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Influence of Pretransplant and Posttransplant Diabetes on Long-Term Heart Transplant Outcomes

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Diabetes mellitus (DM) is increasingly prevalent among heart transplant candidates, but its long-term prognostic significance remains undefined. The impact of posttransplant DM (PTDM) and insulin-dependent PTDM on outcomes has not been fully characterized. This study evaluated associations of pretransplant DM, PTDM, and insulin-dependent PTDM with long-term outcomes after heart transplantation.

Material/Methods: Adult heart transplant recipients in the Scientific Registry of Transplant Recipients between December 2005 and December 2020, with no prior transplant, were included. Recipients were stratified by pretransplant DM status, PTDM development, and insulin dependence among PTDM patients. Overall survival (OS) was assessed using Kaplan-Meier analysis, and independent predictors of mortality and PTDM were evaluated using multivariable Cox and logistic regression.

Results: A total of 30 430 recipients were analyzed, including 8361 with pretransplant DM. Pretransplant DM was associated with worse 10-year OS and independently predicted mortality (HR = 1.39, 95% CI: 1.32-1.46; $P < 0.001$). Recipients with pretransplant DM also had higher rates of acute drug-treated rejection, dialysis requirement, drug-treated infection, and infection- or pulmonary-related death. Among 21 121 recipients without pretransplant DM, 3003 developed PTDM. PTDM was independently associated with worse OS (HR = 1.14; 95% CI, 1.06-1.22; $P = 0.001$), acute rejection, and infection. Among patients with PTDM, insulin-dependent PTDM conferred greater mortality risk than non-insulin-dependent PTDM (HR = 1.58; 95% CI, 1.38-1.80; $P < 0.001$) and was associated with higher rates of rejection, dialysis, infection, and cardiovascular death.

Conclusions: Diabetes across the transplant continuum has distinct prognostic implications after heart transplantation. Pretransplant DM and PTDM are independently associated with worse long-term OS, while insulin-dependent PTDM identifies a particularly high-risk subgroup.

Keywords: Cardiology • Diabetes Mellitus • Heart Transplantation • Longitudinal Studies • Postoperative Complications • Preoperative Care

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Introduction

Heart transplantation remains the definitive treatment for end-stage heart failure. Advances in immunosuppressive strategies, methods for detecting graft rejection, and use of marginal donor hearts have improved transplant outcomes and expanded transplant eligibility. Nonetheless, long-term posttransplant survival continues to be significantly influenced by recipient comorbidities [1,2]. Diabetes mellitus (DM) is an important comorbidity in this context [3,4]. Over the past several decades, the proportion of heart transplant recipients with pretransplant DM has markedly risen, increasing from 16.7% during 1992-2000 to 27.0% during 2010-2018 [5]. However, evidence regarding the impact of pretransplant DM on posttransplant outcomes remains mixed. Several previous studies demonstrated that pretransplant DM was associated with poorer short-term and long-term posttransplant survival, greater susceptibility to infections, increased risks of renal dysfunction and cardiac allograft vasculopathy, and higher rates of graft failure [6-11]. In contrast, some studies reported no significant difference between recipients with and without pretransplant DM in terms of posttransplant survival, acute rejection, infectious complications, cardiac allograft vasculopathy, renal dysfunction, or short-term posttransplant outcomes, including 30-day hospitalization duration and readmission frequency [12-16].

In addition to pretransplant DM, posttransplant diabetes mellitus (PTDM) is a common and clinically significant complication, largely driven by immunosuppressive therapy and posttransplant metabolic stress. PTDM has been reported in more than 20% of heart transplant recipients [17,18]. PTDM has been associated with an increased risk of cardiovascular events, infections, and allograft dysfunction [17], yet its prognostic significance in heart transplant recipients is not fully established [19-21]. Furthermore, the degree of severity of PTDM—particularly insulin dependence—may carry distinct implications for long-term survival and graft function, but data in this area remain scarce [22].

Given the rising prevalence of DM in the general population and the growing number of transplant candidates with DM [5], a clearer understanding of the role of pretransplant DM, PTDM, and insulin dependence among patients with PTDM is critical for risk stratification, patient counseling, and optimization of posttransplant care. To date, no large-scale national study has systematically evaluated the associations between these diabetes-related conditions and long-term outcomes. Therefore, in this study, we aimed to investigate the impact of pretransplant DM, PTDM, and insulin-dependent PTDM on long-term posttransplant outcomes using data from the Scientific Registry of Transplant Recipients (SRTR), a national database with a large sample size and extended follow-up duration.

Material and Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported in the present study were supplied by the Hennepin Healthcare Research Institute as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. This study included adult patients who underwent heart transplantation between December 1, 2005, and December 1, 2020. Patients were excluded if they (1) were younger than 18 years, (2) lacked available information on DM status, (3) had a follow-up duration of less than 30 days, (4) had a history of prior heart transplantation, or (5) underwent combined heart and other solid-organ transplantation. Ethics approval for the present study was granted by the Ethics Committee of the Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, China.

Study Population and Group Stratification

Heart transplant recipients were stratified according to pretransplant DM status. PTDM was defined as newly diagnosed diabetes occurring after transplantation in recipients without known pretransplant DM. Recipients without pretransplant DM were further categorized according to the development of PTDM after transplantation. In subgroup analyses, recipients with PTDM were additionally stratified into insulin-dependent and non–insulin-dependent PTDM groups based on posttransplant insulin dependence status. Recipient-related and donor-related variables were included in the analyses because recipient metabolic factors and donor-associated graft characteristics may influence posttransplant metabolic and survival outcomes. Recipient variables included age (years), body mass index (BMI), serum creatinine level (mg/dL), waiting time (months), sex, race/ethnicity, primary payer, cardiac diagnosis, number of human leukocyte antigen (HLA) mismatches, and cardiac support at the time of listing. Donor variables included age (years), BMI, serum creatinine level (mg/dL), ischemic time (min), sex, ethnicity, cause of death, history of diabetes, history of hypertension, history of cancer, and cardiac arrest after death. The primary outcome was posttransplant overall survival (OS).

Statistical Analysis

Statistical analysis was performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA). The normality of continuous

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variables was assessed using the Kolmogorov-Smirnov test. As all continuous variables showed non-normal distributions ($P < 0.05$), data were presented as median (interquartile range), and comparisons between groups were performed using the Mann-Whitney *U* test. Categorical variables were summarized as frequencies and proportions, with group differences assessed by the chi-square test. OS was analyzed using the Kaplan-Meier method in R software, and differences between groups were compared using the log-rank test. Univariable Cox analyses were performed to identify variables associated with OS, with $P < 0.05$. Variables showing statistically significant associations were further entered into a multivariable Cox proportional hazards model to determine whether they were independent predictors of OS. Univariable logistic regression analyses were performed to identify variables associated with PTDM, and variables with a $P < 0.05$ were considered statistically significant. These variables were subsequently entered into a multivariable logistic regression model to determine independent predictors of PTDM. A 2-sided $P < 0.05$ was considered statistically significant.

Results

Study Population

A total of 30 430 heart transplant recipients met the eligibility criteria for this study, including 22 069 recipients without pretransplant DM and 8361 recipients with pretransplant DM. Among recipients without pretransplant DM, PTDM status was available for 21 121 patients, of whom 3022 (14.3%) developed PTDM after transplantation, while 18 099 did not. Among recipients with PTDM, insulin dependence information was available for 3003 patients, including 1283 with non-insulin-dependent PTDM and 1720 with insulin-dependent PTDM.

Baseline Characteristics

The baseline characteristics of heart transplant recipients and their corresponding donors are summarized in **Table 1**. Compared with recipients without pretransplant DM, those with pretransplant DM were older (median age: 59.0 [53.0-64.0] vs 55.0 [43.0-62.0] years; $P < 0.001$) and had a higher BMI (28.7 [25.5-32.2] vs 26.5 [23.2-30.1] kg/m^2; $P < 0.001$). Serum creatinine level was also significantly higher in the pretransplant DM group (1.2 [1.0-1.5] vs 1.1 [0.9-1.4] mg/dL; $P < 0.001$), while median waiting time on the transplant list showed a small but statistically significant difference (2.8 [0.8-8.4] vs 2.6 [0.7-8.1] months; $P = 0.005$). Sex and race/ethnicity distributions differed significantly between the 2 groups ($P < 0.001$ for both). Male sex more prevalent in both groups, but particularly in the pretransplant DM group (78.8% vs 72.3%). The majority of recipients were White in both groups, followed by Black, Hispanic, and Asian/Pacific islander. The use of public insurance was more common among patients with pretransplant DM (54.9% vs 48.4%; $P < 0.001$). Cardiac etiology differed significantly between groups. Dilated cardiomyopathy was the most common diagnosis, particularly among patients with pretransplant DM (92.1% vs 85.4%; $P < 0.001$). The proportion of restrictive, hypertrophic, valvular, and congenital cardiomyopathies was relatively low across both groups. Regarding cardiac support at time of listing, patients with pretransplant DM more frequently required left ventricular assist device (LVAD) support (42.3% vs 36.1%; $P < 0.001$), while extracorporeal membrane oxygenation (ECMO) (0.9% vs 1.5%; $P < 0.001$) usage was slightly lower in this group. HLA mismatch levels (0-4 vs 5-6; $P = 0.207$) were similar between the 2 groups.

