

## Incidence and relative risk factors in posttransplant diabetes mellitus patients: a retrospective cohort study

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**Background:** Posttransplant diabetes mellitus (PTDM) has a long-term impact on kidney transplantation outcomes, such as graft and patient survival. The incidence and risk factors of PTDM are well studied, but long-term follow-up results remain unavailable. We examined the long-term incidence and relative risk factors of PTDM.

**Methods:** A hospital information system database for kidney transplant recipients (KTRs) for a transplantation center between 1983 and 2018 was used to perform this retrospective cohort study. KTRs with DM diagnosis and continuous use of hypoglycemic agents for more than 3 months were defined as having PTDM. Demographics and comorbidities before transplantation were also collected. Kaplan-Meier analyses were used to determine the cumulative incidence and relative risk factors.

**Results:** A total of 296 PTDM cases were confirmed (28.46%) in this study. An increased cumulative incidence associated with age was noted, which was significantly increased in those aged  $\geq 40$  years. Male sex, hypertension, hyperlipidemia before transplantation, cytomegalovirus (CMV) infection, and tacrolimus-based regimens were also risk factors. No significant correlation was found between the development of PTDM and the increase of human leukocyte antigen mismatches, the primary causes of end-stage renal disease, and acute rejection.

**Conclusions:** PTDM incidence was high in this cohort study. Characteristics such as age  $\geq 40$  years, tacrolimus use, comorbidity of hypertension and hyperlipidemia before transplantation, and CMV infection were associated with a high risk of PTDM. Monitoring and adjusting preventable risk factors such as CMV infection might be useful to prevent PTDM.

**Keywords:** Incidence; Posttransplant diabetes mellitus; Risk factors

### INTRODUCTION

With substantial impacts on graft and patient outcomes,

posttransplant diabetes mellitus (PTDM) is recognized as a common severe complication for patients receiving immunosuppressive agents after kidney transplantation

## HIGHLIGHTS

- The cumulative incidence rates of posttransplant diabetes mellitus (PTDM) are increased with age, especially more than 40 years.
- Pretransplant hypertension, hyperlipidemia, and cytomegalovirus infection posttransplant might be risk factors for PTDM.
- The incidence of PTDM increased with time and was significantly higher in the tacrolimus users than in the cyclosporine users.

[1,2]. PTDM is not only associated with increased mortality and morbidity, but also with higher rates of cardiovascular diseases and infection, which severely affect long-term graft survival and cause patient death [3-5]. Previous studies have revealed that the incidence of PTDM varies from 9.1% to 45.3% in the first year after transplantation [1,6]. Clinical risk factors such as obesity, sedentary lifestyle, and viral infections (e.g., hepatitis C virus and cytomegalovirus [CMV]) have been reported. Immunosuppressive agents with diabetogenic effects are also used in posttransplant therapy, including corticosteroids, tacrolimus, cyclosporine, and mammalian target of rapamycin [7]. However, the long-term patient and graft incidence in Asian patients with PTDM are scant. This study aimed to examine the cumulative incidence of and risk factors for PTDM in Taiwan's kidney transplant recipients (KTRs). Furthermore, the impact of calcineurin inhibitors (CNIs) on PTDM was also determined.

## METHODS

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CE18303B). Written informed consents were waived owing to the use of a decoded database in the Hospital Information System (HIS).

### Study Design

The HIS database of a central Taiwan transplantation center was used for this retrospective cohort study. According

to World Health Organization/American Diabetes Association (WHO/ADA) international consensus guidelines [8,9] and a PTDM consensus meeting held in 2013, patients with PTDM were defined as "clinically stable patients who have developed persistent posttransplant hyperglycemia" [10]. We, therefore, determined the candidates of PTDM through the following criteria: (1) post-KTRs; (2) confirmed diagnosis of diabetes mellitus (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM 250] or International Classification of Diseases, Ten Revision, Clinical Modification, ICD-10-CM, E10-E14); and (3) continuous use of antihyperglycemic agents or insulin for more than 3 months (to reduce the risk of overestimation of transient hyperglycemia into PTDM). If the KTRs received hyperglycemic treatments for less than 3 months after DM was confirmed, they were defined as being "transient hyperglycemic" instead of having PTDM.

### Study Population

A HIS database was used. Anonymous adult KTRs who underwent transplants between May 1983 and November 2018 in the study center were eligible. The KTRs, who had survived with a functioning allograft for at least 1 year after transplantation, were included. Patients with pre-transplant diabetes, a follow-up period of less than 1 year after transplantation, and multiple organ transplants were excluded. Data collected included patient demographics, body mass index (BMI) at the time of transplantation, causes of kidney failure, date of the kidney transplant, kidney source, count of human leukocyte antigen (HLA) mismatches, biopsy-proven acute rejection (BPAR), maintenance immunosuppressants including CNIs (tacrolimus and cyclosporin), which were used for more than 3 months, and comorbidities before transplantation. The comorbidities before the study end date included hypertension, hyperlipidemia, anemia, hepatitis B, hepatitis C, and CMV infection. The end time for PTDM risk analyses was the diagnosis date of PTDM or the study's end date.

### Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]). The Mann-Whitney U-test and chi-square test were used to compare continuous and categorical variables in PTDM-negative and PTDM-positive patients. Survival curves were analyzed using the Kaplan-Meier method. Statistical analysis was performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). The P-values of less than 0.05 were considered statistically significant.

## RESULTS

A total of 1,143 adults who underwent kidney transplantation during the study period were included, and 103 were eventually excluded due to inclusion criteria violation.

Finally, 1,040 eligible KTRs were enrolled, with a median age at transplantation of 44.3 years (IQR, 34.7–52.7 years) and median follow-up period of 12.7 years (IQR, 4.5–20.1 years). A larger portion of this cohort comprised men (580 patients, 55.8%). Among them, 296 patients had

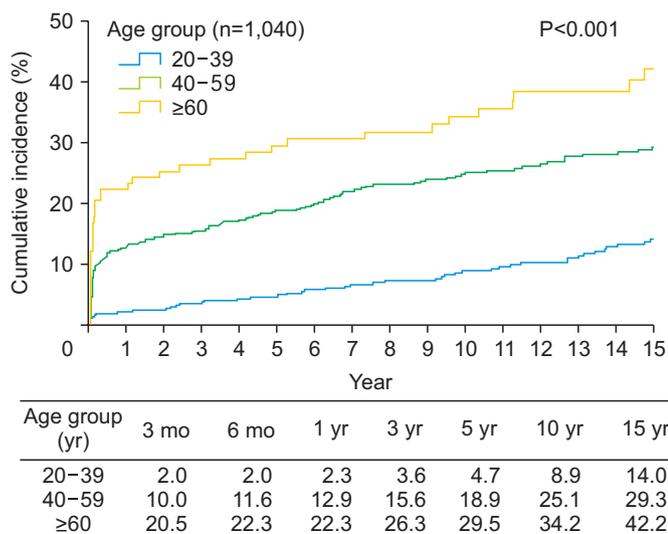
**Table 1.** Characteristics of the renal transplantation study population

Variable	Overall (n=1,040)	Non-PTDM (n=744)	PTDM (n=296)	P-value
Age at transplantation (yr) <sup>a)</sup>	44.3 (34.7–52.7)	42.1 (33.6–51.0)	48.4 (39.5–56.3)	0.001
Age group at transplantation				0.001
20–39 yr	402 (38.7)	326 (43.8)	76 (25.7)	
40–59 yr	521 (50.1)	354 (47.6)	167 (56.4)	
≥60 yr	117 (11.3)	64 (8.6)	53 (17.9)	
Age at PTDM diagnosis (yr) <sup>a)</sup>	-	-	52.8 (46.0–60.6)	-
Sex				0.033
Female	460 (44.2)	345 (46.4)	115 (38.9)	
Male	580 (55.8)	399 (53.6)	181 (61.1)	
BMI at transplantation <sup>a)</sup> (kg/m <sup>2</sup> )	22.9 (20.8–25.7)	22.3 (20.4–24.8)	24.2 (22.5–27.6)	0.001
Donor source				0.474
Cadaveric	852 (81.9)	605 (81.3)	247 (83.4)	
Living	188 (18.1)	139 (18.7)	49 (16.6)	
Count of HLA mismatches	2.94±1.12	2.92±1.13	3.00±1.10	0.776
Primary causes of ESRD				0.144
Hypertension	620 (59.6)	450 (60.5)	170 (57.4)	
Glomerular nephritis	151 (14.5)	110 (14.8)	41 (13.9)	
Drug and Chinese herb	71 (6.8)	52 (7.0)	19 (6.4)	
ADPKD	31 (3.0)	20 (2.7)	11 (3.7)	
Lupus	19 (1.8)	17 (2.3)	2 (0.7)	
Others	148 (14.2)	95 (12.8)	53 (17.9)	
BPAR before PTDM diagnosed				0.642
20–39 yr	27 (25.0)	6 (20.0)	21 (26.9)	
40–59 yr	68 (63.0)	21 (70.0)	47 (60.3)	
≥60 yr	13 (12.0)	3 (10.0)	10 (12.8)	
Comorbidity before kidney transplantation				
Hypertension	906 (87.1)	633 (85.1)	273 (92.2)	0.003
Hyperlipidemia	633 (60.9)	430 (57.8)	203 (68.6)	0.002
Anemia	543 (52.2)	384 (51.6)	159 (53.7)	0.586
Hepatitis B	130 (12.5)	94 (12.6)	36 (12.2)	0.917
Hepatitis C	49 (5.1)	33 (4.8)	16 (6.0)	0.561
CMV infection post transplantation	15 (1.4)	6 (0.8)	9 (3.0)	0.016
Maintenance immunosuppressant (CNI)				0.009
Tacrolimus-based	614 (59.0)	420 (56.5)	194 (65.5)	
Cyclosporine-based	426 (41.0)	324 (43.5)	102 (34.5)	

Values are presented as median (interquartile range), number (%), or mean±standard deviation.

