Saudi Pharmaceutical Journal 30 (2022) 1088–1094

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Analysis of risk factors and establishment of a risk prediction model for post-transplant diabetes mellitus after kidney transplantation

Fang Cheng [a,b], Qiang Li [a,b], Jinglin Wang [a,b], Zhendi Wang [c], Fang Zeng [a,b,*], Yu Zhang [a,b,*]

[a] Department of Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[b] Hubei Province Clinical Research Center for Precision Medicine for Critical Illness, Wuhan 430022, China
[c] Department of Urology Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

ARTICLE INFO

Article history:
Received 10 January 2022
Accepted 30 May 2022
Available online 2 June 2022

Keywords:
Kidney transplantation
Post-transplant diabetes mellitus
Risk factors
Tacrolimus
Graft loss

ABSTRACT

Introduction: Post-transplant diabetes mellitus (PTDM) is a known side effect in transplant recipients administered immunosuppressant drugs, such as tacrolimus. This study aimed to investigate the risk factors related to PTDM, and establish a risk prediction model for PTDM. In addition, we explored the effect of PTDM on the graft survival rate of kidney transplantation recipients.

Methods: Patients with pre-diabetes mellitus before kidney transplant were excluded, and 495 kidney transplant recipients were included in our study, who were assigned to the non-PTDM and PTDM groups. The cumulative incidence was calculated at 3 months, 6 months, 1 year, 2 years, and 3 years post-transplantation. Laboratory tests were performed and the tacrolimus concentration, clinical prognosis, and adverse reactions were analyzed. Furthermore, binary logistic regression analysis was used to identify the independent risk factors of PTDM.

Results: Age $\geq$ 45 years (adjusted odds ratio [aOR] 2.25, 95% confidence interval [CI] 1.14–3.92; P = 0.015), body mass index (BMI) > 25 kg/m^2 (aOR 3.12, 95% CI 2.29–5.43, P < 0.001), tacrolimus concentration > 10 ng/mL during the first 3 months post-transplantation (aOR 2.46, 95%CI 1.41–7.38; P < 0.001), transient hyperglycemia (aOR 4.53, 95% CI 1.86–8.03; P < 0.001), delayed graft function (DGF) (aOR 1.31, 95% CI 1.05–2.39; P = 0.019) and acute rejection (aOR 2.16, 95% CI 1.79–4.69; P = 0.005) were identified as independent risk factors of PTDM. The PTDM risk prediction model was developed by including the above six risk factors, and the area under the receiver operating characteristic curve was 0.916 (95% CI 0.862–0.954, P < 0.001). Furthermore, the cumulative graft survival rate was significantly higher in the non- PTDM group than in the PTDM group.

Conclusions: Risk factors related to PTDM were age $\geq$ 45 years, BMI > 25 kg/m^2, tacrolimus concentration > 10 ng/mL during the first 3 months post-transplantation, transient hyperglycemia, DGF and acute rejection.

1. Introduction

Kidney transplantation is an effective treatment for end-stage renal disease. However, kidney transplant recipients exhibit an increased risk of poor outcomes (Suthanthiran and Strom, 1994). They are at a substantial risk of cardiovascular diseases, dyslipidemia, hyperglycemia, hyperuricemia, severe infections, and even premature death (Holmberg and Jalanko, 2016). With prolonged survival time, cardiovascular complications have become an important problem for recipients of solid organ transplantation. Post-transplant diabetes mellitus (PTDM) is a common cardiovascular adverse reaction in solid organ transplantation (Jenssen and Hartmann, 2019). The incidence of PTDM is 7–39% in the first year, and 10–30% in 3 years after kidney transplantation (Ahmed et al.,

* Corresponding authors at: Department of Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.
E-mail addresses: fangzeng@hust.edu.cn (F. Zeng), 1991XH0661@hust.edu.cn (Y. Zhang).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2022.05.013
1319-0164/

2020). PTDM can lead to graft rejection, dysfunction or even graft loss, and is associated with severe infections and early cardiovascular complications after transplantation, ultimately affecting the long-term survival of patients, and is an independent lethal factor after transplantation (Eide et al., 2016).

The pathogenesis of PTDM has not yet been fully elucidated, and there are no effective prevention or treatment strategies for PTDM. Therefore, a comprehensive evaluation of risk factors of PTDM can provide an important reference point for the prevention of PTDM. The risk factors of PTDM, including insulin resistance, hypertension, hypertriglyceridemia, and obesity, are similar to those of type 2 diabetes mellitus (T2DM), but some specific post-transplantation predisposing factors are also involved (Shivaswamy et al., 2016).The occurrence and progression of PTDM are closely related to age, body mass index (BMI), family history of diabetes mellitus, use of immunosuppressive drugs, hepatitis C virus infection, cytomegalovirus infection, and acute rejection (Han et al., 2016; Mizrahi et al., 2020). However, due to differences in race, immunosuppressive regimen and other factors, the reported risk factors related to PTDM may need to be verified in specific country and regional populations.

Early identification of high-risk patients with PTDM may eventually lead to risk stratification of patients, to effectively prevent the occurrence of PTDM, including lifestyle modifications and early drug treatment, which has great guiding significance for the prevention and treatment of PTDM. Therefore, our study aimed to explore the clinical risk factors related to PTDM, and establish a risk prediction model, to provide a reference for early detection of kidney transplant recipients at a high-risk of showing PTDM.

