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Association of body mass index and fasting plasma glucose concentration with post-transplantation diabetes mellitus in Chinese heart transplant recipients

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Abstract

Objective: Post-transplantation diabetes mellitus (PTDM) is a frequent complication after heart transplantation. We investigated the specific predictors of PTDM in Chinese heart transplant recipients and the prognostic value of these predictors.

Methods: We retrospectively analyzed 122 adult patients who underwent heart transplantation. Comparisons were made between patients with PTDM (n = 44) and those without PTDM (n = 78).

Results: During the median follow-up of 44 months, the cumulative incidence of PTDM was 19.7% at 1 year after transplantation and 36.1% at the endpoint. PTDM was associated with a significantly higher preoperative body mass index (BMI) (odds ratio [OR] = 1.349), fasting plasma glucose (FPG) concentration (OR = 2.538), and serum uric acid concentration (OR = 1.005) after transplantation. The area under the receiver operating characteristic curve was 0.708 and 0.763 for the BMI and FPG concentration, respectively. The incidence of acute rejection and infection were higher and the all-cause mortality rate was considerably greater in patients with than without PTDM.

Conclusions: A higher preoperative BMI (>23 kg/m^2), FPG concentration (>5.2 mmol/L), and uric acid concentration could potentially predict PTDM in Chinese heart transplant recipients. PTDM influences long-term survival after heart transplantation.

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Introduction

Post-transplantation diabetes mellitus (PTDM) is an important complication that occurs in 10% to 40% of patients during the first year after the patient undergoes solid organ transplantation.[1] PTDM potentially exerts a detrimental effect on post-transplant outcomes because PTDM is an independent risk factor for graft failure, cardiovascular disease, and death in kidney[2,3] and liver transplant recipients.[4–6] The incidence of PTDM and its effect on the survival rate depend on the type of organ transplanted, the recipient's characteristics, and the immunosuppressive medication administered. Risk factors for PTDM include predisposing factors for type 2 DM, such as older age, obesity, family history of DM, ethnicity, and susceptibility genes.[1,7–10] Another major predisposing factor specific to PTDM is immunosuppressive therapy, including glucocorticoid and calcineurin inhibitors (cyclosporine and tacrolimus).[7,11] However, most studies of PTDM have involved kidney and liver transplant recipients in Caucasian populations. These results may not be applicable to Chinese heart transplant recipients (HTRs).

Heart transplantation (HT) is an effective therapeutic option for patients with end-stage heart disease. Based on data from the China Heart Transplant Registration Center, 2149 HTs were performed from 2009 to 2016.[12] Despite the increase in the number of HTRs, knowledge of the clinical parameters associated with PTDM in Chinese HTRs remains insufficient. As a potentially modifiable risk factor for PTDM in HTRs,[13] appropriate body mass index (BMI) cut-off points could help to identify patients at high risk of PTDM for intervention. The incidence of new-onset DM varies widely between solid organ transplant recipients and the general population. The use of a BMI cut-off point of $\geq 25\,kg/m^2$ (overweight) or $\geq 30\,kg/m^2$ (obese) may underestimate the risk of PTDM. An elevated serum uric acid concentration is a predictor of type 2 DM in the general population[14,15] and is common among HTRs,[16] but no studies have evaluated this association among HTRs. Therefore, the present study of Chinese HTRs was performed to identify the incidence of and specific risk factors for PTDM and evaluate the effects of PTDM on the outcomes of HT.

Patients and methods

Study population

Two hundred one patients underwent HT in our hospital from 2002 to 2017. Patients who underwent routine follow-up after HT (monthly during the first 6 months, every 2 months during the next 7–12 months, every 3 months during the second year, and every 6 months beginning in the third year) were included in the present study. Patients with a history of DM ($n = 23$), death within 3 months after transplantation ($n = 41$), multiple organ transplantation ($n = 2$), age of <18 years ($n = 2$), and no follow-up data ($n = 11$) were excluded. One hundred twenty-two HTRs were enrolled in this cohort study.

According to the DM classification, the patients were divided into those with PTDM (n = 44) and those without PTDM (n = 78). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Beijing Anzhen Hospital, Capital Medical University (No. 2018061X). All clinical and laboratory information were obtained from the retrospective analysis; thus, informed consent was not deemed necessary by the Ethical Committee.