PTDM, posttransplant diabetes mellitus; BMI, body mass index; HLA, human leukocyte antigen; ESRD, end-stage renal disease; ADPKD, autosomal dominant polycystic kidney disease; BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; CNI, calcineurin inhibitor.

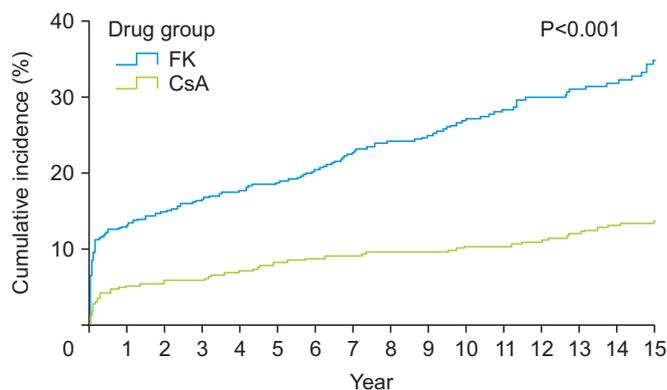
Chi-square test was used for comparisons except for <sup>a)</sup>Mann-Whitney U-test.



**Fig. 1.** The cumulative incidence rates of posttransplant diabetes mellitus in different age groups. Values are presented as percent.

PTDM (28.5%). More male patients were found to develop PTDM than female patients (61.1% vs. 38.9%,  $P < 0.001$ ). Older patients (PTDM vs. non-PTDM, 48.4 vs. 42.1;  $P < 0.001$ ) and higher BMI (PTDM vs. non-PTDM, 24.2 vs. 22.3 kg/m<sup>2</sup>;  $P < 0.001$ ) were found to have higher probabilities of developing PTDM. The donor source was mainly cadaveric (81.9%), but no apparent relationship was confirmed between the donor source and PTDM after transplantation ( $P = 0.474$ ). No significant correlation was found between the development of PTDM and the increase in HLA mismatches ( $P = 0.776$ ), the primary cause of end-stage renal disease ( $P = 0.144$ ), and the occurrence of BPAR before PTDM was diagnosed ( $P = 0.642$ ). However, hypertension ( $P = 0.003$ ) and hyperlipidemia ( $P = 0.002$ ) were the most frequently seen comorbidities before transplantation in the PTDM group compared with the non-PTDM group. The study results revealed that 1.4% of KTRs had CMV infection after transplantation. The incidence of CMV infection in the PTDM group was significantly higher than that in the non-PTDM group (3.0% vs. 0.8%,  $P = 0.016$ ). Regarding immunosuppressants, tacrolimus-based regimens were significantly more prescribed in the PTDM group than in the cyclosporine-based regimens ( $P = 0.009$ ) (Table 1).

Age groups were further divided as “20–39,” “40–59,” and “≥60” when cumulative incidences were examined. Cumulative incidences of PTDM 1, 5, 10, and 15 years post-transplant in the three age groups were 2.3%, 12.9%, and



**Fig. 2.** The cumulative incidence rate of posttransplant diabetes mellitus in the tacrolimus (FK)-based and cyclosporine (CsA)-based groups.

22.3%; 4.7%, 18.9%, and 29.5%; 8.9%, 25.1%, and 34.2%; and 14.0%, 29.3%, and 42.2% ( $P < 0.001$ ), respectively, indicating that the cumulative incidence of PTDM increased proportionally with time after transplantation. The post-hoc test obtained similar results (Fig. 1).

The 1-year cumulative incidence of PTDM was 12.9% for tacrolimus users and 5.2% for cyclosporine users. Their 5-year cumulative incidence was 18.8% and 8.4%, respectively. Their 10-year cumulative incidence was 27.2% and 10.4%, respectively, and their 15-year cumulative incidence was 34.9% and 13.7%, respectively (Fig. 2). The incidence of PTDM increased with time and was significantly higher in the tacrolimus users than in the cyclosporine users ( $P < 0.001$ ).