2. Materials and methods

2.1. Patient selection

This study included 495 kidney transplantation recipients admitted to Tongji Medical College, Huazhong University of Science and Technology from January 1, 2015 to May 1, 2021. The enrolment criteria were as follows: (a) first-time kidney transplant recipients (b) 18–70 years, (c) complete clinical data available, and (d) patients who were followed up regularly for more than 1 year. Exclusion criteria were age less than 18 years, patients with a history of diabetes, or a history of hypoglycemic drugs use, fasting blood glucose $\geq$ 7.0 mmol $\cdot$ L^{-1}, hemoglobin Alc $\geq$ 6.5% before kidney transplantation, combined any other organ transplantation, co-administration of azole antifungal agents, or patients lost to follow-up. This study was approved by Institutional Ethics board of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) ([2018] S331). Verbal informed consent was obtained from all the participants prior to the study. Our research conformed to the ethical standards of the Declaration of Helsinki.

2.2. Data collection

Clinical information collected from the electronic medical record system included demographic data, comorbidities, laboratory tests (routine blood and blood biochemical examination) and pre-transplant medications. Clinical outcomes, adverse reactions, and graft function were assessed during the follow-up period.

2.3. Immunosuppressive regimen

All patients received a triple immunosuppressive regimen based on calcineurin inhibitors (tacrolimus or cyclosporine A, mycophenolate mofetil [MMF] and corticosteroids). Tacrolimus was administered orally twice daily on the second day post-transplantation, with an initial dose of 3.0–5.0 mg. Cyclosporine A was administered orally 12 h before kidney transplantation, at an initial dose of 10–15 mg/kg, twice daily. The dose was adjusted according to therapeutic drug monitoring. MMF was administered at a dose of 0.5–1.0 g twice daily. All patients were administered methylprednisolone (500 mg/d) intravenously three days after kidney transplantation, and 60 mg/d oral methylprednisolone from the fourth day, which gradually reduced to a maintenance dose (20 mg/d). In cases of acute rejection, rabbit anti-human thymocyte immunoglobulin or anti-human T cell rabbit immunoglobulin was administered for 3-7d, or methylprednisolone pulse therapy was administered.

2.4. Tacrolimus therapeutic drug monitoring

Tacrolimus concentration is generally measured twice a week. If rejection or adverse events are suspected, the measurement frequency can be higher. A Roche Cobas® e411 electrochemiluminescence analyzer was used to measure the tacrolimus concentration in whole blood. Tacrolimus concentration was measured twice a week within 1 month, once a week from 1 to 3 months, once a month from 3 to 12 months, and once three months 1 year post-transplantation. When tacrolimus concentration fluctuates for any reason, the monitoring frequency should be increased. The target trough concentration (C_0) range of tacrolimus in the 1–3 months, 3–6 months, 7–12 months, and >1 year were 8–10, 7–9, 5–7 and 4–6 ng/mL, respectively.

2.5. Diagnosis of PTDM

According to the diagnostic criteria of the American Diabetes Association (Hur et al., 2007), PTDM is defined as one or more of the following conditions after transplantation ($\geq$1 month): (1) fasting blood glucose $\geq$ 7.0 mmol·L^{-1} at least twice; (2) random blood glucose $\geq$ 11.1 mmol·L^{-1} at least twice; (3) receiving diet control or hypoglycemic medication. The first month after transplantation was selected to diagnose PTDM, but posttransplant transient hyperglycemia caused by surgical stress and high-dose corticosteroid treatment needs to be excluded. Posttransplant transient hyperglycemia is defined as: random fasting blood glucose $\geq$ 7.0 mmol·L^{-1} in the early 2–4 weeks post-transplantation caused by medications or changes in clinical status, and blood glucose can return to normal levels without hypoglycemic treatment at 1 year after transplantation(Polsky and Ellis, 2015). According to the diagnostic criteria for PTDM, the recipients who met the inclusion criteria were divided into two groups: PTDM and non- PTDM groups.

2.6. Clinical outcomes

Acute rejection is defined as an acute deterioration of graft function in the first year after transplantation, which is related to specific pathological changes in graft biopsy. Chronic kidney allograft dysfunction (CKAD) was defined in according with the guidelines of the Chinese Society of Organ Transplantation of the Chinese Medical Association (Hara, 2015). Graft failure was defined as return to dialysis, or re-transplantation.

2.7. Statistical analysis

Categorical variables were expressed as frequencies and percentages, and compared using the $\chi 2$ test. When the amount of data was less than 5, Fisher's exact test was selected. If the continuous variables were normally distributed, the means of the two groups were compared using an independent *t*-test and presented

as the mean ± standard deviation. Otherwise, the Mann-Whitney test was performed, and the results are presented as the median and interquartile range values. Baseline variables that were considered clinically relevant or showed a univariate relationship with PTDM were entered into the multivariate logistic regression model. Variables for inclusion were carefully chosen to ensure the parsimony of the final model, given the number of available events. Logistic regression analysis was used to examine the association between potential risk factors and PTDM, after adjustingt for potential confounding factors. Interactions between PTDM and potential confounders were tested by the addition of sex, pre-hypertension, pre-anemia, and pre-coronary heart disease in the regression model. A stepwise forward logistic regression model was used to determine the independent risk factors of PTDM, and a risk prediction model was established.

3. Results

3.1. Patient characteristics

A total of 577 kidney transplantation patients were enrolled in this study, including 37 patients with pre-operative diabetes mellitus, three patients with combined organ transplantation, six patients with secondary organ transplantation and 36 patients lost to follow-up. Finally, 495 kidney transplant recipients were included in our study, which PTDM occurred in 55(11.1%) patients from 1 month and 1 year after kidney transplantation (median time: 3 months). During follow-up, the cumulative incidence of PTDM increased over time, with 49 (9.9%) at 3 months, 53 (10.7%) at 6 months, 55(11.1%) at 1 year, 68 (13.7%) at 2 years, and 76 (15.3%) at 3 years, respectively. The inclusion and exclusion process illustrated in Fig. 1.