Clinical data collection

Clinical data were collected from the electronic medical records system used in the hospital and supplemented by reviewing follow-up medical records for individual patients. The preoperative data included age, sex, BMI, serum uric acid concentration, history of smoking, pathological diagnosis of primary cardiac disease, biochemical parameters, and hepatitis C virus infection status. The preoperative fasting plasma glucose (FPG) concentration was obtained within 1 week before HT when the patient was in stable condition. Perioperative data included immunosuppressant drugs and inpatient days after HT. The cumulative prednisone dose during the perioperative period was calculated from the day on which treatment started to the discharge day, excluding the standard intraoperative dose of 500 mg of methylprednisolone that was administered intravenously to all patients. The prednisone dose (mg/kg/day) at discharge was calculated from the prednisone dosage at discharge divided by the body weight of the HTR. The prednisone dosage at discharge was determined from the stable dose for the discharged patient. Postoperative follow-up data included the FPG concentration, immunosuppressive therapy, drug dosage and concentration, complications, and patient survival or death. The FPG measurements after HT were obtained from blood samples drawn at the end of the first, third, and fifth-year follow-up. Other medications, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and statins, were also recorded. The endpoint event was death of the HTRs.

Diagnosis of PTDM

According to the International Consensus Guidelines for PTDM published in 2014[17] and the American Diabetes Association criteria,[18] PTDM is defined as (1) symptoms of DM and an FPG concentration of $\geq$7.0 mmol/L or a randomly measured glucose concentration of $\geq$11.1 mmol/L on more than one occasion, (2) a plasma glucose concentration of $\geq$11.1 mmol/L in a 2-hour oral glucose tolerance test (OGTT), or (3) a blood glycosylated hemoglobin A1c (HbA1c) concentration of $\geq$6.5%. Patients who received antidiabetic treatments during follow-up were also considered to have DM. To rule out transient post-transplantation hyperglycemia caused by operation stress and/or high doses of glucocorticoids, PTDM was diagnosed after HTRs had been discharged from the hospital and their medications had been tapered to maintenance doses.

Immunosuppressive therapy

Basiliximab (Simulect; Novartis, Basel, Switzerland), an interleukin-2 monoclonal antibody, was used in the induction therapy protocol. The maintenance medications consisted of a triple-drug combination including a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil), and a glucocorticoid (prednisone). The starting dose of cyclosporine or tacrolimus was 2.5 mg/kg/day or 0.15 to 0.3 mg/kg/day,

respectively, followed by titration according to the blood drug concentrations. The cyclosporine concentration was 300 to 350 ng/mL for 6 weeks, 250 to 300 ng/mL from 6 weeks to 6 months, and 150 to 200 ng/mL after 1 year. The tacrolimus concentration was 10 to 20 ng/mL immediately after HT and 5 to 15 ng/mL after 3 months. Mycophenolate mofetil was orally administered to patients at 500 mg twice a day. All patients received glucocorticoids (500 mg of methylprednisolone intravenously) during the transplant operation. Postoperative methylprednisolone was intravenously administered at a dose of 1 mg/kg/day. When oral medications were able to be ordered, methylprednisolone was switched to a prednisone dose of 0.5 mg/kg/day divided into two administrations, which was gradually tapered to a maintenance dose of 5 mg/day during the next 3 to 6 months. Maintenance or withdrawal of the glucocorticoid treatment depended on the physician's judgment and the patient's condition.

