The Effect of Posttransplantation Diabetes Mellitus on the Prognosis of Transplantation: a Prospective Cohort Study

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Abstract

Background: Posttransplantation diabetes mellitus (PTDM) constitutes one of the most important complications associated with kidney transplantation and is associated with significant morbidity and mortality. Methods: This study was a single-centred prospective observational study that included 310 consecutive renal transplant recipients. The primary end point was graft failure, including death-censored graft failure and mortality. The secondary endpoints include estimated glomerular filtration rate (eGFR) at 12 months and adverse events after transplantation. The prevalence rate of PTDM and relevant risk factors for PTDM were also explored. Results: The incidence of PTDM was 16.4% within one year. Death-censored graft loss rate differed significantly between recipients without PTDM and those with PTDM(0.77% versus 12%, p<0.001). Compared with non-PTDM group, the mean eGFR was significantly lower in the PTDM group(70.55±20.54 ml/min·1.73 m² versus 63.04±21.92 ml/min·1.73 m², P=0.03). Additionally, compared with the other group, the PTDM group was more easily infected by bacteria(16.2% versus 40%, P<0.001). Multi-factor analysis indicated that higher preoperative fasting plasma glucose (FPG), increased age and use of tacrolimus after transplantation were independent risk factors for PTDM. Conclusion: The incidence rate of PTDM is 16.4% 1 year after surgery. Our study suggests that patients with PTDM are at higher risk of death-censored graft loss and bacterial infection, and worse kidney function. Independent risk factors of PTDM include preoperative FPG level, increased age, and tacrolimus. The PTDM group is more vulnerable to worse graft function, postoperative graft loss and bacterial infection.

Background

Posttransplantation diabetes mellitus (PTDM) is utilized for clinically stable patients who have developed persistent posttransplantation hyperglycaemia, defined by the international consensus[1]. In recent years, with the development of immunosuppressive agents, the survival rate of allografts and patients has greatly increased. Therefore, scholars have gradually paid more attention to the long-term complications after renal transplantation.

Prior studies have indicated that PTDM is associated with worse outcomes, including increased graft failure and mortality[2]. In addition, PTDM has also been shown to increase the risk of cardiovascular events[2], and cardiovascular disease is associated with more than half of kidney transplant deaths. According to a 2013 report by the United States Renal Data System (USRDS), the incidence of PTDM was 41% after 36 months of adult kidney transplantations[3]. The incidence of new-onset diabetes after kidney transplantation usually occurs within 3 to 6 months after surgery, with an average of 4.3 months[4]. KDIGO summarized the risk factors for PTDM, including tacrolimus, acute rejection, obesity, and older age. Many studies have identified the prevalence, risk factors and outcomes of PTDM, but there is still little research in China.

Our study aimed to evaluate the effects of PTDM on the prognosis of kidney transplantation, including the survival rate of both grafts and patients. We also explored the incidence of PTDM in Chinese patients

and the risk factors for PTDM.

Methods

This study was performed with the approval of the Ethics Committee. All patients signed an informed consent form.

Study design and patients

This was a single-centred prospective observational study that included 310 consecutive renal transplant recipients who had undergone allogeneic kidney transplantation between January 2016 and December 2017 in our hospital and been followed up for one year. The grafts were all donated by deceased cardiac donors or living-related donors. During follow up, all patients received introduction therapy and triple maintenance therapy, Calcineurin inhibitor(CNI), prednisone and mycophenolate mofetil (MMF).

Criteria

Inclusion criteria: 1) patients between the ages of 18 and 75 years old, 2) follow-up for more than 3 months, and 3) accepting triple maintenance therapy and didn't change the therapy

Exclusion criteria: 1) transient posttransplantation hyperglycaemia, 2) combined transplantation or a second renal transplantation, 3) diabetes prior to transplantation, 4) discontinue or change the original triple immunosuppression regimens, and 5) graft loss during the preoperative period.

The observation time was one year. Post-transplant follow-up was performed weekly for 3 months, and then monthly from the third month to the twelfth month. Each patient was followed up for at least 6 months.

Diagnosis

The diagnosis of PTDM was made according to the criteria for diabetes, defined by ADA and international consensus, when patients were stable on maintenance immunosuppression, with stable graft function and in the absence of acute infections. The diagnosis was made by symptoms of diabetes plus FPG ≥7.0 mmol/L.

Endpoints

The primary end point was the incidence of graft failure, including death-censored graft failure and mortality. The secondary endpoints included incidence rate of adverse events and renal function as

indicated by estimated glomerular filtration (eGFR), calculated from the Modification of Diet in Renal Disease formula.