Of the 495 patients, 324 (65.5%) were male. There were 440 and 55 patients in the non-PTDM and PTDM group, respectively. The clinical characteristics of the patients were shown in Table 1. The median ages of the two groups (non-PTDM group: 37 years [IQR = 30.0–46.0 years]; PTDM group: 46 years [IQR = 37.0–52.0 years]) showed statistically significant differences, and 54.5% of patients with PTDM were > 45 years compared to 30.7% in the non-PTDM group (P < 0.001). The median BMI in the PTDM group was significantly higher than that in the non-PTDM group (20.99 kg/m^2 *vs* 23.03 kg/m^2, P < 0.001), and patients in the PTDM group had a higher rate of BMI > 25 kg/m^2 than those in the non-PTDM group (41.8% *vs* 10.5%; P < 0.001). However, there were no significant differences in the sex, follow-up time, or pre-existing conditions between the two groups.

Table 1
Demographic characteristics of kidney transplant recipients.

	Non-PTDM (n = 440)	PTDM (n = 55)	P.value
Gender(male)	288(65.5)	36(65.5)	1.000
Age, years, median (IQR)	37(30–46)	46(31–52)	0.036
Age, >45 years	135(30.7)	30(54.5)	<0.001
BMI, kg/m^2, median (IQR)	20.99 (18.75–23.18)	23.03 (23.03–25.18)	<0.001
BMI, >25 kg/m^2	46(10.5)	23(41.8)	<0.001
Follow-up time (months), median (IQR)	34.1(26.4–42.3)	31.5(36.5–41.0)	0.492
Comorbidity			
Hypertension	359(81.6)	42(76.4)	0.351
Anemia	191(43.4)	25(45.5)	0.773
Hepatitis B	46(10.5)	5(9.1)	0.754
Coronary heart disease	9(2.0)	1(1.8)	0.912
Arthrolithiasis	14(3.2)	2(3.6)	0.868
Immunosuppressive regimens			
Cyclosporine-based group, n (%)	44 (97.8)	1(2.2)	
Tacrolimus concertation during first 3 months, median (IQR)	8.7(7.6–9.8)	11.2(9.3–13.1)	
Tacrolimus concertation > 10 ng/mL during first 3 months, n (%)	75(17.0)	38(69.1)	<0.001
Induction agent, n (%)			
Basiliximab	52(11.8)	6(10.9)	0.793
Antithymocyte globulin	388(88.2)	49(89.1)	
Antiproliferative agent, n (%)			
Mycophenolate	422(95.9)	52(94.5)	0.815
Azathioprine	18(4.1)	3(5.5)	
First year cumulative corticosteroids dose (g), median (IQR)	4.10(3.70–4.50)	3.90(3.60–4.20)	0.056

Abbreviations: BMI, body mass index; IQR, inter-quartile range; PTDM, post-transplant diabetes mellitus.

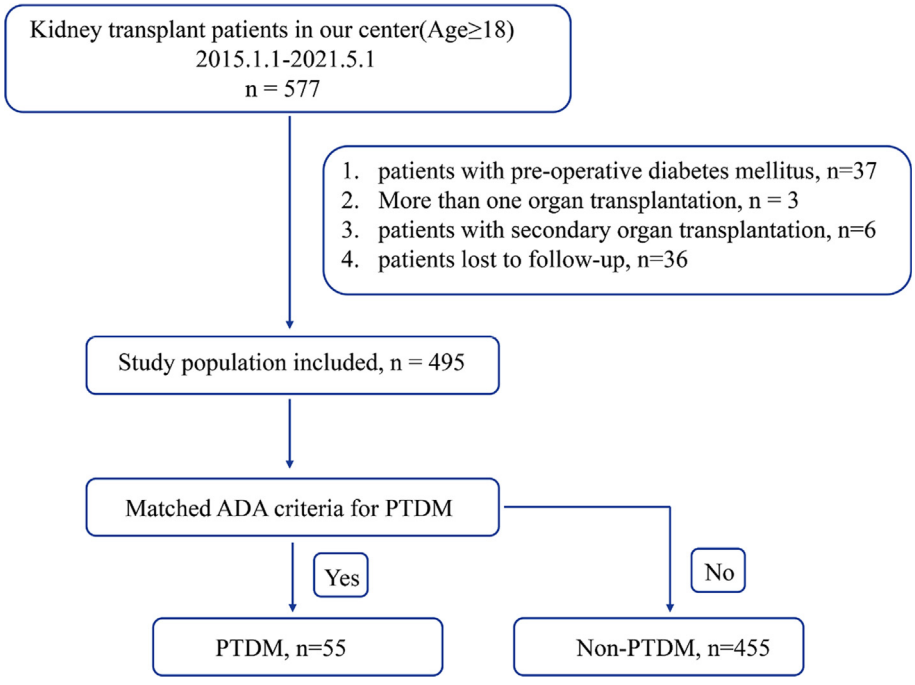

Fig. 1. Flowchart of patient inclusion process.

