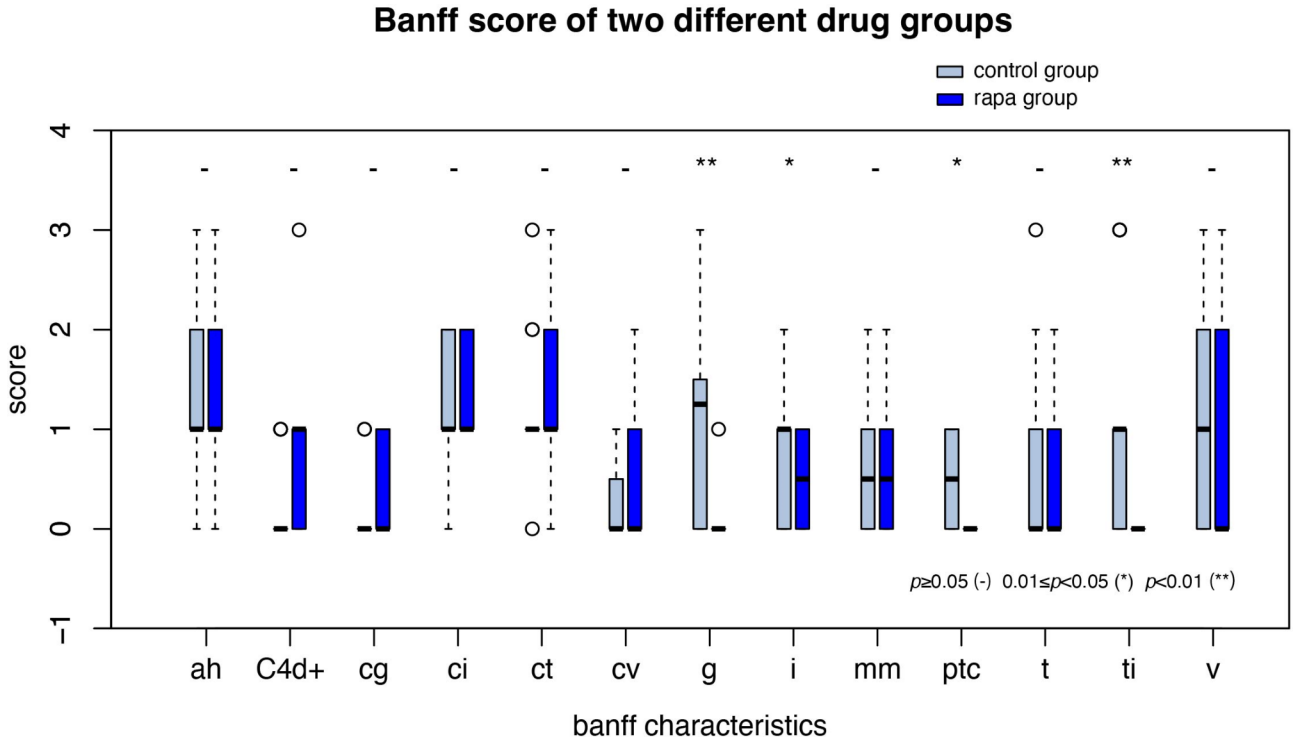


Fig. 4 Banff score of two different drug groups

all possible aspects can be useful for assessing the pathophysiology of CKD, not all risk factors are ultimately treatable. Therefore, individualized treatment is critical, as no single treatment recommendation is appropriate for all patients.

On this basis, more factors, especially those were more amenable to individualized intervention, were urgent to be found to influence the outcome of kidney transplant recipients, including surgical conditions, immunosuppressive drugs, and post-op compliactions [20, 21]. Therefore, in this study, both donor and recipient factors as well as preoperative and postoperative factors were included in the analysis. In addition, another shortcoming of existing studies is that they mainly consider hard endpoints such as patient survival and graft failure, however, these are late events. To predict early prognosis, our study selected eGFR as an alternative endpoint that could be evaluated at an early stage, and determined end events by CKD staging, which allowed us to retain data of patients who died early after surgery or were lost to follow-up at a later stage, thus maximizing data utilization. Thus, we constructed a reliable Cox model and screen out some factors which are more novel than previous studies, having the potential to provide constructive references for the personalized clinical monitoring after kidney transplantation and the quality control and optimization of organ transplantation programs.