Statistical analysis

Descriptive statistics were analysed with SPSS version 22.0 software. Continuous variables were tested for normality and homogeneity of variance. Normal distribution continuous and homogeneity of variables were presented as the mean ± SD and analysed by *t* test. Normal distribution continuous and heteroscedastic variables were presented as the mean ± SD and analysed by *F* test. Non-normally distributed continuous variables will be presented as median (interquartile range) and analysed by rank sum test. Categorical variables expressed as frequencies and percentages. Nominal categorical data between the groups will be compared using the Chi-square test or Fisher's exact test as appropriate. Logistic regression and Cox regression analyses were performed to evaluate the independent risk factors associated with the onset of PTDM among the study population. Time to PTDM, acute rejection, allograft loss and death were analysed with the Kaplan–Meier method, and group differences were assessed by the log-rank test. A *P* value of <0.05 was considered statistically significant.

Result

Patients

From January 2016 to December 2017, a total of 364 patients underwent kidney transplantation. A total of 54 patients were excluded due to exclusion criteria. The scheme of selecting the study participants is depicted in Figure 1. Patients were divided into the PTDM and non-PTDM groups according to the diagnosis criteria of PTDM. The 310 patients had an average follow-up time of 10.8±2.34 months. Fifty patients had PTDM onset, and 74% were diagnosed within 3 months (Figure 2). The demographic, clinical and donor-recipient characteristics are shown in Table 1. The postoperative characteristics are shown in Table 2.

Primary and secondary endpoint

Allograft and patient survival

A one-year follow-up of 310 patients was performed, of which 36 were lost to follow-up and 274 completed a one-year follow-up. Table 3 showed primary and secondary endpoints results. There were 3 cases of postoperative death and 6 cases of postoperative graft failure. A chi-square test showed that the incidence of allograft failure and death-censored graft failure in the non-PTDM population was significantly lower than that in the PTDM population(0.77% versus 12%, p<0.001; 0.03 versus 8%, p<0.001). A logistic regression analysis was performed to explore the independent risk factors for (Table 4). The results showed that PTDM was an independent risk factor for death-censored graft failure. Figure

3 showed the Kaplan-Meier estimates for graft survival rate, death-censored graft survival rate and patient survival rate.

eGFR

Twelve months after transplantation, the overall average eGFR was 68.19 (95% CI = 66.87–71.89) (Table 3). Renal function differed significantly between the two groups. The eGFR was significantly lower in the PTDM group compared with the non-PTDM group (63.04±21.92 ml/min·1.73 m² versus 70.55±20.54 ml/min·1.73 m², p<0.001), as shown in Figure 4.

Adverse events of postoperative complications

As shown in Table 3, in the PTDM population, bacterial infection, hyperlipidaemia and hyperlipidaemia requiring drug treatment were significantly higher than those in the non-PTDM group, but no significant differences were observed in other complications. After logistic regression analysis, it was concluded that PTDM is an independent risk factor for postoperative bacterial infection, but it is not an independent risk factor for hyperlipidaemia and hyperlipidaemia requiring treatment, as shown in Table 5.

Rist factors of PTDM

As shown above, PTDM increases the risk of death-censored graft failure and the incidence of bacterial infection. Therefore, we further analysed the risk factor for PTDM. As shown in Table 6, compared with the non-PTDM group, PTDM patients were older, had higher body mass index (BMI) values, longer dialysis time, higher preoperative fasting plasma glucose (FPG) level, and higher triglyceride (TG) level. BMI, dialysis time, FPG and TG were further stratified according to ROC curve and clinical practice. Polycystic kidney disease patients were easier to onset diabetes after kidney transplantation. Patients who used ciclosporin, MMF and prednisone as post-transplant maintenance therapy were less likely to develop PTDM. To evaluate the independent risk factors of PTDM. COX regression analysis was performed to analyse age, BMI, dialysis time, preoperative FPG, preoperative TG, HLA matches, PKD and tacrolimus. According to the results of the Cox regression analysis, shown in Table 8, the use of tacrolimus as a postoperative maintenance immunosuppressive therapy, preoperative fasting plasma glucose greater than or equal to 5.6 mmol/L, age greater than or equal to 48 years old and polycystic kidney disease were independent risk factors for PTDM.

Discussion

Clinical impact

PTDM is associated with various short-term and long-term complications. In our study, the development of PTDM had an adverse effect upon kidney function, graft survival and bacterial infection.

Death-censored graft failure

The literature is unclear about the effects of PTDM on graft failure. A large, retrospective study suggested that PTDM was associated with an increased risk for both overall allograft failure and death-censored allograft failure. However, this study did not control for acute rejection in the multivariate analysis[4]. An analysis of the data from OPTN/UNOS database 10 found that acute rejection was associated with death-censored graft failure, but PTDM was not associated with any of the outcomes investigated[5]. Whether PTDM affects allograft survival remains unknown. In our study, one-year allograft survival was 90 and 99.97 % in those with and without PTDM, respectively. Additionally, we performed multivariate analysis to suggest that PTDM was an independent risk factor for overall allograft failure. In addition, we excluded those who lost grafts or died during the perioperative period, which might have influenced our results.