3.2. Immunosuppressive therapy

The majority of patients (90.9%) used a tacrolimus-based immunotherapy regimen, 45 patients (9.1%) received cyclosporine A treatment, and only one patient developed PTDM among the patients treated with cyclosporine A. The cumulative corticosteroid dose was higher in the PTDM group in the first year after transplantation, while no significant difference was observed between the PTDM and non-PTDM groups. However, other immunosuppressive drugs, including basiliximab, azathioprine, antithymocyte globulin, and MMF, are not related to the occurrence of PTDM. Patients who developed PTDM had a significantly higher tacrolimus concentration than non-PTDM patients at 3 months post-transplantation (P < 0.001), and more PTDM patients had tacrolimus concentrations > 10 ng/mL during 3 months post-transplantation (69.1% *vs* 17.0%, P < 0.001) than non-PTDM patients.

3.3. Risk factors of PTDM

The crude and adjusted associations between independent risk factors and PTDM was shown in Table 2. The results showed that age ≥ 45 years (aOR 2.25, 95% CI 1.14–3.92; P = 0.015), BMI > 25 kg/m^2 (aOR 3.12, 95% CI 2.29–5.43, P < 0.001), tacrolimus concentration > 10 ng/mL during the first 3 months post-transplantation (aOR 2.46, 95%CI 1.41–7.38; P < 0.001), transient hyperglycemia (aOR 4.53, 95% CI 1.86–8.03; P < 0.001) and DGF (aOR 1.31, 95% CI 1.05–2.39; P = 0.019) and acute rejection (aOR 2.16, 95% CI 1.79–4.69; P = 0.005) were independent risk factors of PTDM. The results showed that potential confounding factors, such as sex, pre-hypertension, pre-anemia, or pre-coronary heart disease did not significantly interfere with the final model.

3.4. Risk prediction models of PTDM

Based on the above risk factors, six risk prediction models of PTDM were constructed (Table 3), and the ROC curve was shown in Fig. 2. Risk prediction model 1 included age ≥ 45 years and BMI > 25 kg/m^2, and the area under the receiver operating characteristic curve (AUROC) was 0.722 (95% CI 0.645–0.800, P < 0.001); risk prediction model 2 included tacrolimus concentration > 10 ng/mL during the first 3 months post-transplantation on the basis of risk prediction model 1, with an AUROC of 0.835 (95% CI 0.771–0.898, P < 0.001); risk prediction model 3 included posttransplant transient hyperglycemia on the basis of risk prediction model 2, with an AUROC of 0.898 (95% CI 0.842–0.931, P < 0.001); DGF

Table 2
Logistic regression analyses of the risk factors associated with PTDM and bootstrap validation in kidney transplant recipients.

	Final model				Bootstrap (n = 1000)	
	OR (95%CI)	P	aOR[a]	P	OR (95%CI)	P
Age, ≥45 years	2.25(1.16–3.84)	0.013	2.25(1.14–3.92)	0.015	2.26(1.17–3.85)	0.011
BMI, >25 kg/m^2	3.16(2.47–5.66)	<0.001	3.12(2.29–5.43)	<0.001	3.15(2.46–5.65)	0.001
Tacrolimus concertation > 10 ng/mL during first 3 months	2.43(1.29–7.04)	<0.001	2.46(1.41–7.38)	<0.001	2.43(1.27–7.08)	0.001
Posttransplant transient hyperglycaemia	4.58(2.03–8.18)	<0.001	4.53(1.86–8.03)	<0.001	4.57(2.02–8.17)	0.001
DGF	1.33(1.05–2.66)	0.022	1.31(1.05–2.39)	0.019	1.32(1.04–2.65)	0.021
Acute rejection	2.15(1.82–4.58)	0.004	2.16(1.79–4.69)	0.005	2.14(1.81–4.58)	0.006

[a] adjusted for gender, pre-hypertension, pre-anemia, and pre-coronary heart disease.
Abbreviations: BMI, body mass index, OR, odds ratio, aOR, adjusted odds ratio, CI, confidence interval, DGF, delayed graft function, PTDM, post-transplant diabetes mellitus.

Table 3
Models for the prediction of PTDM.

Model	OR(95%CI)	P.value
Model 1		
Age, >45 years old	2.43(1.22–3.76)	0.005
BMI, >25 kg/m^2	3.18(1.48–5.28)	<0.001
Model 2		
Age, >45 years old	2.46(1.24–3.87)	0.018
BMI, >25 kg/m^2	3.22(1.51–5.45)	<0.001
Tacrolimus concertation > 10 ng/mL during first 3 months	2.11(1.16–6.43)	<0.001
Model 3		
Age, >45 years old	2.42(1.21–3.82)	0.018
BMI, >25 kg/m^2	3.18(1.48–5.41)	<0.001
Tacrolimus concertation > 10 ng/mL during first 3 months	2.26(1.25–6.62)	<0.001
Posttransplant transient hyperglycaemia	4.39(2.04–7.52)	<0.001
Model 4		
Age, >45 years old	2.39(1.19–3.81)	0.012
BMI, >25 kg/m^2	3.18(1.49–5.42)	<0.001
Tacrolimus concertation > 10 ng/mL during first 3 months	2.21(1.25–6.23)	<0.001
Posttransplant transient hyperglycaemia	4.36 (2.04–8.19)	<0.001
DGF	1.30(1.02–2.34)	0.009
Model 5		
Age, >45 years old	2.25(1.16–3.84)	0.013
BMI, >25 kg/m^2	3.16(2.47–5.66)	<0.001
Tacrolimus concertation > 10 ng/mL during first 3 months	2.43(1.29–7.04)	<0.001
Posttransplant transient hyperglycaemia	4.58(2.03–8.18)	<0.001
DGF	1.33(1.05–2.66)	0.022
Acute rejection	3.15(1.82–4.58)	0.004

Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval; DGF, delayed graft function; PTDM, post-transplant diabetes mellitus.