Among the factors we screened, some conventional factors such as BMI, blood glucose levels, plasma globulin, were found in the model. In recent years, many studies have set a threshold for BMI, believing that patients with BMI higher than this threshold would bear more risks of poor prognosis of kidney transplantation. Shoko Ishikawa's team found in a single-center study that pretransplant BMI should be less than 25 in Japanese kidney transplant recipients and The mechanism behind this has been suggested in the literature that it may be related to the decline of renal function related to obesity [22]. However, in this study, we found that a higher BMI value in the non-obese range is more conducive to the prognosis of kidney transplantation, which may be related to the effect of nutrition on postoperative recovery after transplantation [23, 24]. Hyperglycemia caused by various causes has been recognized as the cause of diabetes, and is directly related to the decline of renal function [25], which is confirmed by our study here. However, whether blood glucose affects the prognosis of kidney transplantation through other ways such as immune rejection remains to be further studied.

More importantly, with the continuous development of immunosuppressant, the prognosis of kidney transplantation has made significant progress in this century, and the selection of postoperative immunosuppressant regimen has become one of the factors affecting the prognosis of kidney transplantation, because drug interaction and drug side effects vary from person to person. In recent years, there has been no consensus on the selection of cyclosporin and tacrolimus for KTx [26], but our

study have confirmed that the addition of rapamycin can improve the long-term prognosis of kidney transplantation, which is also consistent with the short-term outcome of many other studies [27, 28]. Since rapamycin was approved by the FDA in 1994 for the prevention of organ rejection in liver transplant patients [29], many effects of rapamycin in the field of transplantation have been discovered [30]. Many studies have demonstrated its effectiveness in reducing the use of calcineurin inhibitors, slowing the progression of heart graft vasculopathy, and reducing cytomegalovirus infection in the heart transplant maintenance population [31]. The cohort study by Dr. Guang and colleagues demonstrated that rapamycin prevented HCC recurrence in some patients after liver transplantation, but it also caused metabolic disorders, but overall rational use of rapamycin was beneficial to liver transplant recipients [32]. At the same time, our long-term follow-up confirmed that the addition of rapamycin reduced the incidence of rejections and improved graft outcomes, which are exciting results and should inform the development of new immunosuppressive regimens. We further compared the indication biopsy and banff score between the two groups, and the results showed that the addition of rapamycin after transplantation could reduce vascular inflammation and interstitial fibrosis around the renal allograft. More and more studies have focused on myeloid-derived suppressor cells (MDSC). Chao Wei and colleagues found that Exosomal miR-181d-5p Derived from Rapamycin-Conditioned MDSC Alleviated Allograft Rejection by Targeting KLF6 [33]. RAPA nano-micelle ophthalmic solution could improve the immunosuppressive activity of MDSCs through elevated expression of Arg-1 and iNOS [34]. However, the specific types of rejection affected by rapamycin have not been elucidated by enough studies. The clinical utility of rapamycin has changed over the past more than 15 years, including rapamycin with or without CNIs, and switching from CNI-based regimens to rapamycin. Our study also provides a new idea for the formulation of immunosuppression regimens after solid organ transplantation.

Notwithstanding it is important to acknowledge the limitations of this study. Firstly, the inclusion of risk factors is still incomplete as detailed information regarding donors, intraoperative conditions, and postoperative rejection and complications was not thoroughly examined. To address this, future studies should focus on enhancing surgical data recording and conducting more comprehensive follow-up investigations. Collaborating with multiple centers to obtain a larger patient dataset and applying the model to predict graft outcomes would yield more robust and convincing results. As for subsequent studies, new alternative endpoints for renal transplantation survival have been proposed, such as the eGFR slope on renal disease progression which was not adopted in this study. Exploring the potential changes in the model and its predictive ability by adopting eGFR slope as an endpoint is an avenue for further research. Furthermore, the mechanism behind how rapamycin affects the long-term prognosis of KTx is still not complete in existing research, so further experimental research for the molecular level mechanism behind them is urgent.

Conclusions

The overall 20, 15, 10 and 5-year graft survival rate of our center is 20.9%, 46.4%, 62.4 and 87.5%, respectively. The median graft survival time is approximately 14 years. BMI, globulin level, blood glucose and immunosuppressive regimens were recognized as common risk factors. The prognostic model and subgroup analysis suggested that FK506 combined with rapamycin could effectively improve the prognosis of renal transplantation, and reducing vascular inflammation, interstitial fibrosis and finally the rejections in the transplanted kidney may be its mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03730-8.

Supplementary Material 1

Supplementary Material 2

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Declared none.