## DISCUSSION

This study was the first to retrospectively examine the incidence of PTDM after kidney transplantation using the Medical Center's HIS database, which has the second-largest amount of annual kidney transplantation cases in Taiwan. Patients with PTDM were defined as “KTRs having confirmed diagnosis of DM and continuous use of antihyperglycemic drugs or insulin for more than three months” to reduce the potential overestimation of transient hyperglycemic cases, including those who had tremendous amounts of steroids for acute rejection. The incidence of BPAR varied insignificantly between the two study groups among all age groups, showing that this study did not include patients with transient hyperglycemia into PTDM. The PTDM incidence was 28.5% in this study, which was

higher than that (17.0%) reported by Yeh et al. [11] using the National Health Insurance Database of Taiwan but consistent with that reported (14%–37.0%) in another study [12]. The prolonged study period and sample origin might be the leading causes of the differences between the present findings and the results of Yeh et al. [11].

Risks factors for PTDM were identified as: (1) age: the possibility of PTDM development increased with an increase in the age of patients undergoing kidney transplantation, especially for those aged more than 40 years at transplantation; (2) male sex: more male patients developed PTDM than female patients; (3) obesity and comorbidities before transplant: patients with higher BMI, hypertension and hyperlipidemia had a higher risk of PTDM than those without; (4) CMV infection after transplantation; and (5) use of tacrolimus: patients who had received tacrolimus-based immunosuppressive therapy after kidney transplant had a higher risk of PTDM than those who had received cyclosporine-based therapy (Table 1).

A positive correlation has been demonstrated between older age and the development of PTDM [13,14]. Similar results were obtained in our study (Table 1, Fig. 1). Whether sex is a predictor of PTDM development is still controversial [6,15], but more male patients were found to develop PTDM than female patients in the study. Similar results were observed in previous studies [6,16,17]. Therefore, we conclude that sex might not be an independent predictor of PTDM, and large-scale studies are warranted to verify this finding. BMI may affect transplant outcomes, which has been documented in previous studies [7]. Our results also showed that higher BMI have higher PTDM development.

No positive correlation was demonstrated between donor source and PTDM incidence in our study, which was in accordance with the previous study because of donor variables, including age, race, and sex. The age of the recipient was independently correlated with the incidence of PTDM [17]. Diabetes and glucose intolerance are often associated with metabolic syndrome, especially hypertension and hyperlipidemia [10]. Hypertension and hyperlipidemia were the most frequently seen underlying diseases before transplantation for patients who developed PTDM compared to those who did not. Similar results were found in a previous study, which reported that recipients with a history of hypertension were 1.26 times (95% confidence interval, 1.11–1.44) more likely to develop PTDM after transplant [18]. Additionally, if the recipients had a history of hypertension and the primary cause of the end-stage renal

disease was hypertension, the recipients were 3.0 times (21.3% vs. 7.5%,  $P=0.029$ ) as likely to develop PTDM after transplant compared to the non-hypertensive recipients [6]. A previous study [14] showed that patients with high blood lipid profiles (total cholesterol and low-density-lipoprotein-cholesterol and triglyceride levels) before transplantation who later developed PTDM had a higher incidence, which suggested that pretransplant hyperlipidemia is one of the predictors of PTDM; this finding is consistent with our study results.

Several immunosuppressive agents commonly used after transplants have been shown to possess potential diabetogenic effects [19]. The incidence of PTDM was significantly higher among patients receiving tacrolimus than among those receiving cyclosporine [2,20], which was also revealed in our study. However, the correlation between CNI and PTDM incidence is quite tricky because there are many confounding variables [20]. For instance, without a change in tacrolimus' therapeutic concentration (5–10 ng/mL), insulin secretion was enhanced when tacrolimus was administered with a 33% dose reduction, suggesting that the diabetogenic effect of tacrolimus is dose-dependent [21].

The impact of CMV on PTDM development remains controversial. However, a review of current findings revealed that the overall adjusted odds ratio for PTDM development in CMV-positive KTRs was 1.94, indicating that CMV infection is a risk factor for an increasing incidence of PTDM [22]. Similar results were demonstrated in the present study, and prophylaxis against CMV infection after kidney transplantation is strongly suggested. In conclusion, PTDM incidence was as high as 28.46% in this long-term study. Age of more than 40 years, tacrolimus use, pretransplant hypertension, hyperlipidemia, and CMV infection might be risk factors for PTDM. Furthermore, monitoring and adjusting preventable risk factors such as CMV infection might be useful to prevent PTDM development.

## ACKNOWLEDGMENTS

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Author Contributions

Conceptualization: CYC, HYW. Data curation & Formal analysis: CYC. Methodology: CYC, HYW. Writing—original draft: CYC. Writing—review & editing: HYW, YTF.

### Additional Contributions

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