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Trends in the effects of pre-transplant diabetes on mortality and cardiovascular events after kidney transplantation

Ja Young Jeon[1†], Soo Jung Kim[2†], Kyoung Hwa Ha[1], Ji Hyun Park[3], Bumhee Park[3,4], Chang-Kwon Oh[2], Seung Jin Han[1*]

[1]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea, [2]Department of Surgery, Ajou University School of Medicine, Suwon, Korea, [3]Office of Biostatistics, Ajou Research Institute for Innovation Medicine, Ajou University Medical Center, Suwon, Korea, and [4]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea

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***Correspondence**
Seung Jin Han
Tel.: +82-31-219-5126
Fax: +82-31-219-4497
E-mail address:
hsj@ajou.ac.kr

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ABSTRACT

Aims/Introduction: It is not clear whether survival in kidney transplant recipients with pre-transplant diabetes has improved over the past decades. We compared the rates of mortality and major adverse cardiovascular events (MACE) after renal transplantation in patients with and without pre-transplant diabetes. Furthermore, we investigated whether transplant era and recipient age affected the association between diabetes status and adverse events.

Materials and Methods: This retrospective cohort study included 691 patients who underwent renal transplantation between 1994 and 2016 at a single tertiary center. We compared the incidences of post-transplant mortality and four-point MACE in patients with and without pre-transplant diabetes using Kaplan–Meier analysis and the Cox proportional hazard model, and assessed the interactions between diabetes status and transplant era and recipient age.

Results: Of 691 kidney recipients, 143 (20.7%) had pre-transplant diabetes. The mean follow-up duration was 94.5 months. Kaplan–Meier analysis showed that patients with pre-transplant diabetes had higher incidences of post-transplant mortality and four-point MACE compared with those without pre-transplant diabetes (log–rank test, $P < 0.001$ for both). After adjusting for potential confounding factors, pre-transplant diabetes was associated with an increased risk of post-transplant mortality and four-point MACE (hazard ratio 1.90, 95% confidence interval 1.05–3.44, $P = 0.034$; and hazard ratio 1.75; 95% confidence interval 1.02–3.00, $P = 0.043$, respectively). The associations between pre-transplant diabetes status and all-cause mortality and four-point MACE were not affected by transplant era or recipient age.

Conclusions: Pre-transplant diabetes remains a significant risk factor for mortality and four-point MACE in kidney transplant recipients.

INTRODUCTION

The prevalence of diabetes has risen rapidly and more than doubled worldwide over the past two decades[1,2]. Similarly, diabetic nephropathy has increased rapidly globally[3], and has become a leading cause of end-stage renal disease (ESRD)[2,4]. Korea has one of the highest prevalence rates of diabetic nephropathy in patients with ESRD in the world. The prevalence in Korea is similar to that in other Asian countries and the USA, which reported that 48% of the new ESRD cases in 2014 were attributable to diabetes[5].

Kidney transplantation is the preferred renal replacement therapy for ESRD patients with diabetes, because it is associated with better survival and quality of life compared with dialysis[6,7]. Recently, overall and cardiovascular mortality rates decreased markedly among patients with diabetes in developed countries in tandem with improvements in diabetes care and cardiovascular disease management[8-10]. Furthermore, the gap in

†These authors contributed equally to this study.
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mortality between individuals with and without diabetes has decreased continuously over the past decades. In light of these findings, there is growing interest in determining whether mortality rates in kidney transplant recipients with diabetes have improved. However, previous comparisons of outcomes in kidney recipients with and without diabetes have yielded conflicting results. Several studies found that the survival rate was lower in kidney transplant recipients with diabetes than in those without diabetes, which was attributed to a high incidence of cardiovascular events[11-14], whereas others found no significant differences in patient outcomes[15-18]. Furthermore, although two previous studies investigated temporal trends in kidney transplant outcomes in patients with and without diabetes, the findings were inconsistent[19,20].

We compared long-term mortality and major adverse cardiovascular events (MACE) in kidney transplant recipients with or without diabetes before transplantation. Furthermore, we investigated whether transplant era and recipient age modified the associations between diabetes status and mortality and MACE.

METHODS

Study design and population

The present retrospective, observational cohort study included patients who underwent primary renal transplantation between 1994 and 2016 at a single tertiary center and were followed up until March 2019. After excluding patients aged <18 years (n = 13), as well as those lost to follow up (n = 8) and those who had received two or more graft transplantations or multiple-organ transplants (n = 19) or transplantation since 2016 (n = 129), the final analysis included 691 of the 860-recipient cohort. The study protocol was approved by the institutional review board of Ajou University Hospital, and conformed to the ethical guidelines of the Declaration of Helsinki. Relevant data were obtained from the institutional electronic database that included medical records by cohort.