Infections

PTDM has been associated with an increased risk for infection because hyperglycaemia may alter the immune response. Urinary tract infection, pneumonia, CMV and opportunistic infection have also been reported to occur at increased rates with diabetes [6]. The risk of infection in transplant recipients will be closely related to the extent of immunosuppression in a given individual, in addition to many other confounding variables, such as age, acute rejection and medications. Our research showed that PTDM was an independent risk factor for bacterial infection, with delayed graft function, acute rejection and obesity.

Prevalence

In this study, which included 310 non-diabetic patients who underwent renal transplantation, 16.4% of patients developed PTDM during 1 year of follow-up after transplantation. A meta-analysis, published in 2004, which included 35 publications, reported the prevalence rate of new-onset diabetes mellitus after kidney transplantation ranging from 6 to 47 percent[7]. The reported incidence of PTDM is variable and must be interpreted in the context of definition used, time from transplant, study population, and immunosuppressive agents used for individual studies. In particular, in this meta-analysis, PTDM was defined as insulin-dependent diabetes mellitus, which might underestimate the incidence of PTDM. In recent years, several studies have reported the incidence of PTDM, which was defined by the 2009 KDIGO criteria. In the USA[8], the incidence of PTDM was reported as 11%, and in Japan[9] and Korea[10], it was 11.3% and 20.4%, respectively. The prevalence rate in our study, including patients who all came from China, was similar to that in other countries, especially the east Asian countries. The results showed that 74% of patients developed PTDM within 3 months, so we recommended screening diabetes mellitus weekly within 3 months after transplantation instead of weekly within the first month and monthly between the second month and the third month, which was suggested by KDIGO guidelines.

Risk factors

Many prior studies have studied the risk factors of PTDM. These factors can be divided into transplant-related and non-transplant-related factors. The former includes increased age, obesity, African American race, Hispanic ethnicity and family history of diabetes. The latter includes medications, infection and posttransplant hyperglycaemia. According to our results, independent risk factors of PTDM included preoperative FPG greater than or equal to 5.6 mmol/L, age greater than or equal to 46 and tacrolimus use after transplantation. Polycystic kidney disease and post-transplant hyperlipidaemia might be independent risk factors for PTDM.

CNI

Both cyclosporine and tacrolimus increase the risk of PTDM. A meta-analysis published by Penninga et al. in the Cochran library in 2013 showed that tacrolimus was more likely to cause new diabetes after renal transplantation than cyclosporine[11] (RR = 4.24, 95% CI: 1.58–11.4). The conclusion of our study was that the use of tacrolimus as maintenance therapy with prednisone and MMF was an independent risk factor for PTDM, a conclusion similar to that of other investigators. Since CNI-like immunosuppressive agents can regulate the growth and function of islet B cells by activating the T cell nuclear factor pathway[12], the use of CNI inhibitors may lead to elevated blood glucose through this pathway, while tacrolimus The pathogenic effect is clearly stronger than cyclosporine.

Fasting plasma glucose levels before transplantation

Impaired glucose tolerance and impaired fasting glucose have been proven to be risk factors for PTDM[13]. By plotting the ROC curve, the point with the largest Youden index was set as the segmentation point. The obtained segmentation point is approximately 5.6 mmol/L. The results of this study suggest that we should also pay more attention to those whose fasting plasma glucose level is greater than or equal to 5.6 mmol/L because they are at high risk of PTDM.

Age

Older age increases the risk of developing diabetes mellitus. Many studies consider age over 50 years to be a risk factor [14,15], and some studies suggest that age over 45 years is a risk factor [16]. In our study, according to ROC curve and logistics regression, when the age is greater than or equal to 48 years old, patients are more likely to suffer PTDM. This result is similar to those of other research, and this slight difference may be due to sample size, region and race. The mechanism of new-onset kidney transplantation in elderly patients with renal transplantation may be related to the gradual decline of islet B cell function with age[17].

Polycystic kidney disease

A retrospective study of 429 people in 2007 has shown that patients with autosomal dominant polycystic kidney disease (ADPKD) have a 2.4-fold increased risk of developing new-onset diabetes after renal transplantation[18,19]. In 2016, Wisit et al. published a meta-analysis showing that the probability of new-

onset diabetes after ADPKD is 1.92 times that of other kidney diseases[20]. However, the statistical method of this article has been questioned by Zhang C et al. [21]. In the two existing large sample studies, whether ADPKD is an independent risk factor is quite different. A 5000 study by Antoine et al. showed that ADPKD was a risk factor (RR = 1.33, CI: 1.01–1.75)[22]. However, a study of 2,000 people by Cecile et al. showed that ADPKD was not a risk factor (RR = 0.96, CI: 0.6–1.54)[23]. Therefore, according to current research, whether the ADPKD kidney is an independent risk factor for new-onset diabetes after renal transplantation remains to be discussed. In this study, a total of 14 patients developed polycystic kidney disease, 6 of whom developed PTDM, and according to binary logistic regression results, PKD is an independent risk factor for new-onset diabetes after renal transplantation. At present, the mechanism of polycystic kidney disease leading to PTDM is still unclear. Some scholars suggest that polycystic kidney disease may induce diabetes onset after renal transplantation, as insulin resistance genes combined with PKD1 gene transcription and PKD2 gene mutations may interfere with insulin secretion and liver gluconeogenesis.