Definitions of HT-related complications

The primary outcome of interest was all-cause death. The secondary outcomes of interest were transplant-related adverse events including cardiac allograft rejection, cardiac allograft vasculopathy (CAV), renal dysfunction, and infection. Cardiac allograft rejection was diagnosed by performing an endomyocardial biopsy according to the International Society for Heart and Lung Transplantation (ISHLT) criteria.[19] The diagnosis of CAV was based on a retrospective review of coronary angiography results and determined by the attending doctors. Renal dysfunction was considered severe when the estimated glomerular filtration rate was $<60\,mL/min/1.73\,m^2$ for 3 consecutive months after HT.[20] Infection was defined as a bacterial, fungal, or opportunistic infection that required therapeutic intervention. Hypertension was defined as a blood pressure of $\geq$140/90 mmHg, use of antihypertensive medication, or a reported diagnosis of hypertension during follow-up. Hyperlipidemia was defined as a total cholesterol concentration of $\geq$5.17 mmol/L or triglyceride concentration of $\geq$1.70 mmol/L during follow-up medical examinations, use of cholesterol-lowering medication, or a diagnosis of hyperlipidemia during follow-up.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation. One-way analysis of variance with the post-hoc least significant difference test was performed for multiple comparisons. Continuous variables with a skewed distribution are presented as median with interquartile range (IQR) and were compared using nonparametric tests. Categorical variables are presented as percentages and were analyzed by the chi-squared test or Fisher's exact test. Multivariate forward logistic regression analysis was used to identify risk factors for PTDM. The results are reported using odds ratios (ORs) and 95% confidence intervals (CIs). We conducted receiver operating characteristic (ROC) analyses to evaluate the predictive potential of identified signatures for PTDM. The threshold values (maximum Youden's index) obtained from the areas under the ROC curves were used for PTDM prediction. Kaplan–Meier survival analyses using the log-rank test were performed with the PTDM status as the categorical variable. We used Cox regression to analyze risk factors for all-cause mortality. Risk factors assessed were age, sex, baseline body weight, PTDM, acute rejection, CAV, hypertension, hyperlipidemia, infection, and renal dysfunction. The results are reported using hazard ratios (HRs) and

95% CIs. A two-tailed P value of <0.05 was considered statistically significant.

Results

Incidence of PTDM

In total, 122 HTRs were enrolled in this study. Forty-four patients (36.1%) were diagnosed with PTDM after a median follow-up time of 42 months (IQR, 18–82 months). The median time of the first assessment of PTDM was 3.0 months (IQR, 2.7–3.1 months) after HT. During follow-up, the cumulative incidence of PTDM at 1, 3, and 5 years was 19.7%, 29.5%, and 32.8%, respectively. The median time to diagnosis of PTDM was 11 months (IQR, 5–30 months) after HT.

Recipient characteristics

The patients comprised 89 (73%) men and 33 (27%) women with an overall mean age of 43.3 ± 13.5 years. The preoperative characteristics of HTRs are shown in Table 1. The body weight, BMI, FPG concentration, and serum uric acid concentration were considerably higher in patients with than without PTDM (all $P < 0.05$). There was no significant difference in weight gain at 6 months after HT between patients with and without PTDM. The change in the uric acid concentration at 6 months after HT did not differ significantly between the groups.

Postoperative medications and glycemic control

During hospitalization for HT, the cumulative dose of prednisone was significantly higher in patients with than without PTDM ($P = 0.002$). However, no significant difference in the average daily dose of prednisone administered during the perioperative period or the rate of glucocorticoid withdrawal was observed (Table 2). No significant difference in the blood cyclosporine concentration was observed between the two groups at discharge, or at 6 months, 1 year, or 3 years after HT. FPG measurements at the end of the first, third, and fifth year after HT were used to assess the evolution of the FPG concentration during follow-up (Table 2).

Risk factors for PTDM

In the univariate analysis, the HTR's age (OR = 1.036, 95% CI = 1.005–1.067, $P = 0.021$), body weight (OR = 1.067, 95% CI = 1.029–1.107, $P < 0.001$), and uric acid concentration at 6 months after HT (OR = 1.000, 95% CI = 1.000–1.006, $P = 0.033$) were significant risk factors for PTDM. Weight gain of >10% during follow-up did not reach statistical significance in the univariate model. The multivariate logistic regression model included all variables that were retained in the univariate analysis ($P < 0.20$), as shown in Table 3. The independent risk factors were the pretransplant BMI (OR = 1.349, 95% CI = 1.119–1.627, $P = 0.002$), FPG concentration (OR = 2.538, 95% CI = 1.436–4.488, $P = 0.001$), and uric acid concentration (OR = 1.005, 95% CI = 1.002–1.008, $P = 0.003$).

ROC curves were analyzed in this study. An area under the ROC curve exceeding 0.70 for the BMI (0.708, 95% CI = 0.614–0.802, $P < 0.001$) and FPG concentration (0.763, 95% CI = 0.675–0.850, $P < 0.001$) revealed the potential of these parameters to predict PTDM development. The optimal cut-off value for the preoperative BMI in patients with PTDM was 23 kg/m^2, yielding a sensitivity of 77.3% and a specificity of 59.0%. The largest Youden's index was observed for an FPG concentration of 5.2 mmol/L, resulting in a sensitivity of 77.3% and a specificity of 70.5%.