Pre-transplant diabetes was defined as a clinical diagnosis of diabetes before transplantation based on medical records. Of the 143 patients with diabetes, 10 (7%), 132 (92.3%) and one (0.7%) had type 1, type 2 and pancreatogenic diabetes, respectively. Comorbidities at baseline included hypertension (HTN; previous diagnosis by a physician and treatment with antihypertensive drugs before transplantation), coronary artery disease (myocardial infarction, hospitalization for unstable angina, coronary artery bypass graft, percutaneous coronary intervention or stable angina), cerebrovascular disease (ischemic/hemorrhagic stroke or transient ischemic attack) and peripheral arterial disease (peripheral vascular disease or peripheral vascular surgery). A history of cardiovascular disease was defined as a history of coronary artery disease, cerebrovascular disease or peripheral arterial disease.

Immunosuppression protocol

Most patients (n = 589, 85.2%) underwent induction immunosuppression therapy (basiliximab [n = 586, 84.8%] or anti-thymocyte globulin/anti-lymphocyte globulin [n = 3, 0.4%]). All recipients initially received a calcineurin inhibitor (CNI; FK506, 57.7% or cyclosporine A, 42.3%). Of those, 87% of the recipients received maintenance immunosuppression therapy with a CNI-based triple regimen (CNI/anti-proliferative agent/steroid), and the remaining patients received a double regimen (CNI/steroid). Mycophenolate was the most commonly prescribed anti-proliferative agent (n = 579, 96%), and the remaining recipients (n = 22, 4%) received other anti-proliferative agents (sirolimus, azathioprine or everolimus).

Post-transplant outcomes

The primary end-points were all-cause mortality and four-point MACE outcome, defined as cardiovascular death, myocardial infarction, ischemic/hemorrhagic stroke or hospitalization for unstable angina. The secondary outcomes included overall graft loss and death-censored graft loss. Overall graft loss was defined as death or cases requiring dialysis (death-censored graft loss). The causes of graft loss were assessed by the transplant specialist based on kidney biopsy findings or the clinical course of the recipients.

Statistical analysis

Non-parametric continuous variables are shown as medians and interquartile ranges, and categorical variables as numbers and percentages. The Mann–Whitney U-test was used to compare non-parametric continuous variables, and the χ^2-test or Fisher's exact test for categorical variables. The cumulative incidences of four-point MACE and all-cause death were plotted as Kaplan–Meier curves and compared using the log–rank test. All-cause mortality rates and four-point MACE incidence rates were calculated for up to 5 years. Multivariate Cox proportional hazards models were used to assess the association between mortality/four-point MACE outcomes and pre-transplant diabetes. The findings are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Adjusted survival curves were generated using the Cox proportional hazards models. To test for interactions between diabetes status and transplant era and recipient age for all-cause mortality and four-point MACE, first-order interaction terms were added into the models. Two-sided P-values <0.05 were considered statistically significant. All statistical tests were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cohort baseline characteristics

At baseline, the mean age of the study participants was 45 years, 57.3% were men, and 143 patients (20.7%) had diabetes at the time of renal transplantation (Table 1). The patients were followed for a mean of 94.5 months (standard deviation 61.8 months). Patients in the pre-transplant diabetes group were older, had a higher incidence of obesity, were more likely to be smokers, had a higher rate of comorbidities, were

more likely to be treated with FK506 than with cyclosporine and were more likely to receive transplants from older donors than patients without pre-transplant diabetes (Table 1). The main cause of ESRD was diabetic nephropathy in recipients with pre-transplant diabetes, and glomerulonephritis in those without pre-transplant diabetes. Over the past two decades, the proportion of kidney recipients with pre-transplant diabetes doubled from 11.6% in the 1994–2005 period to 23.1% in the 2005–2016 period (Table 1). Furthermore, the prevalence of comorbid cardiovascular disease in kidney recipients also increased over this time period (Table S1).

Comparison of kidney transplant outcomes between recipients with and without pre-transplant diabetes

Of the 691 recipients in the study, 64 (9.3%) died and 80 (11.6%) experienced four-point MACE. Overall, graft loss and death-censored graft failure were observed in 157 (22.7%) and 101 (14.6%) patients, respectively.

The Kaplan–Meier curves for transplant outcomes in patients with and without pre-transplant diabetes are shown in Figure 1. The incidences of all-cause mortality and four-point MACE were significantly higher in recipients with pre-transplant diabetes than in those without pre-transplant diabetes (Figure 1; log–rank test, $P < 0.001$ for both).