Limitations

Our study had some limitations. This study was a single centre study, and the observation time was too short to observe further prognosis of transplantation. In addition, the sample size was not large enough, and 36 patients were lost to follow-up. Therefore, the reliability of some results still requires a large sample study to confirm that PTDM will increase the risk of death-censored graft loss in Chinese patients. We did not perform the OGTT and HbA1c, potentially leading to an underestimation of the incidence of PTDM and a misestimation of the onset timing. Additionally, those who were diagnosed with PKD did not accept gene sequencing, so we had no idea whether these individuals were ADPKD or not. Therefore, we cannot determine whether ADPKD is a risk factor for PTDM.

Conclusion

PTDM is associated with numerous adverse events following kidney transplantation: infection, graft failure, and mortality, and this conclusion is also proven by our study. The prevalence of PTDM in the first year was 16.4%. Through this study, ageing, higher fasting plasma glucose levels and tacrolimus are independent risk factors for new-onset diabetes after renal transplantation. Understanding the incidence, timing, and risk factors for new-onset diabetes after kidney transplantation helps in the development of better screening methods for disease.

Abbreviations

PTDM: new-onset diabetes mellitus after transplantation

eGFR: estimated glomerular filtration rate

WHO: World Health Organization

ADA: American Diabetes Association

USRDS: United States Renal Data System

OGTT: oral glucose tolerance test

HBA1c: haemoglobin A1c

MMF: mycophenolate mofetil

BMI: body mass index

HBV: hepatitis B virus

PKD: polycystic kidney disease

CMV: cytomegalovirus

SBP: systolic blood pressure

DBP: diastolic blood pressure

DGF: delayed graft function;

AR: acute rejection

FPG: fasting plasma glucose

TG: triglyceride

TC: total cholesterol

BUN: blood urea nitrogen

SCR: serum creatine

UA: Uric Acid;

K: potassium

Ca: calcium

P: phosphonium

PTH: parathyroid hormone.

Declarations

Ethics approval and consent to participate: This research was approved by the renji hospital ethical board.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Tables

Table 1: Preoperative characteristics of the patients

Variables	non-PTDM (N=260)	PTDM (N=50)	P- value
Age (year)	39.79 ± 10.58	46.82 ± 10.44	<0.001
≥48	59(11.2%)	28(56.0%)	<0.001
Gender (male)	147(56.5%)	28(56%)	0.944
Hight (cm)	167.22 ± 8.15	166.06 ± 7.64	0.354
Weight (kg)	60.55 ± 12.76	62.48 ± 11.16	0.318
BMI (kg/m²)	21.50 ± 3.41	22.59 ± 3.38	0.04
≥24	61(23.5%)	19(38%)	0.036
≥30	4(1.6%)	2(4%)	0.253
PKD	8(3.15%)	6(12%)	0.006
HBV infection	16(6.15%)	4(8%)	0.632
History of hypertension	203(79.6%)	44(88%)	0.167
SBP	142.89 ± 15.74	145.67 ± 20.76	0.293
DBP	89.93 ± 11.00	87.92 ± 10.48	0.244
History of dialysis	221(85%)	47(94%)	0.098
Haemodialysis	102(46.2%)	19(40.4%)	0.474
Dialysis time (month)	12(26)	22（45）	0.034
DCD	245(94.2%)	50(100%)	0.190
HLA matches	1(2)	0(1)	0.031
<2	207(83.5%)	17(81.0%)	0.767
FPG (mmol/L)	4.14±0.97	4.75±1.18	0.000
5-6.9	33(14.9%)	21(45.7%)	<0.001
5.6-6.9	6(2.8%)	11(23.9%)	<0.001
6.1-6.9	2(0.9%)	5(10.9%)	<0.001
TG (mmol/L)	1.54(1.1)	2.03(1.8)	0.008
Dyslipidaemia	48(22.6%)	21(44.7%)	0.002
TC (mmol/L)	4.85±1.13	5.05±1.12	0.243
eGFR (ml/min·1.73 m²)	5.85±2.30	6.13±2.37	0.436
BUN (mmol/L)	21.76±7.63	19.81±7.18	0.096
SCR(μmol/L)	937.73±313.66	866.96±297.16	0.143

Abbreviations: PTDM post-transplantation diabetes mellitus; BMI body mass index; HBV hepatitis B virus; PKD polycystic kidney disease; CMV cytomegalovirus; SBP systolic blood pressure; DBP diastolic blood pressure; DGF delayed graft function; AR acute rejection; FPG fasting plasma glucose; TG triglyceride; TC total cholesterol; GFR glomerulus filtrate rate; BUN blood urea nitrogen; SCR serum creatine;

