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/m²), 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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Keywords
Heart transplantation, post-transplantation diabetes mellitus, fasting plasma glucose, body mass index, risk factors, outcome

Date received: 27 October 2019; accepted: 11 February 2020

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. 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 and liver transplant recipients. 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. Another major predisposing factor specific to PTDM is immunosuppressive therapy, including glucocorticoid and calcineurin inhibitors (cyclosporine and tacrolimus). 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. 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, 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 25 kg/m² (overweight) or 30 kg/m² (obese) may underestimate the risk of PTDM. An elevated serum uric acid concentration is a predictor of type 2 DM in the general population and is common among HTRs, 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\(^\text{17}\) and the American Diabetes Association criteria,\(^\text{18}\) PTDM is defined as (1) symptoms of DM and an FPG concentration of ≥7.0 mmol/L or a randomly measured glucose concentration of ≥11.1 mmol/L on more than one occasion, (2) a plasma glucose concentration of ≥11.1 mmol/L in a 2-hour oral glucose tolerance test (OGTT), or (3) a blood glycosylated hemoglobin A1c (HbA1c) concentration of ≥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. 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 m² for 3 consecutive months after HT. Infection was defined as a bacterial, fungal, or opportunistic infection that required therapeutic intervention. Hypertension was defined as a blood pressure of ≥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 ≥5.17 mmol/L or triglyceride concentration of ≥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 ± 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%.
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

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**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)    | 2 (1, 4)         | 0.878     |
| Weight gain $^b$                             | 462 (471, 675)| 461 (362, 563)   | 0.001     |
| BMI, kg/m$^2$                                 | 21.9 ± 2.8    | <0.001           |
| BMI gain 6 months after HT, kg/m$^2$          | 0.73 (0.15, 1.47) | 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.
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

| Clinical index                                      | PTDM \( (n = 44) \) | No PTDM \( (n = 78) \) | \( P \) value |
|----------------------------------------------------|----------------------|-------------------------|--------------|
| Inpatient days                                     | 25 (22, 30)          | 24 (20, 32)             | 0.257        |
| Cumulative prednisone dose, 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. *Cumulative prednisone dose in the perioperative period.
34.5% at 5 years after HT. 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. 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, 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/m² in Chinese HTRs.

### Table 3. Risk factors for PTDM.

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | OR (95% CI)         | P value               | OR (95% CI)         | P value               |
| Recipient age                    | 1.036 (1.005–1.067) | 0.021                 | 1.036 (1.005–1.067) | 0.021                 |
| Male                             | 0.421               |                       | 0.421               |                       |
| History of smoking               | 0.499               |                       | 0.499               |                       |
| Pretransplant body weight        | 1.067 (1.029–1.107) | <0.001                | 1.067 (1.029–1.107) | <0.001                |
| Weight gain 6 months after HT    | 0.754               | 0.062                 | 0.754               | 0.062                 |
| Weight gain of ≥10% at 6 months  | 0.062               |                       | 0.062               |                       |
| Pretransplant BMI                | 1.373 (1.174–1.604) | <0.001                | 1.373 (1.174–1.604) | <0.001                |
| BMI gain 6 months after HT       | 0.841               |                       | 0.841               |                       |
| Pretransplant FPG                | 2.989 (1.774–5.037) | <0.001                | 2.989 (1.774–5.037) | <0.001                |
| Pretransplant serum uric acid    | 1.005 (1.002–1.007) | 0.001                 | 1.005 (1.002–1.007) | 0.001                 |
| Uric acid 6 months after HT      | 1.000 (1.000–1.006) | 0.033                 | 1.000 (1.000–1.006) | 0.033                 |
| Absolute uric acid change        | 1.003 (1.001–1.005) | 0.004                 | 1.003 (1.001–1.005) | 0.004                 |
| Cumulative prednisone doses      | 1.000 (1.000–1.006) | 0.033                 | 1.000 (1.000–1.006) | 0.033                 |
| Cyclosporine vs. tacrolimus      | 0.328               |                       | 0.328               |                       |
| ICM vs. no ICM                   | 0.434               |                       | 0.434               |                       |
| Hepatitis C seropositivity       | 0.451               |                       | 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.
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 ≥25 kg/m² (overweight) or ≥30 kg/m² (obese) may underestimate the risk of PTDM. In the present study, the preoperative BMI of 23 kg/m² 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 kidney²⁹ and pancreas³⁰ 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

Figure 1. Kaplan–Meier analysis of survival among all patients with and without PTDM during follow-up. PTDM, post-transplantation diabetes mellitus.
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, while a higher insulin
countent can reduce renal excretion of uric acid.

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 concentra-
tion in renal transplant patients was a pre-
dictive risk factor for PTDM in a previous
study. 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 transplan-
tation (OR = 2.97, 95% CI = 1.009–8.733)
became a risk factor for PTDM. 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 concen-
tration. The discrepancies in these find-
ings 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 accu-
rate conclusions require prospective ran-
donized 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 \( \beta \)-cell apoptosis and reduce insulin
secretion. 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 perioper-
ative 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, 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, consist-
tent with previous retrospective reports.
The all-cause mortality rate was 2.65 times
higher in patients with than without
PTDM. However, Klingenberg et al. reported an association between preopera-
tive DM and a significant reduction in over-
all 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. The OGTT is considered the
gold standard test for patients suspected
to have PTDM. In this study, the FPG
concentration was consecutively tested at
each follow-up visit, and continuous moni-
toring 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/m², 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.

Acknowledgements
The authors would like to extend their sincere thanks to Prof. Xu Meng and Haibo Zhang (Center for Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University) for their help in the data collection.

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Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research was funded by the National Natural Science Foundation of China (No. 81041024), the Funds of Academic Leaders of Beijing (No. 2013-2-006), and the Funds of Beijing Municipal Science & Technology Commission (No. Z131100004013044).

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