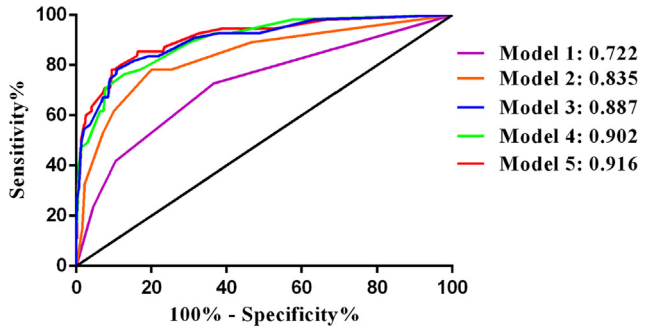

Fig. 2. Receiver operating characteristic (ROC) curve of the post-transplant diabetes mellitus (PTDM) risk prediction model.

was included in risk prediction model 4, the AUROC was 0.902 (95% CI 0.854–0.949, P < 0.001). When age ≥ 45 years, BMI > 25, tacrolimus concentration, transient hyperglycemia, DGF and acute rejection were all included in the risk prediction model 5, the AUROC increased to 0.916 (95% CI 0.862–0.954, P < 0.001). The bootstrap method is often used as a diagnostic tool for the internal validation of model results (Jaki et al., 2018). The bootstrap method (1000 bootstrap samples were obtained by repeated sampling with returns from the original data) was used to evaluate the accuracy of the model internally. The results showed that the model had good ability to predict the risk of PTDM.

3.5. Clinical outcomes of PTDM and non-PTDM groups

The clinical outcomes of the two groups were shown in Table 4. CKAD was observed in 30 (54.5%) individuals in the PTDM group, and 115 (26.1%) individuals in the non-PTDM group, which was significantly different from each other (P < 0.001). The rates of graft loss (16.4% *vs* 5.9%, P = 0.001) was significantly different between the groups. However, no significant differences were observed in the incidence of patient death (1.8% *vs* 1.1%, P = 0.663) between the two groups.

Table 4
Clinical outcomes of the non-PTDM and PTDM groups.

	Non-PTDM (n = 440)	PTDM (n = 55)	P.value
CKAD	115(26.1)	30(54.5)	<0.001
Graft loss	26(5.9)	9(16.4)	0.005
Patient death	5(1.1)	1(1.8)	0.663

Abbreviations: CKAD, chronic kidney allograft dysfunction; PTDM, post-transplant diabetes mellitus.

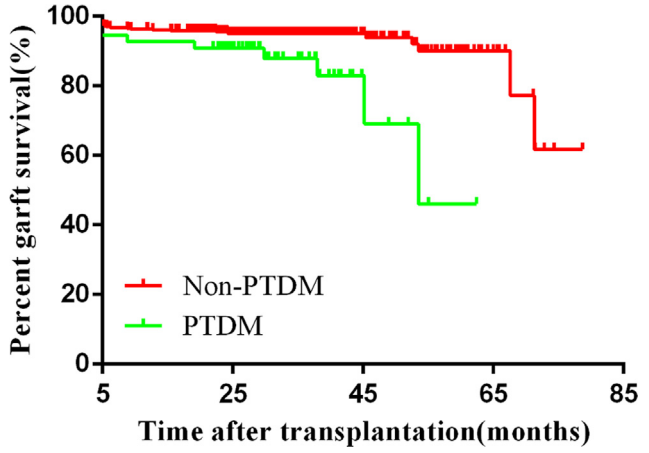

Fig. 3. Cumulative graft survival rates of the PTDM and non-PTDM groups.

The result of Kaplan-Meier analysis indicated that the cumulative graft survival rate was significantly higher in the non-PTDM group than in the PTDM group (P < 0.001; Fig. 3).

4. Discussion

PTDM is a common complication of kidney transplantation, and its risk factors vary depending on the type and race of organ transplantation. We investigated the incidence rate and risk factors for PTDM in Chinese patients underwent kidney transplantation. However, the incidence rate of PTDM in our hospital was lower than that reported in the United States (Cosio et al., 2005) and South Korea (Paek et al., 2019), which may be due to differences in PTDM diagnostic criteria, immunosuppressive therapy, follow-up time, and study population. In addition, we found that age ≥ 45 years, BMI > 25 kg/m^2, tacrolimus concertation > 10 ng/mL during the first 3 months post-transplantation, posttransplant transient hyperglycemia, DGF and acute rejection were identified as crucial risk factors for PTDM.

Elderly recipients are a well-established risk factor for PTDM, which may be attributed to the progressive decline in islet β-cell function with increasing age (Sinangil et al., 2017; de Lucena et al., 2020). A large number of studies have reported that age is a risk factor for PTDM, which selected the age of 45 years as the cutoff to study the relationship between age and PTDM. Studies have reported that kidney transplant patients aged ≥ 45 years have a higher risk of developing PTDM than patients aged < 45 years in Chinese heart transplant (Zhang et al., 2019). In addition, age ≥ 45 years increases PTDM risk 2.2 times when compared to individuals of 18–44 years old in American kidney transplant recipients (Cosio et al., 2001). In our study, we found that age ≥ 45 years was an independent risk factor for PTDM. Therefore, blood glucose should be monitored routinely for the early detection of PTDM and timely intervention should be implemented to reduce the incidence rate of PTDM in elderly patients after kidney transplantation.