Table 2: Postoperative characteristics of the patients

Variables	non-PTDM (N=260)	PTDM (N=50)	P- value
DGF	21(8.3%)	5(10.2%)	0.664
AR	16(6.2%)	5(10.0%)	0.326
Tacrolimus	226(87.3%)	49(98%)	0.025
C min of Tac (ng/ml)			
3 m after transplantation	6.75±2.00	6.51±1.87	0.472
6 m after transplantation	6.20 ±1.51	5.44±1.37	0.007
9 m after transplantation	6.26±1.49	6.26±1.93	0.999
12 m after transplantation	5.76±1.44	5.84±1.16	0.329

Abbreviation: PTDM posttransplantation diabetes mellitus; DGF delayed graft function; AR acute rejection; Tac tacrolimus; CSA ciclosporin a.

Table 3: Endpoints

Variables	non-PTDM	PTDM	P-value
Graft failure	0.77%	12%	<0.001
Death-censored	0.03%	8%	<0.001
Mortality	0.3%	4%	0.109
eGFR (ml/min·1.73 m²)			
Pre-transplantation	5.85±2.30	6.12±2.37	0.436
3 m after transplantation	65.81±20.08	63.21±20.69	0.405
6 m after transplantation	66.98±20.25	62.31±24.49	0.159
9 m after transplantation	70.75±20.70	64.97±23.77	0.108
12 m after transplantation	70.55±20.54	63.04±21.92	0.03
Infection	86(33.1%)	25(50.0%)	0.023
Bacteria	42(16.2%)	20(40.0%)	<0.001
Fungi	5(2.0%)	3(6.0%)	0.241
Virus	61(23.6%)	14(28.0%)	0.502
EBV	20(7.7%)	3(6%)	0.671
CMV	38(15.1%)	12(25.5%)	0.269
BKV	5(1.9%)	1(2.0%)	0.974
Dyslipidaemia	188(72.6%)	42(84%)	0.09
Hyperlipidaemia	169(65.3%)	41(82%)	0.02
Hyperlipidaemia with treatment	17(6.6%)	10(20%)	0.002
Hypercholesterolemia	110(42.5%)	28(56%)	0.078
Cardiovascular disease	2(0.7%)	0(0.0%)	1
Nervous system disease	2(0.7%)	0(0.0%)	1
Digestive system disease	3(1.2%)	0(0.0%)	1

Abbreviations: PTDM post-transplantation diabetes mellitus; eGFR estimated glomerulus filtrate rate; EBV Epstein-Barr virus; CMV cytomegalovirus, HBV hepatitis B virus

Table 4 Logistic regression analysis of the risk factors for graft failure

Variables	β	SE	Wald	OR	CI 95%	P
Acute rejection	2.814	0.969	8.429	12.333	1.334-114.010	0.027
PTDM	3.390	0.619	13.032	9.329	2.775-31.359	<0.001

Table 5: Logistic regression of incidence rate of bacterial infection

Variables	β	SE	Wald	OR	CI（95%）	P
PTDM	1.429	0.415	11.844	4.175	1.850-9.421	0.001
DGF	1.542	0.582	7.006	4.673	1.492-14.635	0.008
BMI≥24	0.809	0.388	4.342	2.246	1.049-4.807	0.037
AR	2.643	0.666	15.776	14.061	3.815-51.823	<0.001

Abbreviation: PTDM new-onset diabetes mellitus; DGF delayed graft function; BMI body mass index; AR acute rejection.

Table 6: COX regression analysis of risk factors for PTDM

Variables	β	SE	Wald	OR	CI（95%）	P-value
Tacrolimus	2.305	1.017	5.135	10.020	1.365-73.542	0.023
PKD	1.037	0.441	5.422	2.792	1.177-6.627	0.020
Age≥48 (yr)	1.156	0.305	14.388	3.176	1.748-5.770	<0.001
FPG: 5.6-6.9 (mmol/L)	1.303	0.357	13.310	3.681	1.828-7.414	<0.001

Abbreviation: PKD polycystic kidney disease; FPG fasting plasma glucose.