Regarding donor characteristics, compared with donors for recipients without pretransplant DM, donors for recipients with pretransplant DM were slightly older (median age: 31.0 [23.0-41.0] vs 30.0 [22.0-40.0] years; $P < 0.001$) and had a higher BMI (26.9 [23.9-31.0] vs 26.1 [23.1-30.1] kg/m^2; $P < 0.001$). Donor serum creatinine level was marginally higher in the pretransplant DM group (1.0 [0.8-1.5] vs 1.0 [0.8-1.4] mg/dL; $P < 0.001$). A significantly greater proportion of male donors was observed among recipients with pretransplant DM (74.0% vs 70.3%; $P < 0.001$), and the prevalence of hypertension in donors was also slightly higher in this group (16.2% vs 14.7%; $P < 0.001$).

No significant differences were observed between the 2 groups in the use of steroids, tacrolimus, mycophenolate, biologics, azathioprine, or cyclosporine at discharge, donor ischemic time, donor race/ethnicity, donor cause of death, history of diabetes, history of cancer, or the incidence of cardiac arrest after death.

Posttransplant Outcomes

Kaplan-Meier survival curves revealed that OS was significantly better in the patients without pretransplant DM than those with pretransplant DM. The 1-, 5-, and 10-year OS rates were 94.6%, 83.0%, and 68.2%, respectively, in the no pretransplant DM group and 92.8%, 78.1%, and 55.8%, respectively, in the pretransplant DM group (log-rank $P < 0.001$, **Figure 1A**). Univariate Cox regression analyses demonstrated that pretransplant DM was significantly associated with worse OS (hazard ratio [HR] = 1.46; 95% CI, 1.39-1.53; $P < 0.001$). **Table 2** shows the results of univariate Cox regression analyses.

Multivariable Cox regression analysis was used to adjusted for confounding factors, and pretransplant DM was considered as an independent risk predictor of OS after heart transplant (HR = 1.39; 95% CI, 1.32-1.46; $P < 0.001$). Other independent risk factors included older recipient age (HR = 1.01; 95% CI, 1.00-1.01; $P < 0.001$), elevated recipient serum creatinine

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Table 1. Demographic and baseline characteristics of recipients and donors.

Variables	No pretransplant DM (n = 22 069)	With pretransplant DM (n = 8361)	*P*
Recipient			
Age (years)	55.0 (43.0-62.0)	59.0 (53.0-64.0)	< 0.001
BMI	26.5 (23.2-30.1)	28.7 (25.5-32.2)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.9-1.4)	1.2 (1.0-1.5)	< 0.001
Waiting time (months)	2.6 (0.7-8.1)	2.8 (0.8-8.4)	0.005
Sex (%)			< 0.001
Female	27.7	21.2	
Male	72.3	78.8	
Race/ethnicity (%)			< 0.001
White	67.7	63.9	
Black	21.2	21.9	
Hispanic	7.7	9.7	
Asian/Pacific islander	3.4	4.4	
Primary payer (%)			< 0.001
Private	51.6	45.1	
Public	48.4	54.9	
Cardiac diagnosis (%)			< 0.001
Dilated cardiomyopathy	85.4	92.1	
Restrictive cardiomyopathy	3.7	1.9	
Hypertrophic cardiomyopathy	3.3	0.9	
Ischemic cardiomyopathy	2.2	3.6	
Valvular cardiomyopathy	1.8	0.8	
Congenital cardiomyopathy	3.7	0.7	
HLA mismatch (%)			0.207
0-4	40.2	39.3	
5-6	59.8	60.7	
Cardiac support at time of listing (%)			
ECMO	1.5	0.9	< 0.001
IABP	10.1	10.3	0.661
IV inotropes	38.6	37.6	0.085
LVAD	36.1	42.3	< 0.001
RVAD ± LVAD or MCS unspecified	5.5	4.0	< 0.001
Steroids at discharge (%)	21 412 (97.6)	8117 (97.8)	0.560
Tacrolimus at discharge (%)	19 548 (89.1)	7416 (89.3)	0.669
Mycophenolate at discharge (%)	20 926 (95.4)	7888 (95.0)	0.115

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Table 1 continued. Demographic and baseline characteristics of recipients and donors.

Variables	No pretransplant DM (n = 22 069)	With pretransplant DM (n = 8361)	*P*
Biologics at discharge (%)	11 155 (50.9)	4223 (50.9)	0.988
Azathioprine at discharge (%)	240 (1.1)	113 (1.4)	0.054
Cyclosporine at discharge (%)	2113 (9.6)	791 (9.5)	0.773
Donor			
Age (years)	30.0 (22.0-40.0)	31.0 (23.0-41.0)	< 0.001
BMI	26.1 (23.1-30.1)	26.9 (23.9-31.0)	< 0.001
Serum creatinine (mg/dL)	1.0 (0.8-1.4)	1.0 (0.8-1.5)	< 0.001
Ischemic time (min)	192.0 (148.0-231.0)	194.0 (149.0-232.0)	0.140
Sex (%)			< 0.001
Female	29.7	26.0	
Male	70.3	74.0	
Race/ethnicity (%)			0.391
White	64.9	65.5	
Black	16.6	16.8	
Hispanic	16.7	16.1	
Asian/Pacific islander	1.9	1.7	
Donor cause of death (%)			0.782
Anoxia	28.4	28.7	
Stroke	18.3	18.6	
Head trauma	50.5	49.9	
Other/unspecified	2.8	2.7	
History of diabetes (%)			0.399
No	96.5	96.3	
Yes	3.5	3.7	
History of hypertension (%)			< 0.001
No	85.3	83.8	
Yes	14.7	16.2	
History of cancer (%)			0.843
No	98.6	98.6	
Yes	1.4	1.4	
Cardiac arrest after death (%)			0.178
No	93.1	93.5	
Yes	6.9	6.5	

Abbreviations: DM, diabetes mellitus; BMI, body mass index; HLA, human leukocyte antigen; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, injection of vein; LVAD, left ventricular assist device; RVAD, right ventricular assist device; MCS, mechanical circulatory support.

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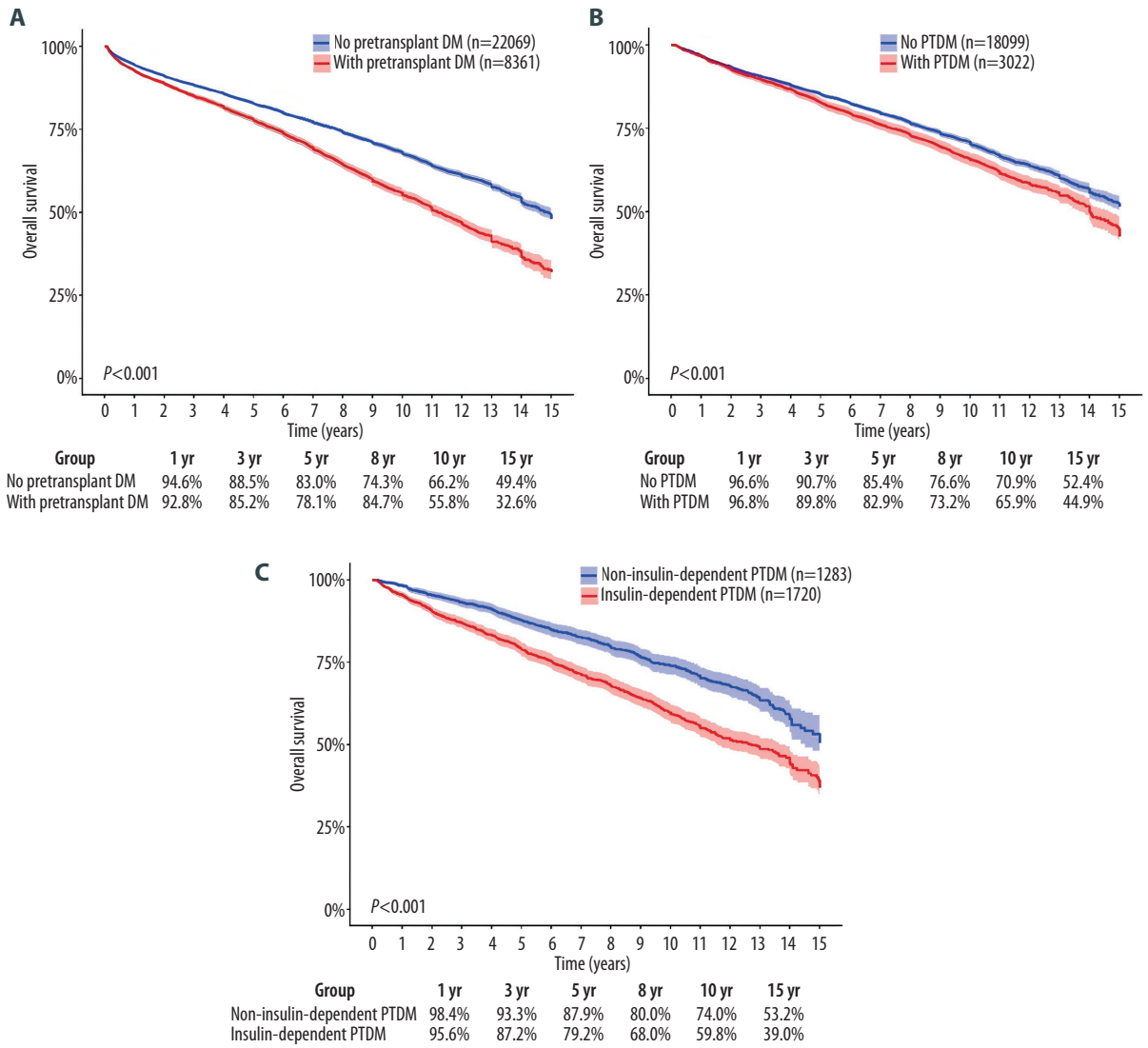

Figure 1. Kaplan-Meier survival curves of post-transplant patient survival stratified by diabetes status. (**A**) Comparison of survival between patients with pretransplant DM and those without pretransplant DM. (**B**) Comparison of survival between patients who developed PTDM and those who did not. (**C**) Comparison of survival between patients with non-insulin-dependent PTDM and those with insulin-dependent PTDM.