Table 1. Recipient characteristics at the time of transplantation and during follow-up.

Characteristics	PTDM (n = 44)	No PTDM (n = 78)	*P* value
Male sex	34 (77.3)	55 (70.5)	0.059
Age, years	47.1 ± 7.1	41.2 ± 15.6	0.005
History of smoking	11 (25.0)	24 (30.8)	0.499
Systolic blood pressure, mmHg	108.2 ± 14.8	108.3 ± 13.7	0.961
Diastolic blood pressure, mmHg	70.7 ± 10.6	69.6 ± 9.8	0.582
Body weight, kg	70.4 ± 11.1	61.9 ± 11.8	<0.001
Weight gain 6 months after HT, kg	2 (0.5, 5)[a]	2 (−1, 4)	0.878
Weight gain[b]			0.062
≥10%	3 (7.3)	16 (20.5)	
<10%	38 (92.7)	62 (79.5)	
BMI, kg/m^2	24.6 ± 3.3	21.9 ± 2.8	<0.001
BMI gain 6 months after HT, kg/m^2	0.73 (0.15, 1.47)[a]	0.41 (−0.37, 1.63)	0.593
Fasting plasma glucose, mmol/L	5.4 (5.2, 6.3)	4.8 (4.4, 5.3)	<0.001
Serum uric acid, μmol/L	564 (471, 675)	461 (362, 563)	0.001
Serum uric acid 6 months after HT, μmol/L	466 (382, 540)	416 (341, 494)	0.068
Absolute uric acid change, μmol/L	−95 (−242, 47)	−26 (−161, 66)	0.116
Serum creatinine, μmol/L	81 (69, 84)	78 (64, 100)	0.415
eGFR, mL/min/1.73 m^2	84 (64, 106)	86 (66, 109)	0.391
Triglycerides, mmol/L	1.07 (0.79, 1.34)	1.02 (0.80, 1.58)	0.936
Total cholesterol, mmol/L	4.27 (3.59, 4.71)	3.96 (3.42, 4.74)	0.143
High-density lipoprotein cholesterol, mmol/L	0.93 (0.86, 1.10)	0.89 (0.75, 1.08)	0.349
Low-density lipoprotein cholesterol, mmol/L	2.66 (2.26, 3.33)	2.65 (2.10, 3.08)	0.312
Hepatitis C seropositivity	0 (0.0)	1 (1.3)	>0.99
Left ventricular ejection fraction, %	25 (21, 30)	29 (23, 33)	0.087
Ischemic time, min	185 ± 36	178 ± 40	0.372
Etiology of heart disease			0.395
Primary cardiomyopathy	35 (79.5)	58 (74.4)	
Ischemic cardiomyopathy	7 (15.9)	11 (14.1)	
Others	2 (4.5)	9 (11.5)	

Data are given as n (%), mean ± standard deviation, or median (25th, 75th percentile). [a]Values were obtained from 41 patients in the PTDM group. [b]Body weight at 6 months compared with baseline weight at the time of transplantation
PTDM, post-transplantation diabetes mellitus; HT, heart transplantation; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Effects of PTDM on clinical outcomes

Significantly higher incidences of rejection, hyperlipidemia, and infection episodes were observed in patients with than without PTDM ($P < 0.05$), but no significant difference was found in the incidence of CAV episodes (Table 4). These clinical endpoints in Table 4 occurred after PTDM. The proportion of patients with renal dysfunction was slightly higher in patients with than without PTDM, although statistical significance was not reached (43.2% vs. 28.2%, respectively). The all-cause mortality rate was significantly higher in patients with than without PTDM (27.3% vs. 10.3%, respectively; $P = 0.015$). Figure 1 shows the Kaplan–Meier estimates of survival in patients with and without PTDM after HT. The estimated mean survival time of

Table 2. Characteristics of medication use and evolution of FPG concentration during follow-up.