After adjusting for age, sex, smoking status, body mass index, HTN, history of cardiovascular disease, donor age, donor type (live or deceased) and transplant era (1994–2005 or 2006–2016), the risks of post-transplant death and four-point MACE remained significantly higher in patients with pre-transplant diabetes than in those without pre-transplant diabetes (Table 2; HR 1.90, 95% CI 1.05–3.44, $P = 0.034$; and HR 1.75, 95% CI 1.02–3.00, $P = 0.043$, respectively).

Table 1 | Patient baseline characteristics according to pre-transplant diabetes status

		No diabetes (n = 548)	Diabetes (n = 143)	P-value
Age (years)		43 (35–51)	52 (46–57)	<0.001
Sex (male)		305 (55.7%)	91 (63.6%)	0.105
BMI (kg/m^2)		22.1 (20–24)	23.50 (22–26)	<0.001
Type of dialysis	PD	86 (15.7%)	14 (9.8%)	0.110
	HD	457 (83.4%)	126 (88.1%)	
	Pre-emptive	5 (0.9%)	3 (2.1%)	
Smoking		97 (17.7%)	49 (34.3%)	<0.001
Comorbidities				
HTN		367 (67.0%)	127 (88.8%)	<0.001
Cardiovascular disease		16 (2.9%)	32 (22.4%)	<0.001
CAD		7 (1.3%)	19 (13.3%)	<0.001
CVD		10 (1.8%)	13 (9.1%)	<0.001
PAD		1 (0.2%)	7 (4.9%)	<0.001
Waiting time (months)		30.4 (4–66)	26.4 (3–61)	0.485
Immunosuppressive drugs	FK506	303 (55.6%)	95 (66.4%)	0.025
	CsA	242 (44.4%)	48 (33.6%)	
Cause of ESRD	GN[†]	122 (22.3%)	2 (1.4%)	<0.001
	DM	0	104 (72.7%)	
	PCKD	20 (3.7%)	0	
	HTN	18 (3.3%)	0	
	Lupus	10 (1.8%)	0	
	Miscellaneous[‡]	6 (1.1%)	0	
	Unknown	372 (67.9%)	37 (25.9%)	
Donor characteristics				
Age (years)		42 (31–51)	47 (33–54)	0.014
ABO incompatible		5 (0.9%)	2 (1.4%)	0.639
Living		288 (52.8%)	79 (55.2%)	0.676
Transplant era	1994–2005	129 (23.5%)	17 (11.9%)	0.003
	2006–2016	419 (76.5%)	126 (88.1%)	

Non-parametric continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers and percentages. [‡]Miscellaneous includes Alport syndrome, interstitial nephritis, pyelonephritis and poststreptococcal glomerulonephritis. BMI, body mass index; CsA, cyclosporine A; CVD, cerebrovascular disease; DM, diabetes; ESRD, end-stage renal disease; FK506, tacrolimus; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension: CAD, coronary artery disease; PAD, peripheral artery disease; PCKD, polycystic kidney disease; PD, peritoneal dialysis. [†]Glomerulonephritis includes immunoglobulin A nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis and membranous glomerulonephritis.