(HR = 1.08; 95% CI, 1.06-1.11; $P < 0.001$), Black recipient race (HR = 1.26; 95% CI, 1.19-1.33; $P < 0.001$), public insurance (HR = 1.32; 95% CI, 1.26-1.38; $P < 0.001$), RVAD ± LVAD or unspecified mechanical circulatory support at listing (HR = 1.25; 95% CI, 1.13-1.37; $P < 0.001$), older donor age (HR = 1.01; 95% CI, 1.01-1.01; $P < 0.001$), Black donor race (HR = 1.11; 95% CI, 1.05-1.18; $P = 0.001$), Asian/Pacific islander donor race (HR = 1.28; 95% CI, 1.08-1.50; $P = 0.003$), and biologics use at discharge (HR = 1.08; 95% CI, 1.03-1.13; $P = 0.002$). In contrast, steroids at discharge (HR = 0.85; 95% CI, 0.74-0.96; $P = 0.010$), tacrolimus at discharge (HR = 0.78; 95% CI, 0.72-0.86; $P = 0.004$), and mycophenolate at discharge (HR = 0.91; 95% CI, 0.86-0.97; $P < 0.001$) were associated with improved OS. **Table 3** shows the results of multivariate analyses.

Acute Complications

As shown in **Table 4**, several acute posttransplant complications differed significantly between recipients with and without pretransplant DM. Compared with those without DM, recipients with pretransplant DM had higher incidence of acute drug-treated rejection (11.1% vs 10.8%; $P < 0.001$), dialysis requirement (11.0% vs 8.8%; $P < 0.001$), drug-treated infections (27.9% vs 23.4%; $P < 0.001$), and other surgical procedures (18.0% vs

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Table 2. Univariate Cox regression analyses identifying factors significantly associated with patient survival, stratified by pretransplant DM, PTDM, and PTDM insulin dependence.

Risk factors	Pretransplant DM		PTDM		PTDM insulin dependence	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	P
Recipient						
Age (years)	1.009 (1.007-1.011)	< 0.001	1.004 (1.002-1.016)	< 0.001	1.00 (1.00-1.01)	0.193
BMI	1.00 (1.00-1.00)	0.757	1.00 (1.00-1.00)	0.810	1.00 (0.99-1.01)	0.730
Serum creatinine (mg/dL)	1.10 (1.09-1.12)	< 0.001	1.09 (1.06-1.12)	< 0.001	1.24 (1.10-1.39)	< 0.001
Waiting time (months)	1.002 (1.000-1.004)	0.026	1.00 (1.00-1.00)	0.628	1.00 (1.00-1.01)	0.589
Male recipients	1.08 (1.02-1.13)	0.006	1.10 (1.03-1.17)	0.006	1.06 (0.92-1.23)	0.412
With pretransplant DM	1.46 (1.39-1.53)	< 0.001	/		/	
With PTDM	/		1.19 (1.11-1.27)	< 0.001	/	
PTDM with insulin dependence	/		/		1.65 (1.45-1.87)	< 0.001
Race/ethnicity						
White	1.0		1.0		1.0	
Black	1.30 (1.23-1.37)	< 0.001	1.45 (1.35-1.55)	< 0.001	1.30 (1.13-1.50)	< 0.001
Hispanic	0.93 (0.86-1.02)	0.116	0.93 (0.83-1.05)	0.237	1.06 (0.83-1.36)	0.631
Asian/Pacific islander	0.92 (0.81-1.04)	0.193	0.98 (0.82-1.16)	0.782	1.02 (0.72-1.44)	0.924
Public payer	1.40 (1.34-1.46)	< 0.001	1.41 (1.33-1.49)	< 0.001	1.30 (1.15-1.47)	< 0.001
Cardiac diagnosis						
Dilated cardiomyopathy	1.0		1.0		1.0	
Restrictive cardiomyopathy	0.98 (0.85-1.12)	0.776	1.09 (0.93-1.28)	0.302	1.29 (0.83-1.98)	0.256
Hypertrophic cardiomyopathy	0.55 (0.46-0.67)	< 0.001	0.59 (0.47-0.73)	< 0.001	0.54 (0.30-0.98)	0.043
Ischemic cardiomyopathy	1.00 (0.87-1.14)	0.953	0.99 (0.82-1.20)	0.949	0.89 (0.59-1.35)	0.582
Valvular cardiomyopathy	0.80 (0.67-0.96)	0.018	0.89 (0.72-1.10)	0.270	0.90 (0.57-1.44)	0.666
Congenital cardiomyopathy	0.88 (0.76-1.02)	0.080	0.87 (0.74-1.03)	0.114	0.67 (0.44-1.02)	0.065
HLA mismatch 5-6	1.04 (0.99-1.09)	0.125	1.05 (0.99-1.12)	0.126	1.10 (0.96-1.26)	0.182
Cardiac support at time of listing (Ref. No.)						
ECMO	1.15 (0.89-1.47)	0.281	1.03 (0.73-1.44)	0.882	1.06 (0.40-2.82)	0.911
IABP	1.06 (0.97-1.15)	0.189	1.10 (0.98-1.23)	0.092	1.22 (0.96-1.55)	0.104
IV inotropes	1.01 (0.97-1.06)	0.599	1.05 (0.99-1.11)	0.113	1.10 (0.97-1.24)	0.147
LVAD	1.06 (1.02-1.12)	0.008	1.01 (0.95-1.07)	0.808	1.00 (0.87-1.14)	0.967

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Table 2 continued. Univariate Cox regression analyses identifying factors significantly associated with patient survival, stratified by pretransplant DM, PTDM, and PTDM insulin dependence.

Risk factors	Pretransplant DM		PTDM		PTDM insulin dependence	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	P
RVAD ± LVAD or MCS unspecified	1.13 (1.03-1.23)	0.008	1.09 (0.97-1.22)	0.133	1.18 (0.92-1.50)	0.191
Steroids at discharge	0.84 (0.74-0.96)	0.007	0.92 (0.78-1.08)	0.301	1.17 (0.77-1.79)	0.456
Tacrolimus at discharge	0.91 (0.86-0.97)	0.003	0.94 (0.87-1.01)	0.102	0.94 (0.80-1.09)	0.407
Mycophenolate at discharge	0.75 (0.69-0.82)	< 0.001	0.84 (0.75-0.95)	0.004	0.87 (0.69-1.10)	0.247
Biologics at discharge	1.08 (1.03-1.13)	< 0.001	1.07 (1.01-1.13)	0.028	1.04 (0.92-1.18)	0.524
Azathioprine at discharge	1.17 (0.98-1.40)	0.087	1.22 (0.97-1.55)	0.096	1.24 (0.79-1.95)	0.353
Cyclosporine at discharge	1.05 (0.98-1.11)	0.150	1.05 (0.97-1.13)	0.246	1.09 (0.92-1.28)	0.316
Donor						
Age (years)	1.011(1.009-1.012)	< 0.001	1.011 (1.009-1.014)	< 0.001	1.00 (1.00-1.01)	0.074
BMI	1.008(1.004-1.012)	< 0.001	1.010 (1.005-1.015)	< 0.001	1.01 (1.00-1.02)	0.089
Serum creatinine (mg/dL)	1.02 (1.00-1.03)	0.057	1.02 (1.00-1.04)	0.132	0.99 (0.94-1.04)	0.634
Ischemic time (min)	1.001 (1.000-1.001)	< 0.001	1.000 (1.000-1.001)	0.044	1.00 (1.00-1.00)	0.248
Male donor	1.04 (0.99-1.09)	0.125	1.05 (0.99-1.12)	0.102	1.08 (0.94-1.25)	0.258
Race/ethnicity						
White	1.0		1.0		1.0	
Black	1.10 (1.04-1.17)	0.001	1.11 (1.03-1.20)	0.008	0.98 (0.83-1.16)	0.794
Hispanic	1.02 (0.96-1.09)	0.469	1.04 (0.96-1.12)	0.383	1.04 (0.87-1.23)	0.691
Asian/Pacific islander	1.20 (1.03-1.41)	0.023	1.26 (1.03-1.54)	0.026	0.97 (0.62-1.51)	0.878
Donor cause of death						
Anoxia	1.0		1.0		1.0	
Stroke	1.10 (1.03-1.18)	0.004	1.15 (1.05-1.25)	0.002	0.94 (0.77-1.16)	0.564
Head trauma	0.97 (0.92-1.03)	0.373	0.99 (0.92-1.07)	0.880	1.00 (0.84-1.20)	0.968
Other/Unspecified	1.02 (0.89-1.17)	0.749	1.10 (0.92-1.31)	0.286	0.80 (0.54-1.20)	0.288
With history of diabetes	1.16 (1.03-1.30)	0.016	1.15 (0.98-1.34)	0.087	1.05 (0.74-1.49)	0.796
With history of hypertension	1.15 (1.09-1.23)	< 0.001	1.10 (1.01-1.19)	0.024	0.93 (0.77-1.12)	0.427
With history of cancer	1.23 (1.04-1.45)	0.018	1.17 (0.93-1.46)	0.184	1.25 (0.79-1.96)	0.344
Cardiac arrest after death	1.03 (0.94-1.12)	0.572	1.07 (0.95-1.20)	0.271	1.08 (0.85-1.38)	0.530

Abbreviations: DM, diabetes mellitus; HR, hazard ratio; PTDM, posttransplant diabetes mellitus; BMI, body mass index; HLA, human leukocyte antigen; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, injection of vein; LVAD, left ventricular assist device; RVAD, right ventricular assist device; MCS, mechanical circulatory support.