BMI was also an important risk factor for PTDM in the present study. A previous study showed that the risk of PTDM in kidney transplant recipients with BMI > 25 kg/m^2 increased by 3.46 times (Yu et al., 2016). A prospective cohort study of 481 kidney transplant patients followed up for 57 months indicated that BMI > 25 kg/m^2 was a risk factor for PTDM (Gaynor et al., 2015). This may be related to the pathogenesis of PTDM, in which obesity stimulates islet β-cells to induce insulin resistance, thereby reducing the blood glucose clearance (Glatz et al., 2018). Lifestyle modifications (dietary advice, physical activity, and weight loss encouragement) in kidney transplant recipients has been reported to facilitate the reversal of impaired glucose tolerance to normal glucose tolerance within 6-months (Sharif et al., 2008). Therefore, lifestyle modifications to reduce PTDM risk in kidney transplant recipients should be actively encouraged.

Our study also found that another important risk factor for PTDM was post-transplant transient hyperglycemia. A study in kidney transplant recipients indicated that transient hyperglycemia in hospitalized patients significantly increased the risk of PTDM (Chakkera et al., 2010). It is worth noting that some patients with transient hyperglycemia in our study may have had impaired insulin sensitivity, insulin resistance, and subclinical diabetes before kidney transplantation. Non-diabetic patients with these conditions before transplantation were more likely to develop PTDM after kidney transplantation (Nagaraja et al., 2013), which may explain why patients with transient hyper-

glycemia had a higher risk of PTDM in our study. Post-transplant transient hyperglycemia is recommended to be reversed, and insulin remains the first choice.

Immunosuppressive regimens have a significant impact on blood glucose parameters, and risk of PTDM and cardiovascular disease (Porrini et al., 2016). However, the regulation of immunosuppressive therapy and its role in PTDM development remain unclear. Compared to cyclosporine A, tacrolimus is more closely associated with a higher incidence of PTDM, and switching from tacrolimus to cyclosporine A is considered an effective strategy to reduce the risk of PTDM (Jenssen and Hartmann, 2019). However, only 45 patients (9.1%) received cyclosporine A treatment, while 1 patient developed PTDM among the patients with cyclosporine A in our study. To avoid bias in the results, we only performed a descriptive analysis of cyclosporine-based immunosuppressive regimen, and did not investigate the relationship between tacrolimus, cyclosporine and PTDM.

Tacrolimus-induced PTDM may involve various changes through different mechanisms, including decreased insulin secretion, increased insulin resistance and increased insulin resistance β changes in cell function and peripheral insulin resistance (Dai et al., 2020). A previous study indicated that higher tacrolimus concentration was closely associated with PTDM (Alghanem et al., 2020). It has been reported that tacrolimus concentration > 15–20 ng/mL within the first month post-transplantation was an important risk factor for PTDM (Ajabnoor et al., 2020). Another study found that tacrolimus concentrations > 15 ng/mL were closely associated with PTDM in kidney transplant (Maes et al., 2001). In our study, the incidence rate of PTDM was the highest in the first 3 months after transplantation, and the target trough concentration range of tacrolimus in the 1–3 months was 8–10 ng/mL, we selected the median tacrolimus concentration of 10 ng/mL in the first 3 months as the cut-off value to explore the relationship between tacrolimus concentration and PTDM. We found that a tacrolimus concentration > 10 ng/mL was an important risk factor for PTDM. Therefore, patients should monitor tacrolimus concentration more frequently in the early stages after kidney transplantation to ensure that it is within the target concentration range.

Acute rejection was another risk factor for PTDM in kidney transplant, which was consistent with the results of previous studies (Cole et al., 2008; Matas et al., 2008). The increase in blood glucose levels induced by acute rejection may be related to the following mechanisms. Firstly, high-dose corticosteroid therapy was needed for acute rejection, in which corticosteroids could increase the blood glucose levels. In addition, corticosteroids can increase insulin resistance, reduce the sensitivity of peripheral tissues to insulin, and cause an increase in blood glucose (De Lucena and Rangel, 2018). Moreover, acute rejection was a type of stress response, that can mobilize the secretion of catecholamine, glucocorticoids, growth hormones, glucagon and other insulin antagonistic hormones, and further increase the level of plasma glucose (Rekers et al., 2016). Therefore, clinicians may prefer to minimize steroid use after transplantation because of the potential risk of rejection. It is also suggested that urine volume and renal function should be monitored closely in the early stage after kidney transplantation, and countermeasures should be taken to reduce the occurrence of acute rejection. In our study, the association between DGF and PTDM may be related to the susceptibility of DGF to acute rejection.

Our study has some limitations. Firstly, this study was conducted at a single center and only recruited a relatively limited number of patients, and different immunotherapy regimens may affect the incidence of PTDM, multicenter and long-term studies are required to further prove the validity of our results. In addition, we did not obtain the patients' family history of T2DM, thus increasing the risk of coincidence bias in the overall results. Furthermore, to better realize the clinical practicability and extrapolation of the model, it is necessary to recollect patient data for external verification. We have also been collecting new patient data, but follow-up will take a very long time. Because of the limited number of cases affected by the COVID-19 epidemic, it is very difficult to implement, but we will continue to collect data to complete the model verification in the future, and we will further study the relationship between tacrolimus trough to dose ratio and PTDM.

5. Conclusion

In conclusion, age $\geq$ 45 years, BMI > 25 kg/m^2, tacrolimus concentration > 10 ng/mL during the first 3 months post-transplantation, transient hyperglycemia, DGF and acute rejection were determined as the independent risk factors of PTDM. Our study also established a risk prediction model for PTDM, to provide a reference for the early detection of high-risk PTDM groups in kidney transplant recipients. Understanding the risk factors of PTDM can help transplantation teams better manage the patients according to their risk profiles. Screening and monitoring should be strengthened for high-risk groups of PTDM, including elderly or overweight patients, especially in the early stages after transplantation. In addition, patients could benefit from achieving a lower tacrolimus concentration (<10 ng/mL) in the first 3 months post-transplantation. In the future, we will continue to follow up these patients to explore the relationship between PTDM and long-term outcomes (such as overall death). In addition, we will explore the optimal immunosuppressive regimen for patients who are at a high risk of PTDM.