Author contributions

Data curation, Yisheng Ji and Xiang Gao; Formal analysis, Yisheng Ji and Shuang Fei; Methodology, Zijie Wang, Hao Chen and Xiaobing Ju; Project administration, Min Gu; Resources, Zhijian Han, Jun Tao, Zijie Wang, Ruoyun Tan and Min Gu; Software, Yisheng Ji; Supervision, Xiaobing Ju, Ruoyun Tan and Min Gu; Visualization, Yisheng Ji; Original draft, Yisheng Ji and Shuang Fei; Review & editing, Zijie Wang, Hao Chen, Li Sun, Shuang Fei and Xiaobing Ju.

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Data availability

Raw collected data including the patients' basic information and follow-up information could be shared to those who are interested in a cooperation on multiple-center study through E-mailing the corresponding authors through the contacts offered in the article within 3 years after this article is published.

Declarations

Ethics approval and consent to participate

The study involving human participants were approved by the ethics committees of the First Affiliated Hospital with Nanjing Medical University (2016-SR-029). Written informed consents were obtained from all the recipients involved.

Consent for publication
All procedures involving human participants was in accordance with the guidelines of the Declaration of Helsinki. Written informed consents were obtained from all the recipients involved.

Competing interests
The authors declare no competing interests.

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References

1. Yang C, Wang H, Zhao X, et al. CKD in China: Evolving Spectrum and Public Health Implications. Am J Kidney Dis. 2020;76(2):258–64. https://doi.org/10.1053/j.ajkd.2019.05.032.
2. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012;379(9818):815–22. https://doi.org/10.1016/S0140-6736(12)60033-6.
3. Augustine J. Kidney transplant: new opportunities and challenges. Cleve Clin J Med. 2018;85(2):138–44. https://doi.org/10.3949/ccjm.85gr.18001.
4. Moudgil A. Renal transplantation. Indian J Pediatr. 2003;70(3):257–64. https://doi.org/10.1007/BF02725594.
5. Timsit MO, Kleinclauss F, Thuret R. [History of kidney transplantation surgery]. Prog Urol. 2016;26(15):874–81. https://doi.org/10.1016/j.purol.2016.08.003.
6. Zhu KL, Feng YH, Hu MY, et al. [Analysis of prognostic factors of pediatric kidney transplantation]. Zhonghua Er Ke Za Zhi. 2022;60(9):888–93. https://doi.org/10.3760/cma.j.cn112140-20220330-00257.
7. Domínguez-Gil B, Morales JM. Transplantation in the patient with hepatitis C. Transpl Int. 2009;22(12):1117–31. https://doi.org/10.1111/j.1432-2277.2009.00926.x.
8. Fang X, Chen S, Fu J, et al. Risk factors for renal allograft survival with China novel donation category: donation after brain death followed by cardiac arrest. Transpl Immunol. 2022;72:101591. https://doi.org/10.1016/j.trim.2022.101591.
9. Banas B, Krämer BK, Krüger B, Kamar N, Undre N. Long-term kidney transplant outcomes: role of prolonged-release Tacrolimus. Transpl Proc. 2020;52(1):102–10. https://doi.org/10.1016/j.transproceed.2019.11.003.
10. Wang Y, Jarad G, Tripathi P, et al. Activation of NFAT signaling in podocytes causes glomerulosclerosis. J Am Soc Nephrol. 2010;21(10):1657–66. https://doi.org/10.1681/ASN.2009121253.
11. Astor BC, Chester H, Fox, Isakova T, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713–35. https://doi.org/10.1053/j.ajkd.2014.01.416.
12. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and Cystatin C. N Engl J Med. 2012;367(1):20–9. https://doi.org/10.1056/NEJMoa1114248.
13. Poggio ED, Augustine JJ, Arrigain S, Brennan DC, Schold JD. Long-term kidney transplant graft survival-making progress when most needed. Am J Transpl. 2021;21(8):2824–32. https://doi.org/10.1111/ajt.16463.
14. Hariharan S, Israni AK, Danovitch G. Long-term survival after kidney transplantation. N Engl J Med. 2021;385(8):729–43. https://doi.org/10.1056/NEJMra2014530.
15. Purnell TS, Luo X, Kucirka LM, et al. Reduced racial disparity in kidney transplant outcomes in the United States from 1990 to 2012. JASN. 2016;27(8):2511–8. https://doi.org/10.1681/ASN.2015030293.