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Table 3. Multivariate Cox regression analyses identifying factors significantly associated with patient survival, stratified by pretransplant DM, PTDM, and PTDM insulin dependence.

Risk factors	Pretransplant DM		PTDM		PTDM insulin dependence	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Recipient						
Age (years)	1.01 (1.00-1.01)	< 0.001	1.00 (1.00-1.00)	0.237	/	
Serum creatinine (mg/dL)	1.08 (1.06-1.11)	< 0.001	1.07 (1.03-1.10)	< 0.001	1.21 (1.07-1.36)	0.003
Waiting time (months)	1.00 (1.00-1.00)	0.156	/		/	
Male recipients	1.03 (0.97-1.09)	0.297	1.08 (1.01-1.16)	0.029	/	
With pretransplant DM	1.39 (1.32-1.46)	< 0.001	/		/	
With PTDM	/		1.14 (1.06-1.22)	0.001	/	
PTDM with insulin dependence	/		/		1.58 (1.38-1.80)	< 0.001
Race/ethnicity						
White	1.0		1.0		1.0	
Black	1.26 (1.19-1.33)	< 0.001	1.36 (1.27-1.46)	< 0.001	1.17 (1.01-1.36)	0.031
Hispanic	0.88 (0.81-0.97)	0.007	0.87 (0.77-0.99)	0.034	1.02 (0.80-1.31)	0.877
Asian/Pacific islander	0.95 (0.83-1.08)	0.421	0.99 (0.83-1.19)	0.940	0.99 (0.70-1.40)	0.953
Public insurance	1.32 (1.26-1.38)	< 0.001	1.33 (1.25-1.42)	< 0.001	1.21 (1.07-1.38)	0.003
Cardiac diagnosis					/	
Dilated cardiomyopathy	1.0		1.0			
Restrictive cardiomyopathy	1.08 (0.93-1.24)	0.306	1.16 (0.98-1.37)	0.084		
Hypertrophic cardiomyopathy	0.71 (0.58-0.86)	< 0.001	0.67 (0.54-0.84)	< 0.001		
Ischemic cardiomyopathy	1.00 (0.87-1.15)	0.968	1.01 (0.83-1.23)	0.914		
Valvular cardiomyopathy	0.82 (0.68-0.99)	0.038	0.88 (0.71-1.10)	0.269		
Congenital cardiomyopathy	1.15 (0.98-1.34)	0.086	1.03 (0.86-1.23)	0.757		
Cardiac support at time of listing (Ref. No.)						
LVAD	1.03 (0.98-1.09)	0.247	/		/	
RVAD ± LVAD or MCS unspecified	1.25 (1.13-1.37)	< 0.001	/		/	
Steroids at discharge	0.85 (0.74-0.96)	0.010	/		/	
Tacrolimus at discharge	0.78 (0.72-0.86)	0.004	/		/	
Mycophenolate at discharge	0.91 (0.86-0.97)	< 0.001	0.83 (0.73-0.93)	0.002	/	
Biologics at discharge	1.08 (1.03-1.13)	0.002	1.06 (1.00-1.13)	0.049	/	
Donor						
Age (years)	1.01 (1.01-1.01)	< 0.001	1.011 (1.008-1.014)	< 0.001	/	
BMI	/		1.004 (0.998-1.009)	0.196	/	

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Table 3 continued. Multivariate Cox regression analyses identifying factors significantly associated with patient survival, stratified by pretransplant DM, PTDM, and PTDM insulin dependence.

Risk factors	Pretransplant DM		PTDM		PTDM insulin dependence	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Serum creatinine (mg/dL)	1.01 (0.99-1.02)	0.570	/		/	
Ischemic time (min)	/		1.001 (1.000-1.001)	0.010	/	
Race/ethnicity					/	
White	1.0		1.0			
Black	1.11 (1.05-1.18)	0.001	1.12 (1.03-1.22)	0.006		
Hispanic	1.05 (0.98-1.12)	0.148	1.07 (0.99-1.16)	0.108		
Asian/Pacific islander	1.28 (1.08-1.50)	0.003	1.28 (1.04-1.58)	0.020		
Donor cause of death					/	
Anoxia	1.0		1.0			
Stroke	0.98 (0.91-1.06)	0.575	0.99 (0.90-1.10)	0.883		
Head trauma	1.00 (0.94-1.06)	0.895	1.02 (0.94-1.10)	0.700		
Other/unspecified	1.00 (0.87-1.16)	0.994	1.12 (0.94-1.35)	0.210		
History of diabetes	1.08 (0.96-1.23)	0.210	0.94 (0.86-1.03)	0.210	/	
History of hypertension	1.00 (0.93-1.07)	0.979	/		/	
History of cancer	1.10 (0.92-1.32)	0.294	/		/	

Abbreviations: DM, diabetes mellitus; PTDM, posttransplant diabetes mellitus; HR, hazard ratio; BMI, body mass index; LVAD, left ventricular assist device; RVAD, right ventricular assist device; MCS, mechanical circulatory support.

15.7%; $P = 0.001$). The following complications showed no significant differences between the 2 groups: stroke (2.6% vs 2.3%; $P = 0.146$), permanent pacemaker implantation (3.0% vs 2.9%; $P = 0.621$), airway dehiscence (0.3% vs 0.2%; $P = 0.300$), cardiac re-operation (12.6% vs 11.6%; $P = 0.100$), and prolonged chest drainage over 2 weeks (6.5% vs 5.7%; $P = 0.087$). Notably, data for some variables, including infection-related and surgical complications, were only recorded up to March 25, 2015, due to subsequent missing data in the registry.

Causes of Mortality

The causes of mortality are shown in **Table 4**. Recipients with pretransplant DM had significantly higher proportions of deaths attributed to infection (19.8% vs 16.1%; $P = 0.001$), pulmonary disease (12.0% vs 8.1%; $P < 0.001$), and cerebrovascular events (5.3% vs 3.9%; $P = 0.020$) than those without pretransplant DM. In contrast, cardiovascular events (18.7% vs 25.7%; $P < 0.001$), and graft failure (10.7% vs 14.3%; $P < 0.001$) were more common causes of death among recipients without pretransplant DM. Other causes of death, such as hemorrhage (1.5% vs 1.4%; $P = 0.822$), malignancy (15.3% vs 15.1%; $P = 0.843$), other organ failure (13.9% vs 12.5%; $P = 0.139$), and other causes (2.9% vs 3.0%; $P = 0.860$), showed no statistically significant differences between the 2 groups.

Subgroup Analyses/Comparison Between Recipients With and Without PTDM

Stratified analyses were undertaken to evaluate the association between PTDM and its insulin dependence with heart transplant outcomes.

Baseline Characteristics

The characteristics of patients without PTDM (n = 18 099) and with PTDM (n = 3022) are summarized in **Table 5**. Recipients who developed PTDM had higher BMI (27.5 [24.1-31.2] vs 26.3 [23.1-29.9]; $P < 0.001$) and serum creatinine levels (1.2 [0.9-1.5] vs 1.1 [0.9-1.4] mg/dL; $P < 0.001$) than those without PTDM. A greater proportion of patients with PTDM were male (74.7% vs 72.1%; $P = 0.003$) and Black (25.2% vs 20.4%; $P < 0.001$), with a lower proportion identifying as White (63.9% vs 68.6%). Public insurance was more common in the PTDM

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Table 4. Acute post-Tx complications and causes of death stratified by pre-Tx DM, PTDM, and PTDM insulin dependence.

Events	No pre-Tx DM (n = 22 069)	With pre-Tx DM (n = 8361)	*P*	No PTDM (n = 18 099)	With PTDM (n = 3022)	*P*	NID PTDM (n = 1283)	ID PTDM (n = 1720)	*P*
Acute post-Tx complications (%)									
Any acute drug-treated rejection	10.8	11.1	< 0.001	10.6	12.4	0.003	10.4	13.8	0.006
Stroke	2.3	2.6	0.146	2.1	1.8	0.229	1.5	2.0	0.313
Dialysis	8.8	11.0	< 0.001	7.8	7.8	0.961	6.3	8.9	0.009
Permanent pacemaker	2.9	3.0	0.621	2.9	3.2	0.490	3.6	2.8	0.208
Airway dehiscence	0.2	0.3	0.300	0.2	0.2	0.744	0.2	0.1	0.433
Any drug-treated infection*	23.4	27.9	< 0.001	21.6	25.0	0.002	22.6	27.2	0.022
Cardiac re-operation*	11.6	12.6	0.100	11.0	9.8	0.141	8.7	10.8	0.120
Other surgical procedures*	15.7	18.0	0.001	14.7	14.9	0.882	12.9	16.4	0.036
Chest drain > 2 weeks*	5.7	6.5	0.087	5.5	4.3	0.039	4.0	4.6	0.509
Causes of death (%)									
Graft failure	14.3	10.7	< 0.001	15.3	13.4	0.196	14.3	12.9	0.598
Infection	16.1	19.8	0.001	13.3	14.2	0.527	11.9	15.6	0.176
Cardiovascular event	25.7	18.7	< 0.001	27.3	28.2	0.626	23.4	30.8	0.036
Pulmonary disease	8.1	12.0	< 0.001	8.3	8.1	0.888	10.3	7.1	0.128
Cerebrovascular event	3.9	5.3	0.020	4.1	2.2	0.014	2.8	1.9	0.425
Hemorrhage	1.4	1.5	0.822	1.1	1.3	0.502	1.6	1.2	0.706
Malignancy	15.1	15.3	0.843	17	17	0.982	20.6	14.3	0.029
Other organ failure	12.5	13.9	0.139	10.6	13	0.066	11.5	13.9	0.356
Other causes	3.0	2.9	0.860	3.2	2.7	0.452	3.6	2.3	0.311