Figures

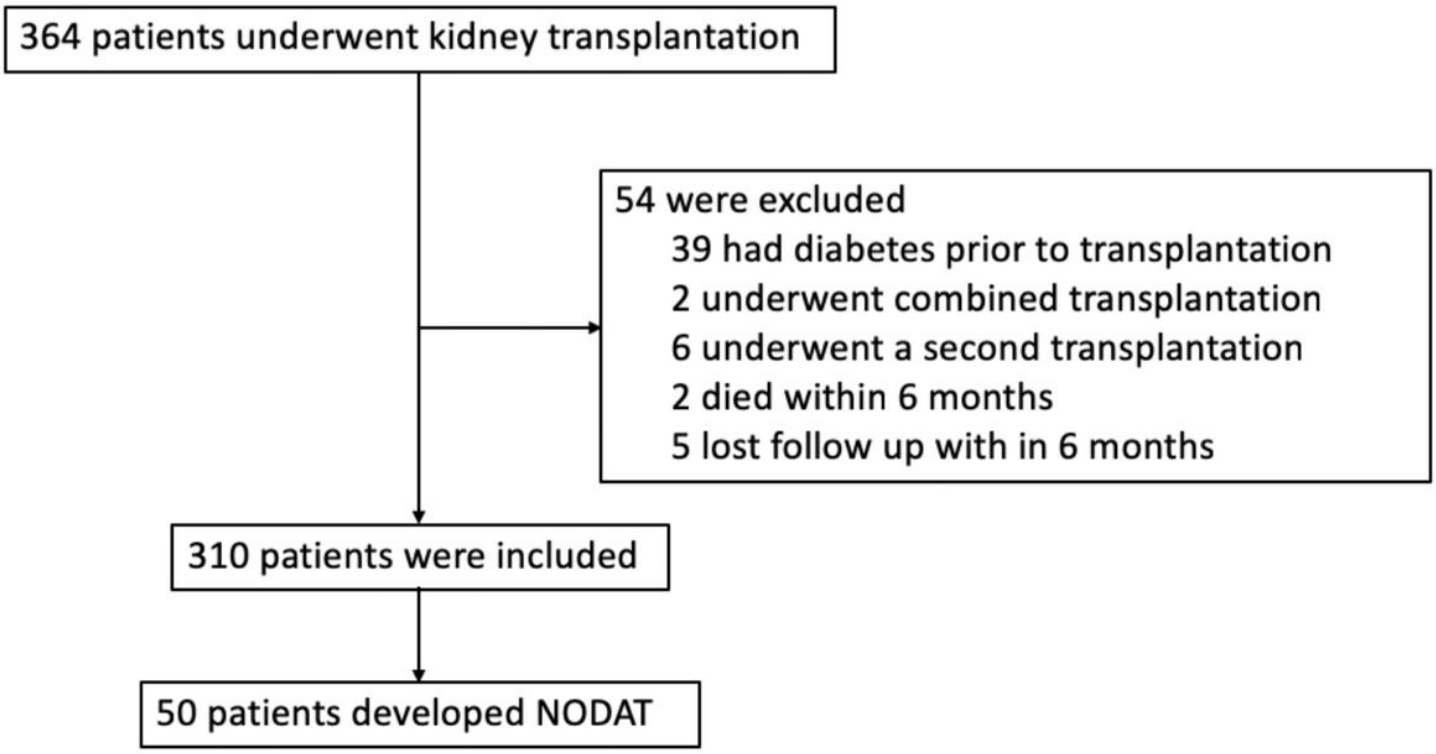

Figure 1

Enrolment and outcomes. A total of 310 patients were enrolled, and 50 patients developed PTDM.