Clinical index	PTDM (n = 44)	No PTDM (n = 78)	*P* value
Inpatient days	25 (22, 30)	24 (20, 32)	0.257
Cumulative prednisone dose[a], mg	750 (642, 871)	640 (500, 800)	0.002
Prednisone at discharge, mg/kg/day	0.33 (0.27, 0.42)	0.32 (0.27, 0.40)	0.979
Glucocorticoid withdrawal	15 (34.1)	34 (43.6)	0.304
Calcineurin inhibitors			0.323
Cyclosporine	40 (90.9)	66 (84.6)	
Tacrolimus	4 (9.1)	12 (15.4)	
Cmin of cyclosporine, ng/mL			
Discharge after HT	296 (221, 384)	266 (205, 367)	0.185
6 months after HT	186 (125, 226)	178 (121, 262)	0.715
1 year after HT	153 (129, 210)	160 (122, 194)	0.747
3 year after HT	173 (100, 201)	135 (105, 179)	0.658
Cmin of tacrolimus, ng/mL			
Discharge after HT	12.6 (8.6, 26.3)	12.2 (7.8, 15.6)	0.661
6 months after HT	6.9 (5.2, 21.0)	7.3 (5.8, 13.8)	0.825
1 year after HT	7.0 (5.5, 7.4)	7.4 (5.6, 12.0)	0.385
3 year after HT	6.2 (6.0, 7.4)	6.2 (4.6, 10.1)	0.875
Evolution of fasting plasma glucose concentration, mmol/L			
1 year after HT	6.8 (5.4, 8.4)	5.5 (5.1, 5.7)	<0.001
3 years after HT	6.8 (5.8, 7.7)	5.6 (5.2, 5.9)	<0.001
5 years after HT	6.3 (5.6, 8.5)	5.6 (5.3, 5.9)	0.096
Post-HT medication			
Diuretic	34 (77.3)	65 (83.3)	0.579
ACEi/ARB	13 (29.5)	24 (30.8)	0.888
Beta-blocker	12 (27.3)	15 (19.2)	0.304
Calcium channel blocker	5 (11.4)	2 (2.6)	0.097
Statin	5 (11.4)	6 (7.7)	0.523
Insulin	23 (52.3)	–	–
Oral hypoglycemic agent	21 (47.7)	–	–

Data are given as n (%) or median (25th, 75th percentile). PTDM, post-transplantation diabetes mellitus; FPG, fasting plasma glucose; HT, heart transplantation; Cmin, minimum concentration; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. [a]Cumulative prednisone dose in the perioperative period.

patients at the endpoint was 104 months (95% CI = 86–123) among patients with PTDM and 118 months (95% CI = 109–127) among patients without PTDM. The survival curve of patients without PTDM was noticeably different from that of patients with PTDM (log-rank test, $P = 0.024$). In the multivariate Cox proportional hazards analysis, PTDM (HR = 4.957, 95% CI = 1.684–14.598, $P = 0.004$) and age (HR = 0.959, 95% CI = 0.923–0.997, $P = 0.035$) were significant risk factors for all-cause mortality.

Discussion

PTDM occurs in a substantial percentage of HTRs and is associated with adverse outcomes.[1,13] The incidence of PTDM in HTRs ranges from 15.7% to 40.0%.[13,21–24] The registry of the ISHLT reported an incidence of PTDM of 21.0% at 1 year and

Table 3. Risk factors for PTDM.

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Recipient age	1.036 (1.005–1.067)	0.021		
Male		0.421		
History of smoking		0.499		
Pretransplant body weight	1.067 (1.029–1.107)	<0.001		
Weight gain 6 months after HT		0.754		
Weight gain of ≥10% at 6 months		0.062		
Pretransplant BMI	1.373 (1.174–1.604)	<0.001	1.349 (1.119–1.627)	0.002
BMI gain 6 months after HT		0.841		
Pretransplant FPG	2.989 (1.774–5.037)	<0.001	2.538 (1.436–4.488)	0.001
Pretransplant serum uric acid	1.005 (1.002–1.007)	0.001	1.005 (1.002–1.008)	0.003
Uric acid 6 months after HT	1.000 (1.000–1.006)	0.033		
Absolute uric acid change		0.158		
Cumulative prednisone doses	1.003 (1.001–1.005)	0.004		
Cyclosporine vs. tacrolimus		0.328		
ICM vs. no ICM		0.434		
Hepatitis C seropositivity		0.451		

Only variables with a *P* value of <0.20 in the univariate analysis were included in the multivariate analysis. PTDM, post-transplantation diabetes mellitus; OR, odds ratio; CI, confidence interval; HT, heart transplantation; BMI, body mass index; FPG, fasting plasma glucose; ICM, ischemic cardiomyopathy.

Table 4. Clinical impact of PTDM and no PTDM.