Abbreviations: post-Tx, posttransplant; pre-Tx pretransplant, DM diabetes mellitus; PTDM, posttransplant diabetes mellitus; NID-PTDM, non–insulin-dependent posttransplant diabetes mellitus; ID-PTDM, insulin-dependent posttransplant diabetes mellitus.
* These data were only recorded up to March 25, 2015, as they are entirely missing beyond this date.

group (50.5% vs 47.9%; $P = 0.008$). Steroid use at discharge was comparable between the PTDM and non-PTDM groups (98.0% vs 97.7%; $P = 0.216$). Compared with non-PTDM recipients, those with PTDM had significantly lower rates of tacrolimus use (85.6% vs 90.0%; $P < 0.001$), mycophenolate use (94.2% vs 95.8%; $P < 0.001$), and biologics use (47.4% vs 51.3%; $P < 0.001$) at discharge, but higher rates of azathioprine use (1.5% vs 1.0%; $P = 0.028$) and cyclosporine use (13.0% vs 9.0%; $P < 0.001$). Donor BMI was also slightly higher in the PTDM group (26.5 [23.2-30.4] vs 26.1 [23.1-30.1]; $P = 0.002$), and recipients in the PTDM group were more likely to receive hearts from donors with head trauma (55.5% vs 49.7%; $P < 0.001$). Other clinical and donor characteristics were comparable between groups.

Posttransplant Outcomes

Kaplan-Meier survival curves revealed that OS was significantly better in patients in the non-PTDM group than in those in the PTDM group. The 1-, 5-, and 10-year OS rates were 96.8%, 85.4%, and 70.9%, respectively, in the non-PTDM group vs 96.8%, 82.9%, and 65.9%, respectively, in the PTDM group (log-rank $P < 0.001$, **Figure 1B**). The results of the univariate Cox regression analyses are presented in **Table 2**. PTDM was

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Table 5. Demographic and baseline characteristics of recipients and donors stratified by PTDM status.

Variable	No PTDM (n = 18 099)	With PTDM (n = 3022)	*P*
Recipient			
Age (years)	55.0 (43.0-62.0)	54.0 (45.0-61.0)	0.365
BMI	26.3 (23.1-29.9)	27.5 (24.1-31.2)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.9-1.4)	1.2 (0.9-1.5)	< 0.001
Waiting time (months)	2.6 (0.7-8.1)	2.5 (0.7-8.0)	0.547
Sex (%)			0.003
Female	27.9	25.3	
Male	72.1	74.7	
Race/ethnicity (%)			< 0.001
White	68.6	63.9	
Black	20.4	25.2	
Hispanic	7.7	7.3	
Asian/Pacific islander	3.3	3.6	
Primary payer (%)			0.008
Private	52.1	49.5	
Public	47.9	50.5	
Cardiac diagnosis (%)			< 0.001
Dilated cardiomyopathy	85.0	88.0	
Restrictive cardiomyopathy	4.0	2.1	
Hypertrophic cardiomyopathy	3.4	2.2	
Ischemic cardiomyopathy	2.1	2.4	
Valvular cardiomyopathy	1.8	1.7	
Congenital cardiomyopathy	3.7	3.5	
HLA mismatch (%)			0.941
0-4	40.1	40.1	
5-6	59.9	59.9	
Cardiac support at time of listing (%)			
ECMO	1.6	0.5	< 0.001
IABP	10.5	8.2	< 0.001
IV inotropes	37.9	42.4	< 0.001
LVAD	36.8	32.3	< 0.001
RVAD ± LVAD or MCS unspecified	5.3	5.5	0.744
Steroids at discharge (%)	97.7	98.0	0.216
Tacrolimus at discharge (%)	90.0	85.6	< 0.001
Mycophenolate at discharge (%)	95.8	94.2	< 0.001

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Table 5 continued. Demographic and baseline characteristics of recipients and donors stratified by PTDM status.

Variable	No PTDM (n = 18 099)	With PTDM (n = 3022)	*P*
Biologics at discharge (%)	51.3	47.4	< 0.001
Azathioprine at discharge (%)	1.0	1.5	0.028
Cyclosporine at discharge (%)	9.0	13.0	< 0.001
Donor			
Age (years)	30.0 (22.0-40.0)	29.0 (22.0-40.0)	0.229
BMI	26.1 (23.1-30.1)	26.5 (23.2-30.4)	0.002
Serum creatinine (mg/dL)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.389
Ischemic time (min)	192.0 (148.0-230.0)	193.0 (151.0-231.0)	0.496
Sex (%)			0.081
Female	29.7	28.1	
Male	70.3	71.9	
Race/ethnicity (%)			0.009
White	64.7	66.2	
Black	16.5	17.4	
Hispanic	16.9	14.5	
Asian/Pacific islander	1.8	2.0	
Donor cause of death (%)			< 0.001
Anoxia	29.8	20.4	
Stroke	17.8	20.7	
Head trauma	49.7	55.5	
Other/Unspecified	2.7	3.4	
History of diabetes (%)			0.876
No	96.5	96.4	
Yes	3.5	3.6	
History of hypertension (%)			0.991
No	85.4	85.4	
Yes	14.6	14.6	
History of cancer (%)			0.500
No	98.7	98.5	
Yes	1.3	1.5	
Cardiac arrest after death (%)			0.745
No	93.1	92.9	
Yes	6.9	7.1	

Abbreviations: PTDM, posttransplant diabetes mellitus; BMI, body mass index; HLA, human leukocyte antigen; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; RVAD, right ventricular assist device; MCS, mechanical circulatory support.

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Table 6. Multivariate logistic regression analysis of factors associated with PTDM and insulin-dependent PTDM.

Variables	PTDM		Insulin-dependent PTDM	
	OR (95% CI)	P	OR (95% CI)	P
Recipient				
BMI	/		1.01 (0.99-1.02)	0.438
Serum creatinine (mg/dL)	1.04 (0.99-1.11)	0.147	1.27 (1.07-1.51)	0.006
Male recipients	1.11 (1.01-1.22)	0.027	/	
Race/ethnicity				
White	1.0		1.0	
Black	1.40 (1.27-1.54)	<0.001	1.50 (1.25-1.79)	<0.001
Hispanic	1.01 (0.86-1.18)	0.950	1.09 (0.82-1.46)	0.554
Asian/Pacific islander	1.23 (0.99-1.52)	0.064	0.81 (0.54-1.20)	0.285
Public insurance	1.08 (0.99-1.17)	0.074	1.29 (1.11-1.50)	0.001
Cardiac diagnosis			/	
Dilated cardiomyopathy	1.0			
Restrictive cardiomyopathy	0.50 (0.38-0.65)	<0.001		
Hypertrophic cardiomyopathy	0.64 (0.49-0.83)	0.001		
Ischemic cardiomyopathy	1.15 (0.89-1.50)	0.295		
Valvular cardiomyopathy	0.89 (0.65-1.21)	0.448		
Congenital cardiomyopathy	0.98 (0.79-1.22)	0.866		
Cardiac support at time of listing (Ref. No.)				
ECMO	0.37 (0.22-0.61)	<0.001	/	
IABP	0.72 (0.62-0.83)	<0.001	/	
IV inotropes	1.13 (1.03-1.24)	0.008	/	
LVAD	0.76 (0.69-0.84)	<0.001	/	
Tacrolimus at discharge	0.85 (0.66-1.10)	0.206	/	
Mycophenolate at discharge	0.82 (0.68-1.00)	0.051	/	
Biologics at discharge	0.82 (0.76-0.89)	<0.001	/	
Azathioprine at discharge	1.11 (0.76-1.62)	0.588	/	
Cyclosporine at discharge	1.17 (0.89-1.52)	0.258	/	
Donor				
BMI	1.01 (1.00-1.02)	0.005	1.01 (1.00-1.03)	0.080
Race/ethnicity			/	
White	1.0			
Black	0.97 (0.87-1.08)	0.598		

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Table 6 continued. Multivariate logistic regression analysis of factors associated with PTDM and insulin-dependent PTDM.