6. Statement of ethics

The study was approved by the Institutional Ethics Board of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) ([2018] S331). Because this investigation did not interfere with patients' diagnosis or the treatment process, verbal informed consent was obtained from all participants prior to the study.

7. Data Availability Statement

The datasets used or analyzed in the current study are available from the corresponding author upon reasonable request.

Funding

This work was supported by Key R&D Program of Hubei Province of China (No.2020BCA060).

Author Contributions

Conception and design: Fang Zeng and Yu Zhang; Provision of study materials or patients: Zhendi Wang; Collection and assembly of data: Fang Cheng and Qiang Li; Data analysis and interpretation: Fang Cheng and Jinglin Wang; Manuscript writing: All authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ahmed, S.H., Biddle, K., Augustine, T., Azmi, S., 2020. Post-Transplantation Diabetes Mellitus. Diabetes Ther. 11 (4), 779–801.

Ajabnoor, A., Nasser, M., Khan, N., Habhab, W., 2020. Evaluation of tacrolimus trough level in patients who developed post-transplant diabetes mellitus after kidney transplantation: A retrospective single-center study in Saudi Arabia. Transplant Proc. 52 (10), 3160–3167. https://doi.org/10.1016/j.transproceed.2020.05.014.

Alghanem, S.S., Soliman, M.M., Alibrahim, A.A., Gheith, O., Kenawy, A.S., Awad, A., 2020. Monitoring tacrolimus trough concentrations during the first year after kidney transplantation: A national retrospective cohort study. Front. Pharmacol. 11,. https://doi.org/10.3389/fphar.2020.566638 566638.

Chakkera, H.A., Knowler, W.C., Devarapalli, Y., Weil, E.J., Heilman, R.L., Dueck, A., Mulligan, D.C., Reddy, K.S., Moss, A.A., Mekeel, K.L., Mazur, M.J., Hamawi, K., Castro, J.C., Cook, C.B., 2010. Relationship between inpatient hyperglycemia and insulin treatment after kidney transplantation and future new onset diabetes mellitus. Clin. J. Am. Soc. Nephrol. 5 (9), 1669–1675.

Cole, E.H., Johnston, O., Rose, C.L., Gill, J.S., 2008. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clin. J. Am. Soc. Nephrol. 3 (3), 814–821. https://doi.org/10.2215/cjn.04681107.

Cosio, F.G., Kudva, Y., van der Velde, M., Larson, T.S., Textor, S.C., Griffin, M.D., Stegall, M.D., 2005. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. Kidney Int. 67 (6), 2415–2421.

Cosio, F.G., Pesavento, T.E., Osei, K., Henry, M.L., Ferguson, R.M., 2001. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney Int. 59 (2), 732–737. https://doi.org/10.1046/j.1523-1755.2001.059002732.x.

Dai, C., Walker, J.T., Shostak, A., Padgett, A., Spears, E., Wisniewski, S., Poffenberger, G., Aramandla, R., Dean, E.D., Prasad, N., Levy, S.E., Greiner, D.L., Shultz, L.D., Bottino, R., Powers, A.C., 2020. Tacrolimus- and sirolimus-induced human β cell dysfunction is reversible and preventable. JCI Insight 5 (1). https://doi.org/10.1172/jci.insight.130770.

de Lucena, D.D., de Sá, J.R., Medina-Pestana, J.O., Rangel, É., B., 2020. Modifiable variables are major risk factors for posttransplant diabetes mellitus in a time-dependent manner in kidney transplant: An observational cohort study. J. Diabetes Res. 2020, 1938703. https://doi.org/10.1155/2020/1938703.

De Lucena, D.D., Rangel, É.B., 2018. Glucocorticoids use in kidney transplant setting. Expert Opin. Drug Metab. Toxicol. 14 (10), 1023–1041. https://doi.org/10.1080/17425255.2018.1530214.

Eide, I.A., Halden, T.A.S., Hartmann, A., Åsberg, A., Dahle, D.O., Reisaeter, A.V., Jenssen, T., 2016. Mortality risk in post-transplantation diabetes mellitus based on glucose and HbA1c diagnostic criteria. Transpl. Int. 29 (5), 568–578.

Gaynor, J.J., Ciancio, G., Guerra, G., Sageshima, J., Hanson, L., Roth, D., Goldstein, M.J., Chen, L., Kupin, W., Mattiazzi, A., Tueros, L., Flores, S., Barba, L.J., Lopez, A., Rivas, J., Ruiz, P., Vianna, R., Burke, G.W., 2015. Multivariable risk of developing new onset diabetes after transplant-results from a single-center study of 481 adult, primary kidney transplant recipients. Clin. Transplant. 29 (4), 301–310.

Glatz, J.F.C., Dyck, J.R.B., Des Rosiers, C., 2018. Cardiac adaptations to obesity, diabetes and insulin resistance. Biochim. Biophys. Acta (BBA) Mol. Basis Dis. 1864 (5), 1905–1907.

Han, E., Kim, M.S., Kim, Y.S., Kang, E.S., 2016. Risk assessment and management of post-transplant diabetes mellitus. Metabolism 65 (10), 1559–1569. https://doi.org/10.1016/j.metabol.2016.07.011.