Transplant outcomes	PTDM (n = 44)	No PTDM (n = 78)	*P* value
Acute rejection	12 (27.3)	9 (11.5)	0.027
Cardiac allograft vasculopathy	4 (9.1)	1 (1.3)	0.056
Hypertension	13 (29.5)	15 (19.2)	0.193
Hyperlipidemia	29 (65.9)	29 (27.2)	0.002
Infection	27 (61.4)	10 (12.8)	<0.001
Renal dysfunction	19 (43.2)	22 (28.2)	0.093
All-cause death	12 (27.3)	8 (10.3)	0.015

Data are given as n (%). PTDM, post-transplantation diabetes mellitus.

34.5% at 5 years after HT.[25] Ethnicity may play a role in the development of PTDM; non-white race has been identified as an independent risk factor for PTDM in HTRs.[13] We evaluated PTDM in Chinese HTRs and found that the incidence of PTDM was 19.7% at 1 year and 32.8% at 5 years. We also identified several risk factors for PTDM and their appropriate cut-off points to classify recipients at high risk for PTDM, including an increased BMI, FPG concentration, and uric acid concentration.

Consistent with previous reports,[11,13,21] we found that an increased BMI before HT was an independent risk factor for PTDM. Moreover, we found that the BMI cut-off point to predict PTDM development was 23 kg/m^2 in Chinese HTRs. BMI cut-off points are used clinically to

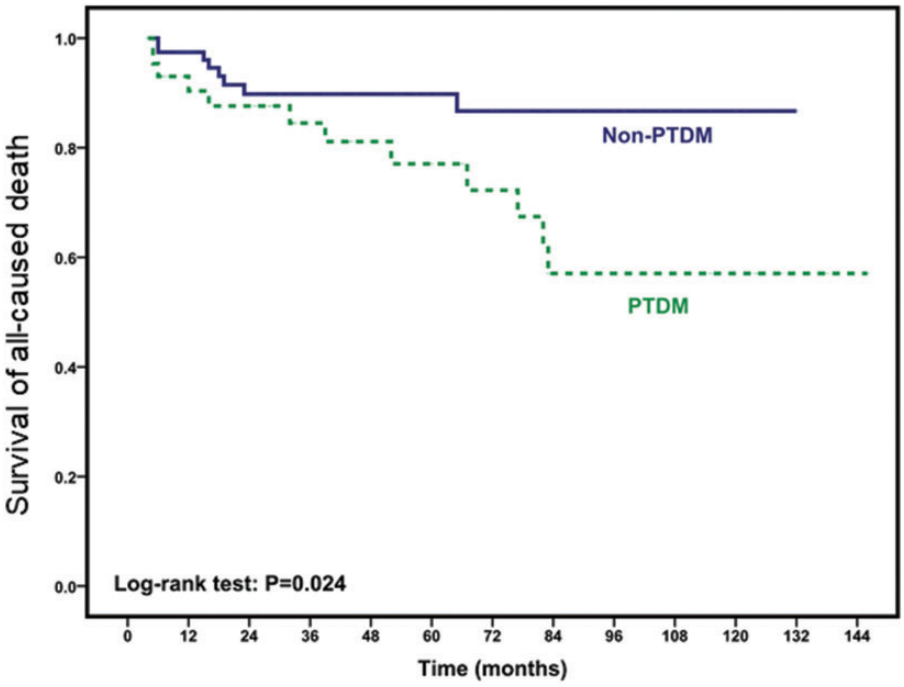

Figure 1. Kaplan–Meier analysis of survival among all patients with and without PTDM during follow-up. PTDM, post-transplantation diabetes mellitus.

identify high-risk individuals for screening. Because of ethnic differences, Chinese people develop DM at a lower BMI level than do Europeans in the general population.[26,27] Both general risk factors for DM and transplant-specific factors can lead to PTDM in solid organ transplant recipients.[7,28] The use of a BMI cut-off point of $\geq 25\,kg/m^2$ (overweight) or $\geq 30\,kg/m^2$ (obese) may underestimate the risk of PTDM. In the present study, the preoperative BMI of $23\,kg/m^2$ yielded a sensitivity of 77.3% and a specificity of 59.0% for prediction of PTDM. Weight gain after transplantation reportedly impacts the development of PTDM in kidney[29] and pancreas[30] transplant recipients. Considering that the median time to diagnosis of DM was 11 months after HT, we analyzed weight gain at 6 months after transplantation instead of 1 year in the present study. We found no significant difference between weight gain and BMI gain at 6 months in either patients with or without PTDM.