Variables	PTDM		Insulin-dependent PTDM	
	OR (95% CI)	P	OR (95% CI)	P
Hispanic	0.78 (0.70-0.88)	<0.001		
Asian/Pacific islander	1.04 (0.78-1.38)	0.816		
Donor cause of death			/	
Anoxia	1.0			
Stroke	1.67 (1.48-1.90)	<0.001		
Head trauma	1.64 (1.48-1.82)	<0.001		
Other/unspecified	1.87 (1.48-2.36)	<0.001		

Abbreviations: PTDM, posttransplant diabetes mellitus; OR, odds ratio; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, injection of vein; LVAD, left ventricular assist device; BMI, body mass index.

associated with a significantly increased risk of posttransplant mortality (HR = 1.19; 95% CI, 1.11-1.27; $P < 0.001$). After adjusting for potential confounders, PTDM remained independently associated with worse posttransplant OS (HR = 1.14; 95% CI, 1.06-1.22; $P = 0.001$), suggesting an adverse prognostic impact of PTDM. Additional adverse prognostic factors included elevated recipient serum creatinine level (HR = 1.07; 95% CI, 1.03-1.10; $P < 0.001$), male sex (HR = 1.08; 95% CI, 1.01-1.16; $P = 0.029$), Black recipient race (HR = 1.36; 95% CI, 1.27-1.46; $P < 0.001$), public insurance (HR = 1.33; 95% CI, 1.25-1.42; $P < 0.001$), biologics use at discharge (HR = 1.06; 95% CI, 1.00-1.13; $P = 0.049$), older donor age (HR = 1.011; 95% CI, 1.008-1.014; $P < 0.001$), prolonged ischemic time (HR = 1.001; 95% CI, 1.000-1.001; $P = 0.010$), Black donor race (HR = 1.12; 95% CI, 1.03-1.22; $P = 0.006$), and Asian/Pacific islander donor race (HR = 1.28; 95% CI, 1.04-1.58; $P = 0.020$). By contrast, hypertrophic cardiomyopathy (HR = 0.67; 95% CI, 0.54-0.84; $P < 0.001$) and mycophenolate use at discharge (HR = 0.83; 95% CI, 0.73-0.93; $P = 0.002$) were associated with reduced mortality risk. **Table 3** shows the results of multivariate analyses.

Acute Complications

As shown in **Table 4**, patients in the PTDM group experienced significantly more acute complications than those in the non-PTDM group. These included acute drug-treated rejection (12.4% vs 10.6; $P = 0.003$), and drug-treated infection (25.0% vs 21.6%; $P = 0.002$).

Causes of Mortality

The causes of mortality among recipients with and without PTDM are summarized in **Table 4**. While most causes of death were similar between the 2 groups, cerebrovascular mortality was significantly lower in the PTDM group (2.2% vs 4.1%; $P = 0.014$). Infection-related, cardiovascular, and malignancy-related mortality did not differ significantly between the groups.

Factors Associated with PTDM

The results of the multivariable logistic regression analysis are shown in **Table 6.** In the model evaluating factors associated with PTDM after heart transplantation, immunosuppressive strategies at discharge were differentially associated with the odds of PTDM. Among maintenance immunosuppressants, tacrolimus use at discharge was not independently associated with PTDM (odds ratio [OR] = 0.85; 95% CI, 0.66-1.10; $P = 0.206$). Similarly, azathioprine (OR = 1.11; 95% CI, 0.76-1.62; $P = 0.588$) and cyclosporine (OR = 1.17; 95% CI, 0.89-1.52; $P = 0.258$) showed no significant associations with PTDM. Mycophenolate mofetil showed a nonsignificant trend toward lower odds of PTDM (OR = 0.82; 95% CI, 0.68-1.00; $P = 0.051$). Notably, biologics use at discharge was independently associated with significantly lower odds of PTDM (OR = 0.82; 95% CI, 0.76-0.89; $P < 0.001$).

Sensitivity Analysis for Immortal Time Bias

To minimize potential immortal time bias, a sensitivity analysis excluding recipients who died within 90 days after transplantation was performed. Univariate and multivariate Cox regression analyses were reperformed in the remaining 20 993 patients, and the multivariate results demonstrated that PTDM remained an independent risk factor for OS (HR = 1.13; 95% CI, 1.05-1.21; $P = 0.001$, **Table 7**).

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Table 7. Sensitivity analysis using multivariate Cox regression to identify factors associated with patient survival after immortal time bias correction.

Risk factors	Non-PTDM/PTDM	
	HR (95% CI)	*P*
Recipient		
Age (years)	1.00 (1.00-1.00)	0.525
Serum creatinine (mg/dL)	1.07 (1.03-1.10)	< 0.001
Male recipients	1.06 (0.98-1.14)	0.132
With PTDM	1.13 (1.05-1.21)	0.001
Race/ethnicity		
White	1.0	
Black	1.37 (1.27-1.48)	< 0.001
Hispanic	0.88 (0.78-1.00)	0.049
Asian/Pacific islander	1.02 (0.85-1.22)	0.838
Public insurance	1.34 (1.26-1.42)	< 0.001
Cardiac diagnosis		
Dilated cardiomyopathy	1.0	
Restrictive cardiomyopathy	1.13 (0.96-1.34)	0.155
Hypertrophic cardiomyopathy	0.68 (0.54-0.84)	0.001
Ischemic cardiomyopathy	1.00 (0.82-1.22)	0.986
Valvular cardiomyopathy	0.88 (0.71-1.10)	0.257
Congenital cardiomyopathy	1.03 (0.86-1.23)	0.754
Mycophenolate at discharge	0.88 (0.78-0.99)	0.038
Donor		
Age (years)	1.01 (1.01-1.01)	< 0.001
Male donors	1.08 (1.00-1.17)	0.043
BMI	1.01 (1.00-1.01)	0.092
Race/ethnicity		
White	1.0	
Black	1.11 (1.03-1.21)	0.011
Hispanic	1.07 (0.98-1.16)	0.134
Asian/Pacific islander	1.29 (1.05-1.60)	0.018
Donor cause of death		
Anoxia	1.0	
Stroke	1.01 (0.91-1.11)	0.914
Head trauma	1.01 (0.93-1.10)	0.798
Other/Unspecified	1.08 (0.90-1.30)	0.389
History of hypertension	0.96 (0.88-1.05)	0.389

Abbreviations: PTDM, posttransplant diabetes mellitus; HR, hazard ratio; BMI, body mass index.

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Table 8. Demographics of baseline characteristics of recipients and donors stratified by insulin dependence in patients with PTDM.

Variables	Non–insulin-dependent PTDM (n = 1283)	Insulin-dependent PTDM (n = 1720)	*P*
Recipient			
Age (years)	55.0 (44.0-61.0)	54.0 (45.0-62.0)	0.863
BMI	27.3 (23.9-30.9)	27.8 (24.4-31.3)	0.015
Serum creatinine (mg/dL)	1.1 (0.9-1.4)	1.2 (1.0-1.5)	< 0.001
Waiting time (months)	2.3 (0.6-8.4)	2.6 (0.8-7.8)	0.261
Sex (%)			0.474
Female	24.6	25.7	
Male	75.4	74.3	
Race/ethnicity (%)			< 0.001
White	68.2	60.6	
Black	20.3	29.0	
Hispanic	7.2	7.3	
Asian/Pacific islander	4.3	3.0	
Primary payer (%)			< 0.001
Private	53.9	46.0	
Public	46.1	54.0	
Cardiac diagnosis (%)			0.074
Dilated cardiomyopathy	88.7	87.5	
Restrictive cardiomyopathy	2.7	1.8	
Hypertrophic cardiomyopathy	2.4	2.1	
Ischemic cardiomyopathy	2.1	2.6	
Valvular cardiomyopathy	1.6	1.8	
Congenital cardiomyopathy	2.6	4.3	
HLA mismatch (%)			0.281
0-4	41.1	39.1	
5-6	58.9	60.9	
Cardiac support at time of listing (%)			
ECMO	0.6	0.4	0.405
IABP	8.2	8.1	0.919
IV inotropes	43.8	41.2	0.147
LVAD	31.4	33.1	0.333
RVAD ± LVAD or MCS unspecified	5.3	5.7	0.637
Steroids at discharge (%)	98.2	98.1	0.377
Tacrolimus at discharge (%)	86.1	85.7	0.424
Mycophenolate at discharge (%)	94.3	94.2	0.765
Biologics at discharge (%)	48.7	47.5	0.122

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Table 8 continued. Demographics of baseline characteristics of recipients and donors stratified by insulin dependence in patients with PTDM.

Variables	Non–insulin-dependent PTDM (n = 1283)	Insulin-dependent PTDM (n = 1720)	*P*
Azathioprine at discharge (%)	1.4	1.5	0.699
Cyclosporine at discharge (%)	12.1	12.9	0.097
Donor			
Age (years)	29.0 (22.0-40.0)	29.0 (22.0-41.0)	0.684
BMI	26.1 (23.1-30.2)	26.6 (23.3-30.8)	0.038
Serum creatinine (mg/dL)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.766
Ischemic time (min)	192.0 (152.0-229.0)	193.0 (150.0-232.0)	0.658
Sex (%)			0.139
Female	26.7	29.2	
Male	73.3	70.8	
Race/ethnicity (%)			0.990
White	66.2	66.3	
Black	17.3	17.4	
Hispanic	14.4	14.5	
Asian/Pacific islander	2.0	1.9	
Donor cause of death (%)			0.564
Anoxia	19.3	21.1	
Stroke	21.4	20.3	
Head trauma	56.1	54.9	
Other/Unspecified	3.2	3.6	
History of diabetes (%)			0.349
No	96.8	96.2	
Yes	3.2	3.8	
History of hypertension (%)			0.371
No	84.7	85.8	
Yes	15.3	14.2	
History of cancer (%)			0.595
No	98.4	98.6	
Yes	1.6	1.4	
Cardiac arrest after death (%)			0.361
No	92.4	93.3	
Yes	7.6	6.7	

Abbreviations: PTDM, posttransplant diabetes mellitus; BMI, body mass index; HLA, human leukocyte antigen; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; RVAD, right ventricular assist device; MCS, mechanical circulatory support.

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Comparison Between Recipients With Insulin-Dependent and Non–Insulin-Dependent PTDM

Baseline Characteristics

Among patients with PTDM, those who required insulin therapy had slightly higher BMI (27.8 [24.4-31.3] vs 27.3 [23.9-30.9] kg/m^2; $P = 0.015$) and higher serum creatinine levels (1.2 [1.0-1.5] vs 1.1 [0.9-1.4] mg/dL; $P < 0.001$). They were more likely to be Black (29.0% vs 20.3%; $P < 0.001$) and were more frequently supported by public insurance (54.0% vs 46.1%; $P < 0.001$). The baseline characteristics of the 2 groups are summarized in **Table 8**.