Hara, S., 2015. Banff 2013 update: Pearls and pitfalls in transplant renal pathology. Nephrology (Carlton) 20 (Suppl 2), 2–8. https://doi.org/10.1111/nep.12474.

Holmberg, C., Jalanko, H., 2016. Long-term effects of pediatric kidney transplantation. Nat. Rev. Nephrol. 12 (5), 301–311. https://doi.org/10.1038/nrneph.2015.197.

Hur, K.Y., Kim, M.S., Kim, Y.S., Kang, E.S., Nam, J.H., Kim, S.H., Nam, C.M., Ahn, C.W., Cha, B.S., Kim, S.I., Lee, H.C., 2007. Risk factors associated with the onset and progression of post-transplantation diabetes in renal allograft recipients. Diabetes Care 30 (3), 609–615.

Jaki, T., Su, T.L., Kim, M., Lee Van Horn, M., 2018. An evaluation of the bootstrap for model validation in mixture models. Commun. Stat. Simul. Comput. 47 (4), 1028–1038. https://doi.org/10.1080/03610918.2017.1303726.

Jenssen, T., Hartmann, A., 2019. Post-transplant diabetes mellitus in patients with solid organ transplants. Nat. Rev. Endocrinol. 15 (3), 172–188. https://doi.org/10.1038/s41574-018-0137-7.

Maes, B.D., Kuypers, D., Messiaen, T., Evenepoel, P., Mathieu, C., Coosemans, W., Pirenne, J., Vanrenterghem, Y.F.C., 2001. Post-transplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation 72 (10), 1655–1661.

Matas, A.J., Gillingham, K.J., Humar, A., Ibrahim, H.N., Payne, W.D., Gruessner, R.W. G., Dunn, T.B., Sutherland, D.E.R., Najarian, J.S., Kandaswamy, R., 2008. Posttransplant diabetes mellitus and acute rejection: impact on kidney transplant outcome. Transplantation 85 (3), 338–343.

Mizrahi, N., Braun, M., Ben Gal, T., Rosengarten, D., Kramer, M.R., Grossman, A., 2020. Post-transplant diabetes mellitus: incidence, predicting factors and outcomes. Endocrine 69 (2), 303–309. https://doi.org/10.1007/s12020-020-02339-9.

Nagaraja, P., Ravindran, V., Morris-Stiff, G., Baboolal, K., 2013. Role of insulin resistance indices in predicting new-onset diabetes after kidney transplantation. Transpl. Int. 26 (3), 273–280. https://doi.org/10.1111/tri.12026.

Paek, J.H., Kang, S.S., Park, W.Y., Jin, K., Park, S.B., Han, S., Kim, C.-D., Ro, H., Lee, S., Jung, C.W., Park, J.B., Huh, K.H., Yang, J., Ahn, C., 2019. Incidence of post-transplantation diabetes mellitus within 1 year after kidney transplantation and related factors in Korean cohort study. Transplant. Proc. 51 (8), 2714–2717.

Polsky, S., Ellis, S.L., 2015. Obesity, insulin resistance, and type 1 diabetes mellitus. Curr. Opin. Endocrinol. Diabetes Obes. 22 (4), 277–282. https://doi.org/10.1097/med.0000000000000170.

Porrini, E.L., Díaz, J.M., Moreso, F., Delgado Mallén, P.I., Silva Torres, I., Ibernon, M., Bayés-Genís, B., Benitez-Ruiz, R., Lampreabe, I., Lauzurrica, R., Osorio, J.M., Osuna, A., Domínguez-Rollán, R., Ruiz, J.C., Jiménez-Sosa, A., González-Rinne, A., Marrero-Miranda, D., Macía, M., García, J., Torres, A., 2016. Clinical evolution of post-transplant diabetes mellitus. Nephrol. Dial. Transplant. 31 (3), 495–505.

Rekers, N.V., de Fijter, J.W., Claas, F.H., Eikmans, M., 2016. Mechanisms and risk assessment of steroid resistance in acute kidney transplant rejection. Transpl. Immunol. 38, 3–14. https://doi.org/10.1016/j.trim.2016.07.005.

Sharif, A., Moore, R., Baboolal, K., 2008. Influence of lifestyle modification in renal transplant recipients with postprandial hyperglycemia. Transplantation 85 (3), 353–358. https://doi.org/10.1097/TP.0b013e3181605ebf.

Shivaswamy, V., Boerner, B., Larsen, J., 2016. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr. Rev. 37 (1), 37–61. https://doi.org/10.1210/er.2015-1084.

Sinangil, A., Celik, V., Barlas, S., Koc, Y., Basturk, T., Sakaci, T., Akin, E.B., Ecder, T., 2017. The incidence of new onset diabetes after transplantation and related factors: Single center experience. Nefrologia 37 (2), 181–188.

Suthanthiran, M., Strom, T.B., 1994. Renal transplantation. N. Engl. J. Med. 331 (6), 365–376. https://doi.org/10.1056/nejm199408113310606.

Yu, H., Kim, H., Baek, C.H., Baek, S.D., Jeung, S., Han, D.J., et al., 2016. Risk factors for new-onset diabetes mellitus after living donor kidney transplantation in Korea - a retrospective single center study. BMC Nephrol. 17 (1), 106. https://doi.org/10.1186/s12882-016-0321-8.

Zhang, M., Han, Y., Yuan, Y., Cai, J., Zhang, J., Wang, Y., Xiang, H., Zhou, H., 2019. Risk factors for new-onset diabetes mellitus after heart transplantation in chinese patients: A single center experience. Ann. Nutr. Metab. 74 (4), 331–338.