16. Miller G, Ankerst DP, Kattan MW, et al. Kidney transplantation outcome predictions (KTOP): a Risk Prediction Tool for kidney transplants from brain-dead deceased donors based on a large European cohort. Eur Urol. 2023;83(2):173–9. https://doi.org/10.1016/j.eururo.2021.12.008.
17. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. World J Transpl. 2015;5(4):183–95. https://doi.org/10.5500/wjt.v5.i4.183.
18. Kukla A, Adulla M, Pascual J, et al. CKD stage-to-stage progression in native and transplant kidney disease. Nephrol Dial Transpl. 2008;23(2):693–700. https://doi.org/10.1093/ndt/gfm590.
19. Carminatti M, Tedesco-Silva H, Silva Fernandes NM, Sanders-Pinheiro H. Chronic kidney disease progression in kidney transplant recipients: a focus on traditional risk factors. Nephrology. 2019;24(2):141–7. https://doi.org/10.1111/nep.13483.
20. Hart A, Singh D, Brown SJ, Wang JH, Kasiske BL. Incidence, risk factors, treatment, and consequences of antibody-mediated kidney transplant rejection: a systematic review. Clin Transpl. 2021;35(7):e14320. https://doi.org/10.1111/ctr.14320.
21. Colliou É, Del Bello A, Milongo D, et al. [Kidney failure after liver transplantation]. Nephrol Ther. 2022;18(2):89–103. https://doi.org/10.1016/j.nephro.2021.11.002.
22. Ishikawa S, Tasaki M, Ikeda M, Nakagawa Y, Saito K, Tomita Y. Pretransplant BMI should be < 25 in Japanese kidney transplant recipients: a single-center experience. Transpl Proc. 2023;55(1):72–9. https://doi.org/10.1016/j.transproceed.2022.10.058.
23. Tran MH, Foster CE, Kalantar-Zadeh K, Ichii H. Kidney transplantation in obese patients. World J Transpl. 2016;6(1):135–43. https://doi.org/10.5500/wjt.v6.i1.135.
24. Di Cocco P, Okoye O, Almario J, Benedetti E, Tzvetanov IG, Spaggiari M. Obesity in kidney transplantation. Transpl Int. 2020;33(6):581–9. https://doi.org/10.1111/tri.13547.
25. Tsimihodimos V, Karanatsis N, Tzavela E, Elisaf M. Antidiabetic drugs and the kidney. Curr Pharm Des. 2017;23(41):6310–20. https://doi.org/10.2174/1381612823666170307103222.
26. Savikko J, Teppo AM, Taskinen E, von Willebrand E. Different effects of tacrolimus and cyclosporine on PDGF induction and chronic allograft injury: evidence for improved kidney graft outcome. Transpl Immunol. 2014;31(3):145–51. https://doi.org/10.1016/j.trim.2014.08.003.
27. Hoff U, Markmann D, Thurn-Valassina D, et al. The mTOR inhibitor rapamycin protects from premature cellular senescence early after experimental kidney transplantation. PLoS ONE. 2022;17(4):e0266319. https://doi.org/10.1371/journal.pone.0266319.
28. Blagosklonny MV. Rapamycin for longevity: opinion article. Aging. 2019;11(19):8048–67. https://doi.org/10.18632/aging.102355.
29. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. Kidney Int. 2001;59(1):3–16. https://doi.org/10.1046/j.1523-1755.2001.00460.x.
30. Gambari R, Zuccato C, Cosenza LC, et al. The Long Scientific Journey of Sirolimus (Rapamycin): from the soil of Easter Island (Rapa Nui) to Applied Research and clinical trials on β-Thalassemia and other hemoglobinopathies. Biology (Basel). 2023;12(9):1202. https://doi.org/10.3390/biology12091202.
31. Fine NM, Kushwaha SS. Recent advances in mammalian target of rapamycin inhibitor use in Heart and Lung Transplantation. Transplantation. 2016;100(12):2558–68. https://doi.org/10.1097/TP.0000000000001432.
32. Fan GH, Zhang CZ, Gao FQ, et al. A mixed blessing for liver transplantation patients - rapamycin. Hepatobiliary Pancreat Dis Int. 2023;22(1):14–21. https://doi.org/10.1016/j.hbpd.2022.10.004.
33. Wei C, Sun Y, Zeng F, et al. Exosomal miR-181d-5p derived from rapamycin-conditioned MDSC alleviated allograft rejection by targeting KLF6. Adv Sci (Weinh). 2023;10(34):e2304922. https://doi.org/10.1002/advs.202304922.
34. Wei C, Wang Y, Ma L, et al. Rapamycin Nano-Micelle Ophthalmic Solution reduces corneal allograft rejection by potentiating myeloid-derived suppressor cells' function. Front Immunol. 2018;9:2283. https://doi.org/10.3389/fimmu.2018.02283.

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