Posttransplant Outcomes

Kaplan-Meier survival curves revealed that OS was significantly better in the patients with non–insulin-dependent PTDM than in those with insulin-dependent PTDM. The 1-, 5-, and 10-year OS rates were 98.4%, 87.9%, and 74.0%, respectively, in the non–insulin-dependent PTDM group and 95.6%, 79.2%, and 59.8%, respectively, in the insulin-dependent PTDM group (log-rank $P < 0.001$, **Figure 1C**). The results of the univariate Cox regression analyses are presented in **Table 2**. Insulin dependence among patients with PTDM was associated with significantly increased mortality risk (HR = 1.65; 95% CI, 1.45-1.87; $P < 0.001$), which was stronger than the effect of PTDM alone. This association remained robust after adjustment. In the adjusted analysis, insulin-dependent PTDM remained independently associated with increased risk of posttransplant death (HR = 1.58; 95% CI, 1.38-1.80; $P < 0.001$). Higher recipient serum creatinine levels (HR = 1.21; 95% CI, 1.07-1.36; $P = 0.003$), Black recipient race (HR = 1.17; 95% CI, 1.01-1.36; $P = 0.031$), and public insurance (HR = 1.21; 95% CI, 1.07-1.38; $P = 0.003$) were also independently associated with increased mortality. **Table 3** shows the results of multivariate analyses.

Acute Complications

As shown in **Table 4**, compared with those with non–insulin-dependent PTDM, patients with insulin-dependent PTDM had higher rates of acute rejection (13.8% vs 10.4%; $P = 0.006$), dialysis requirement (8.9% vs 6.3%; $P = 0.009$), drug-treated infections (27.2% vs 22.6%; $P = 0.022$), and other surgical procedures (16.4% vs 12.9%; $P = 0.036$). The rates of other complications did not differ significantly.

Causes of Mortality

As summarized in **Table 4**, recipients with insulin-dependent PTDM had a higher rate of cardiovascular death than those with non–insulin-dependent PTDM (30.8% vs 23.4%; $P = 0.036$), whereas malignancy-related mortality was more common in the non–insulin-dependent PTDM group (14.3% vs 20.6%; $P = 0.029$). No significant differences were observed in other causes of death.

Factors Associated with Insulin-Dependent PTDM

The results of the multivariable logistic regression analysis are shown in **Table 6**. Higher recipient serum creatinine levels were independently associated with significantly higher odds of insulin-dependent PTDM (OR = 1.27; 95% CI, 1.07-1.51; $P = 0.006$). Black recipients had significantly higher odds of insulin-dependent PTDM (OR = 1.50; 95% CI, 1.25-1.79; $P < 0.001$) than White recipients. Having public insurance was also independently associated with higher odds of insulin-dependent PTDM compared with having private insurance (OR = 1.29; 95% CI, 1.11-1.50; $P = 0.001$). In contrast, recipient BMI and donor BMI were not significantly associated with insulin-dependent PTDM after adjustment.

Discussion

Previous multicenter clinical studies have indicated that the prevalence of pretransplant DM gradually increased from 16.7% in the 1990s to 27.5% in the most recent decade [5]. The present study revealed a 27.0% prevalence of pretransplant DM among heart transplant recipients, which is consistent with prior findings. The incidence of DM in the heart transplant population has progressively risen over recent decades. The increasing prevalence of pretransplant DM among heart transplant recipients may partly reflect the growing global burden of metabolic diseases, including obesity, hypertension, and DM, which are increasingly recognized contributors to end-stage heart failure and dilated cardiomyopathy. Consistent with this concept, dilated cardiomyopathy remained the predominant diagnosis in our cohort and was even more prevalent among recipients with pretransplant DM. These findings suggest that metabolic dysfunction may contribute substantially to the contemporary heart transplant population [5].

In this large, nationally representative cohort of heart transplant recipients, we found DM was more prevalent among men, older adults, and those with lower socioeconomic status, consistent with previous reports [23,24]. Compared with recipients without PTDM, those with PTDM showed no significant age differences, but were more frequently male, had higher BMI, and were disproportionately represented among lower-income groups. Within the PTDM cohort, patients with insulin-dependent PTDM did not differ in age or sex from those with non–insulin-dependent PTDM, but demonstrated higher BMI and were more frequently from lower-income backgrounds. The results of our study also demonstrated that both pretransplant DM and PTDM were independently associated

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with worse long-term survival. Importantly, insulin dependence among PTDM patients conferred the highest risk, exceeding that of PTDM alone. The above findings indicate that diabetes, regardless of whether it occurs before or after heart transplantation, is associated with poor posttransplant outcomes.

Our results confirm and extend prior reports that pretransplant DM adversely affects heart transplant outcomes. Earlier single-center and registry-based studies demonstrated increased risks of mortality, renal dysfunction, and infection among recipients with DM, which are consistent with our findings [4,11,25]. In our analysis, pretransplant DM remained a robust independent predictor of mortality after adjustment for recipient and donor factors.

We found that, compared with recipients without pretransplant DM, those with pretransplant DM exhibited significantly higher rates of posttransplant infections. Similarly, higher infection rates were also observed among recipients with PTDM compared with those without PTDM, as well as among recipients with insulin-dependent PTDM compared with those with non–insulin-dependent PTDM. Moreover, infection-related and pulmonary disease-related mortality was also significantly more frequent in the pretransplant DM group. Notably, most pulmonary disease–related deaths were likewise attributable to infection. These findings suggest that infection represents an important contributor to the inferior posttransplant outcomes observed in patients with pretransplant DM, PTDM, and insulin-dependent PTDM.

The potential mechanisms underlying the increased susceptibility to infections in DM include the following pathways. First, hyperglycemia can directly impair the chemotactic, phagocytic, and bactericidal functions of neutrophils and macrophages, and can lead to dysregulation of T-cell subsets, thereby affecting cellular immunity. The accumulation of advanced glycation end products may activate Toll-like receptor 4, promote the release of pro-inflammatory cytokines, impair immune cell function, and contribute to a chronic inflammatory state [26]. Second, diabetes-induced microangiopathy results in poor tissue perfusion and hypoxia, which hinders the recruitment of leukocytes to infection sites and reduces the concentration of antibiotics in tissues [27]. Third, persistent hyperglycemia and lipotoxicity in PTDM upregulate the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IFN-γ, which further exacerbate insulin resistance, pancreatic β-cell dysfunction and vascular endothelial injury [17].

Innate immunity acts as an initial trigger of posttransplant complications. Ischemia-reperfusion injury, surgical stress, and metabolic disorders such as PTDM activate neutrophils, macrophages, and the complement system, leading to the release of damage-associated molecular patterns and pro-inflammatory mediators to initiate local tissue inflammation and allograft injury [28,29]. Adaptive immune responses, characterized by activation of T and B lymphocytes, further amplify immune damage. Imbalanced differentiation of Th1/Th17 cells and impaired regulatory T-cell function promote allograft rejection, while dysregulated B-cell activity increases the risk of antibody-mediated injury [30,31]. Collectively, aberrant innate and adaptive immune activation synergistically increase the susceptibility to infection, allograft dysfunction and other adverse posttransplant complications.

Our study demonstrated that both pretransplant DM and insulin-dependent PTDM were significantly associated with a higher incidence of posttransplant acute dialysis-requiring complications. The potential reasons for posttransplant renal failure in diabetes include: first, diabetic kidney disease, where many patients with diabetes already have varying degrees of diabetic nephropathy (ranging from microalbuminuria to clinical nephropathy) prior to transplantation [32]. The stress of transplant surgery, intraoperative hypotension, and the use of contrast agents can further impair already compromised kidneys [33]. Second, calcineurin inhibitors, such as tacrolimus and cyclosporine, exhibit nephrotoxicity, causing renal vasoconstriction and a decline in glomerular filtration rate [34].

Our study further evaluated the prognostic effect of steroids and immunosuppressive agents in heart transplant recipients. In the overall cohort, multivariable Cox regression analysis demonstrated that the use of steroids, tacrolimus, and mycophenolate at discharge was independently associated with improved OS, whereas the use of biologics at discharge was independently associated with worse OS. In the subgroup analysis stratified by PTDM status, mycophenolate remained a protective factor and biologics remained a risk factor, while no significant associations were observed in the subgroup analysis stratified by insulin dependence among recipients with PTDM.

The observed protective association of steroids may reflect the importance of adequate maintenance immunosuppression in preventing graft rejection after heart transplantation [35,36]. Although long-term steroid exposure is associated with metabolic complications, appropriate steroid therapy may still improve survival through better control of immune-mediated graft injury [37]. Similarly, tacrolimus was identified as a protective factor despite its known diabetogenic effects. As a calcineurin inhibitor, tacrolimus provides potent suppression of T-cell activation and has been associated with lower rejection rates and improved graft survival compared with cyclosporine-based regimens [38]. These findings suggest that the survival benefit associated with more effective immunologic control may outweigh the adverse metabolic effects in selected recipients.

The use of mycophenolate at discharge consistently showed a protective association in both the overall cohort and the

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subgroup analysis stratified by PTDM status. Mycophenolate effectively inhibits lymphocyte proliferation while exhibiting relatively lower nephrotoxic and diabetogenic potential, making it an important component of long-term maintenance immunosuppression [39,40]. In addition, recipients able to maintain mycophenolate therapy may represent a more clinically stable population with better treatment tolerance.