The serum uric acid concentration has been identified as a risk factor for type 2 DM in the general population,[15,31] but it has not been reported as a risk factor for PTDM. Most patients with end-stage heart disease undergoing HT have an elevated serum uric acid concentration, which is partly caused by diuretic and immunosuppressive medications and impaired renal function. A retrospective analysis of kidney transplant patients showed that the uric acid concentration did not predict PTDM but that pretransplant use of gout medication did.[8] In our study, the pretransplant uric acid concentration was generally high, but urate-lowering medications were rarely used. An elevated serum uric acid

concentration before HT, but not at 6 months after HT, was correlated with PTDM. The mechanisms underlying the association between uric acid and DM remain unclear. One possible explanation is that hyperuricemia may be related to insulin resistance,[32] while a higher insulin concentration can reduce renal excretion of uric acid.[33]

In the present study, the preoperative FPG concentration (OR = 2.538, $P = 0.001$) was an independent risk factor for PTDM in HTRs, but its cut-off point was 5.2 mmol/L, which is less than 5.6 mmol/L (upper limit of physiological FPG range). An elevated FPG concentration in renal transplant patients was a predictive risk factor for PTDM in a previous study.[34] The association of the preoperative FPG concentration with the risk of PTDM in solid organ transplantation recipients remains controversial. A kidney transplant cohort study showed that the preoperative FPG concentration did not predict PTDM and that an FPG concentration of >5.6 mmol/L at 3 months after transplantation (OR = 2.97, 95% CI = 1.009–8.733) became a risk factor for PTDM.[35] For lung transplant recipients, the preoperative glucose concentrations measured in a 1-hour OGTT (OR = 1.73, $P = 0.004$) and 2-hour OGTT (OR = 1.84, $P = 0.004$) were risk factors in addition to the FPG concentration.[36] The discrepancies in these findings may be attributed to the different organs transplanted and comorbidities. In the present study, a correlation was observed between the preoperative FPG concentration and PTDM, but more accurate conclusions require prospective randomized controlled trials.

The use of cyclosporine and tacrolimus as calcineurin inhibitors in this study did not affect PTDM development. More patients in this study used cyclosporine than tacrolimus, which may be a possible explanation for this finding. However, calcineurin inhibitors such as cyclosporine and tacrolimus cause pancreatic β-cell apoptosis and reduce insulin secretion.[37] Conversely, glucocorticoid use is a risk factor for PTDM because it results in insulin resistance and increased hepatic gluconeogenesis. In the present study, the cumulative prednisone dose in the perioperative period increased the risk of PTDM. Appropriate treatment of PTDM should be initiated as early as possible.

Acute allograft rejection is the main complication in patients undergoing HT. In contrast to earlier findings,[22,38] we found that PTDM increased the number of postoperative acute rejection episodes. Moreover, PTDM increased the rate of patient infection in our study. A substantial difference in the incidence of CAV was not observed between the two groups, consistent with previous retrospective reports.[38] The all-cause mortality rate was 2.65 times higher in patients with than without PTDM. However, Klingenberg et al.[38] reported an association between preoperative DM and a significant reduction in overall survival, whereas PTDM did not reduce survival. Our study provides evidence that PTDM increases all-cause mortality after HT.

This study has several limitations. It was a retrospective study and not a multi-center study; patients were not routinely screened for PTDM using an OGTT or measurement of the HbA1c concentration. In fact, the reliability of HbA1c measurement may be adversely affected by blood transfusions and higher red blood cell turnover in the early post-transplant period, and HbA1c alone is not sufficient to screen for PTDM.[7] The OGTT is considered the gold standard test for patients suspected to have PTDM.[18] In this study, the FPG concentration was consecutively tested at each follow-up visit, and continuous monitoring of the FPG concentration can be used to achieve a definitive diagnosis.

In conclusion, this study evaluated the long-term incidence of and specific risk factors for PTDM in Chinese HTRs. The most notable finding of our study was that a preoperative BMI of $>23\,kg/m^2$, FPG concentration of $>5.2\,mmol/L$, and elevated serum uric acid concentration can be used to potentially predict PTDM in Chinese HTRs. PTDM influences long-term survival after HT. We expect that further investigations of PTDM management will be helpful to reduce graft-related adverse events and improve long-term survival.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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