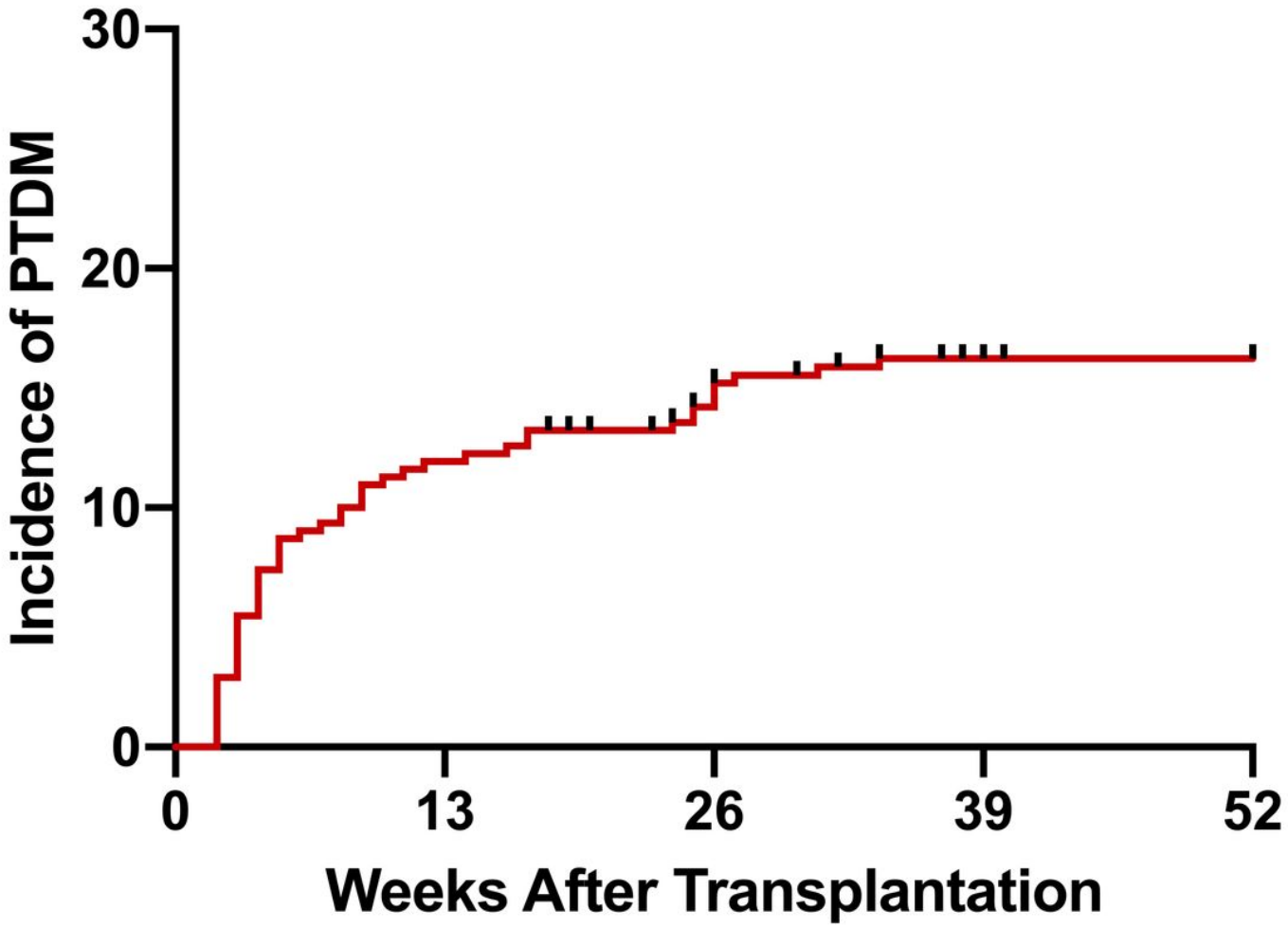

Figure 2

The incidence of PTDM within 1 year. The Kaplan-Meier estimates of event rates are presented here. A total of 16.4% of patients developed PTDM within one year.