In contrast, biologics at discharge were independently associated with poor prognosis. However, this association should be interpreted cautiously because biologics are often administered to recipients with severe rejection episodes or high immunologic risk [41]. Therefore, the observed adverse association may reflect confounding by indication rather than a direct harmful effect of biologic therapy itself.

Interestingly, the use of biologics at discharge was also independently associated with a lower risk of PTDM. This seemingly paradoxical finding may reflect the distinct metabolic and clinical effects of biologic therapies in heart transplantation. From a metabolic perspective, some biologics may attenuate chronic inflammation and improve insulin sensitivity, thereby reducing PTDM risk [42]. In addition, the use of biologics may facilitate reductions in steroids or calcineurin inhibitor exposure, both of which are strongly associated with PTDM development [43]. Collectively, these findings suggest that biologic therapies may be associated with favorable metabolic profiles while simultaneously identifying recipients with more severe underlying clinical conditions, which could explain their protective association with PTDM but adverse association with long-term survival.

The prognostic significance of immunosuppressive agents was no longer observed in the subgroup analysis stratified by insulin dependence among recipients with PTDM. This may be partly explained by reduced statistical power after subgroup stratification. Moreover, insulin-dependent PTDM may represent a more severe metabolic phenotype characterized by greater insulin resistance, inflammation, and cardiovascular risk, which could outweigh the prognostic impact of different immunosuppressive regimens [44,45].

Our multivariable logistic regression analysis identified elevated pretransplant serum creatinine levels, Black recipient race, and public insurance coverage as independent risk factors for insulin-dependent PTDM, suggesting that these high-risk groups warrant intensive glycemic surveillance after heart transplantation. Risk-stratified and individualized management is central to PTDM care. Comprehensive assessment using oral glucose tolerance tests (OGTTs), fasting and postprandial glucose levels, HbA1c, serum C-peptide levels, and endogenous insulin secretion status may help evaluate residual pancreatic β-cell function [46]. According to the 2022 International Consensus on Post-Transplantation Diabetes Mellitus, the OGTT is recommended for diagnosis and screening when starting on the transplant waiting list, and repeat OGTTs during follow-up may be beneficial for individuals with pretransplant DM or PTDM risk factors. Greater clinical attention should be directed toward at-risk groups, which can be defined by clinical phenotypes or polygenic risk scores, although the optimal approach requires further investigation. Immunosuppressive regimens should not be routinely modified solely to reduce PTDM risk; however, individualized adjustment may be considered in selected patients after balancing competing risks. Lifestyle modification, including dietary measures and physical activity, should be emphasized. For transplant candidates with obesity refractory to lifestyle intervention, bariatric or pharmacologic interventions may be considered. Early exogenous insulin may be considered for posttransplant hyperglycemia and possible PTDM prevention, although evidence remains limited and hypoglycemia risk should be considered. When available, glucose-lowering therapy should be individualized, with sodium-glucose linked transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) considered according to patient-specific factors [47].

Intensive glycemic monitoring and management in the posttransplant setting may be both clinically feasible and economically justified, particularly among recipients with pretransplant DM or PTDM. Given the high baseline risk and cost of posttransplant complications, improved glycemic control has the potential to reduce the risks of infection, rejection, and rehospitalization, thereby enhancing overall outcomes while lowering healthcare utilization [47,48]. Accordingly, structured strategies—including early insulin-based therapy, continuous glucose monitoring, and multidisciplinary care—could be incorporated into routine follow-up and may improve short-term and long-term outcomes, including survival and quality of life [47,49]. However, implementation requires careful consideration of hypoglycemia risk, treatment burden, and potential drug-drug interactions with immunosuppressive regimens. Emerging approaches such as telemedicine and real-time glucose monitoring may further improve feasibility and adherence [50]. Despite these promising implications, robust prospective data specific to heart transplant populations remain limited; thus, further studies are needed to clarify the long-term clinical effectiveness and cost-effectiveness of intensive glycemic management in this high-risk population.

A single-center study conducted by Muir et al demonstrated that DM, whether pre-existing or developing after transplantation, was independently associated with an increased risk of adverse transplant-related outcomes, including acute rejection and mortality following heart transplantation [51]. A small-sample, single-center study conducted by Mateo et al reported that heart transplant recipients who developed grade 2

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rejection exhibited higher blood glucose levels compared with those who experienced grade 1 rejection [52]. These findings are consistent with the results of our study. However, the precise mechanisms by which diabetes contributes to transplant rejection remain incompletely understood. A study from the University of Chicago suggested that diabetes and obesity may exacerbate allograft rejection by inducing gut microbiota dysbiosis, thereby promoting systemic inflammation. Notably, the investigators identified a commensal bacterium, *Alistipes onderdonkii*, with the potential to improve transplant outcomes and mitigate PTDM [53].

Our study demonstrated that PTDM was associated with poorer survival, consistent with prior smaller studies [11,19]. Immunosuppressive therapy, particularly with steroids and calcineurin inhibitors, plays a key role in PTDM pathogenesis by promoting insulin resistance and beta-cell toxicity [3]. In addition to metabolic complications, PTDM in our cohort was associated with higher rates of infection, acute rejection, and other posttransplant complications, which may account for the poorer survival observed in this group. Interestingly, patients with PTDM had lower cerebrovascular mortality than did patients without PTDM, suggesting competing risks or differences in underlying vascular biology that warrant further investigation.

The most novel finding of our study is the differential prognostic impact of insulin dependence among patients with PTDM. Insulin-dependent PTDM was associated with a markedly higher risk of mortality than non–insulin-dependent PTDM, even after multivariable adjustment. This subgroup also experienced significantly higher rates of acute rejection, dialysis requirement, and infection, suggesting that insulin dependence may identify a more severe phenotype of metabolic dysfunction and immunologic vulnerability. Prior literature has largely treated PTDM as a binary variable [3,11,19,20], and our results emphasize the importance of stratifying PTDM by treatment intensity in future studies and clinical practice.

This study has several limitations. First, its retrospective design limits the ability to fully account for potential confounding factors that may have affected transplant outcomes. Second, several clinically relevant variables were unavailable in the SRTR database, including medication adherence, posttransplant lifestyle factors, glycemic control after transplantation, and detailed metabolic assessments such as HbA1c levels and longitudinal glucose measurements. These unmeasured factors are important determinants of both prognosis and diabetes severity. Moreover, insulin dependence may partly reflect greater metabolic dysfunction, impaired β-cell reserve, or intensified immunosuppressive exposure rather than a direct causal effect of insulin therapy itself, which could not be adequately evaluated in the present study. Third, this study did not include data regarding healthcare costs or quality-of-life outcomes; therefore, the clinical feasibility, economic burden, and patient-centered impact of intensive glycemic monitoring and individualized glucose-lowering strategies after heart transplantation could not be comprehensively assessed. Fourth, the SRTR dataset may introduce potential bias due to inter-center variability in data collection and reporting practices. In particular, incomplete or inaccurate documentation of pretransplant DM status and incident PTDM may have resulted in misclassification bias, potentially affecting the observed associations. Fifth, the SRTR database lacks detailed information regarding the use of newer antidiabetic therapies such as SGLT2 inhibitors and GLP-1 RAs. Previous studies in heart transplant recipients treated with SGLT2 inhibitors and/or GLP-1 RAs have reported weight loss, reduced insulin requirements, lower HbA1c levels, and improved low-density lipoprotein cholesterol levels, without significant adverse events requiring drug discontinuation [54]. Moreover, SGLT2 inhibitors and GLP-1 RAs have shown cardiovascular and renal benefits in broader cardiovascular populations [55-57]. The absence of data regarding the use of these agents precludes assessment of their potential impact on glycemic control, progression to insulin-dependent PTDM, and long-term survival in our cohort. Finally, the exact timing of PTDM onset after transplantation was unavailable in the SRTR database, precluding time-dependent Cox regression analyses. Therefore, the potential for immortal time bias should be acknowledged when interpreting the observed associations between PTDM and survival outcomes.

Future studies are needed to clarify the mechanisms by which pretransplant DM and PTDM affect outcomes after heart transplantation. Optimizing perioperative glycemic control, evaluating less diabetogenic immunosuppressive regimens and adjunctive metabolic therapies, and developing individualized risk prediction and prevention strategies are essential for reducing complications and improving long-term survival. In parallel, emerging antidiabetic therapies, such as SGLT2 inhibitors and GLP-1 RAs, may provide new opportunities to improve metabolic and cardiovascular outcomes after heart transplantation. Importantly, intensive glucose-lowering strategies should be designed to balance potential benefits against risks such as hypoglycemia and other adverse effects. Integrated basic, clinical, and translational studies are needed to guide precision-based metabolic management and improve prognosis and quality of life among heart transplant recipients.

Conclusions

In this large national cohort, we demonstrated that diabetes across the transplant continuum—before and after heart transplantation—has important and distinct prognostic implications. Pretransplant DM was independently associated with reduced long-term survival and higher risks of infection-related

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and pulmonary mortality, suggesting that impaired immune and metabolic resilience contributes to poorer posttransplant recovery. PTDM also increased mortality risk, and its severity, reflected by insulin dependence, identified the highest-risk subgroup with markedly elevated rates of rejection, dialysis requirement, and infection. The use of biologics was independently associated with a significantly reduced risk of PTDM. These findings indicate that the management and treatment of diabetes are of high importance not only before but also after heart transplantation.

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Ethics Approval

Ethics approval for the present study was granted by the Ethics Committee of the Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, China.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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