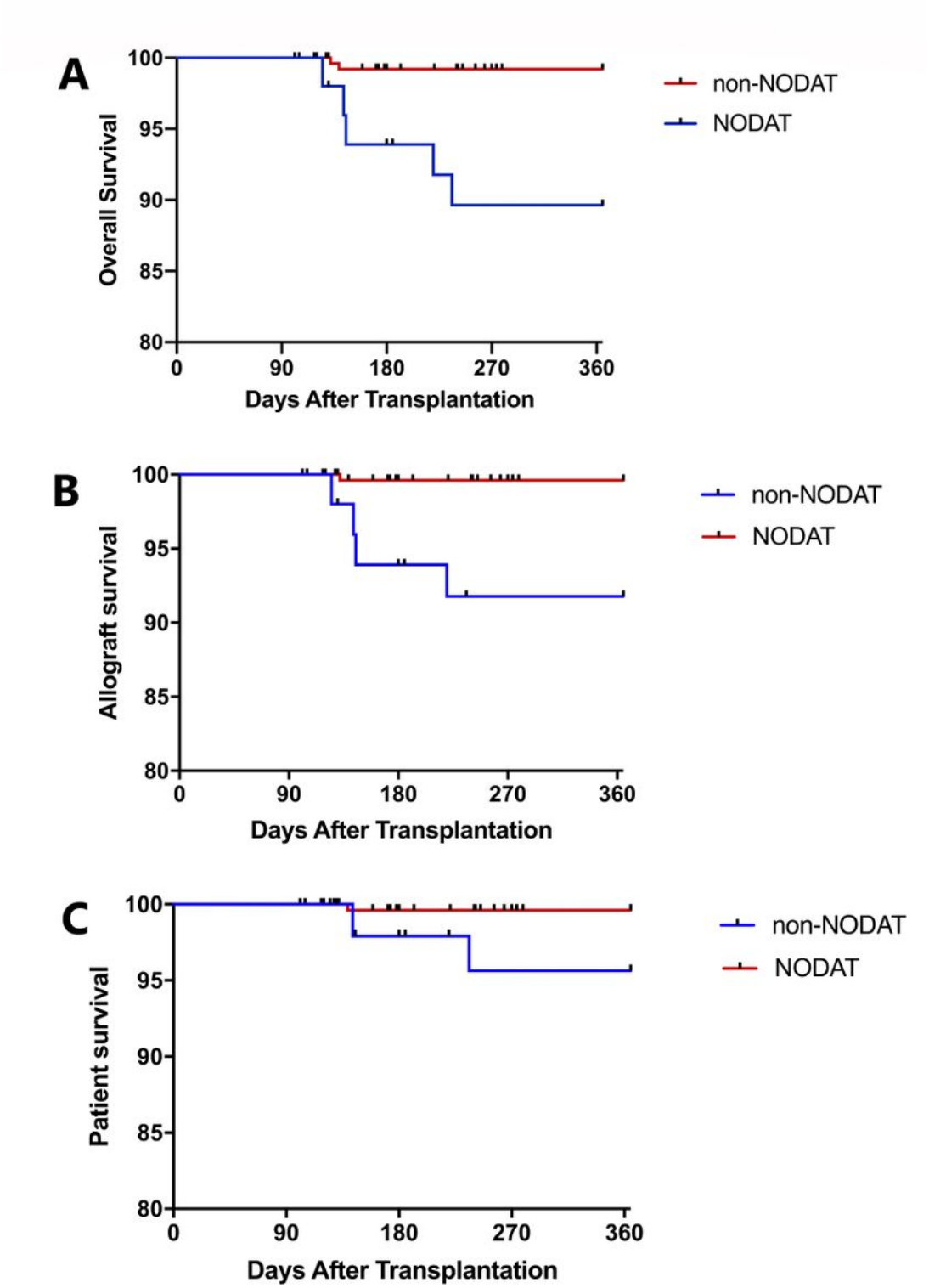

Figure 3

3A: Graft survival rate. The graft survival rate of non-PTDM is 99.23%, while the survival rate of PTDM is 88%. P<0.001. 3B: Death-censored allograft survival rate. The survival rate of non-PTDM is 99.97%, while the survival rate of PTDM is 90%. P<0.001. 3C: Patient survival rate. The survival rate of non-PTDM is 99.7%, while the survival rate of PTDM is 96%. P=0.109.

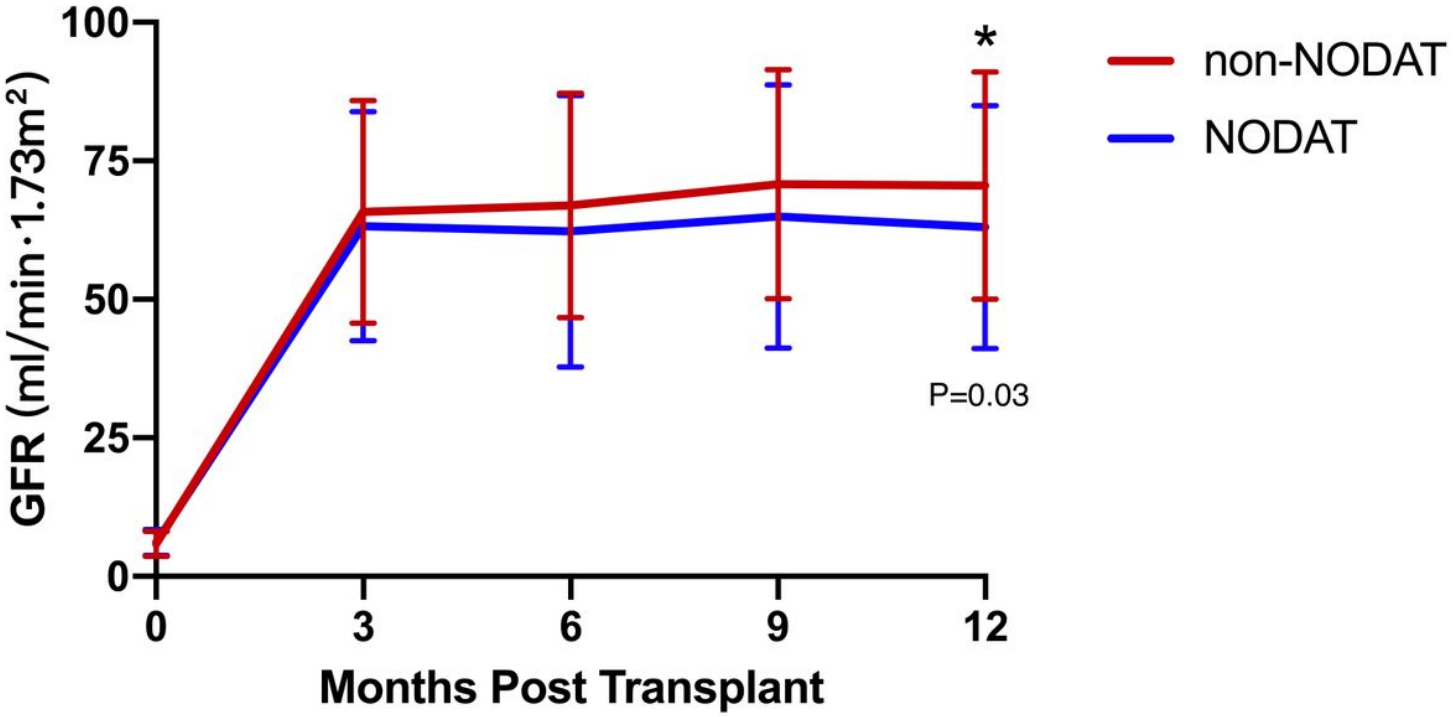

Figure 4

Mean levels of eGFR. Patients in the PTDM group had lower eGFR at 12 months (p=0.03).