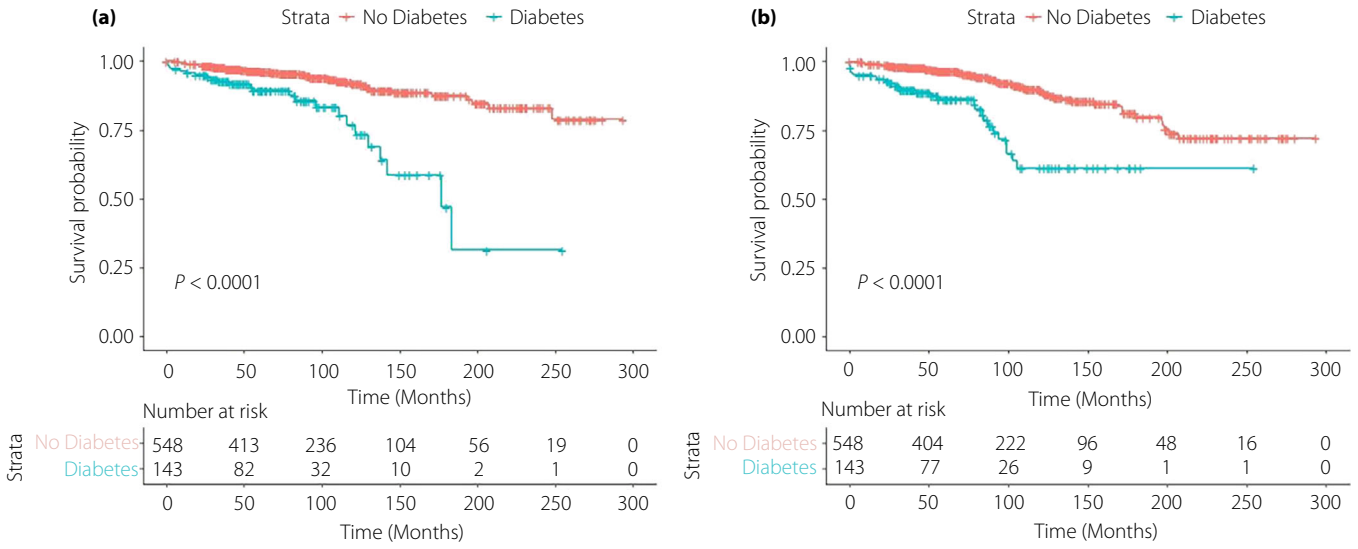

Figure 1 | Kaplan–Meier curves for all-cause mortality and four-point major adverse cardiovascular events according to diabetes status (log–rank test, $P < 0.001$ and $P < 0.001$). (a) All-cause mortality. (b) Four-point major adverse cardiovascular events.

The incidence of overall graft loss was similar between patients with and without pre-transplant diabetes (21.0% vs 23.2%); however, death with a functioning graft was higher in the diabetes group than in the non-diabetes group (15.4% vs 6.2%; Table S2). Overall graft loss was not significantly different between recipients with and without pre-transplant diabetes in the adjusted model (HR 1.09, 95% CI 0.69–1.72, $P = 0.728$; Table 2). Although patients with pre-transplant diabetes tended to experience less death-censored graft failure, the association was not statistically significant (HR 0.46, 95% CI 0.20–1.01, $P = 0.054$).

Additionally, there were no significant differences in death-censored graft failure and all-cause death between the post-transplant diabetes group and non-diabetes group among patients without pre-transplant diabetes in adjusted model (HR 1.05, 95% CI 0.62–1.78, $P = 0.851$; and HR 0.66, 95% CI 0.28–1.53, $P = 0.328$, respectively).

Comparisons of all-cause mortality and four-point MACE between recipients with and without pre-transplant diabetes stratified by transplant era and recipient age

Multivariate Cox regression analysis showed that all-cause mortality was significantly associated with an earlier transplant era, older age and pre-transplant diabetes (Table 2), suggesting that kidney transplant-related mortality has decreased over the past decade. Figure 2a and b show the adjusted survival curves for

Table 2 | Multivariate analysis of all-cause death and four-point major adverse cardiovascular events in kidney transplant recipients

Variables	All-cause death		Four-point MACE	
	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
DM	1.90 (1.05–3.44)	0.034	1.75 (1.02–3.00)	0.043
2006–2016 transplant era (vs 1994–2005)	0.46 (0.24–0.89)	0.021	1.46 (0.74–2.89)	0.280
Age (per year increase)	1.06 (1.03–1.10)	<0.001	1.04 (1.01–1.07)	0.004
Female sex	1.15 (0.64–2.07)	0.643	0.70 (0.41–1.20)	0.197
Smoker	1.33 (0.68–2.58)	0.405	1.53 (0.88–2.67)	0.132
BMI (per 1-kg/m^2 increase)	0.99 (0.90–1.09)	0.876	1.02 (0.94–1.10)	0.727
HTN	1.12 (0.61–2.04)	0.720	2.19 (1.21–3.99)	0.010
Cardiovascular disease	1.52 (0.67–3.43)	0.313	3.23 (1.79–5.85)	<0.001
Donor age (per 1-year increase)	1.01 (0.99–1.04)	0.172	0.99 (0.98–1.01)	0.350
Deceased-donor (vs living donor)	1.57 (0.91–2.70)	0.102	2.57 (1.57–4.19)	<0.001

A Cox proportional hazards model adjusted for diabetes status, age, sex, smoking, body mass index (BMI), hypertension (HTN), cardiovascular disease, donor age, donor type, and transplant era was used to estimate the hazard ratios (HR) and confidence intervals (CI). MACE, major adverse cardiovascular events.

all-cause mortality and four-point MACE according to diabetes status and transplant era, generated using the same model described in Table 2. To determine whether the impact of diabetes on all-cause mortality and four-point MACE has decreased, we analyzed the interaction effect of diabetes status and transplant era on survival. The adjusted survival curves showed that the differences in mortality and four-point MACE between the diabetes and non-diabetes groups did not differ by transplant era. The analysis of the interactions between diabetes status and transplant era using the first-order interaction terms added into the same logistic model showed that there was no significant interaction between diabetes status and transplant era in relation to all-cause mortality (*P*-value for interaction = 0.493) or four-point MACE (*P*-value for interaction = 0.337). This suggests that the association of diabetes with poor transplantation outcomes has not diminished in the recent transplant era.

The causes of death in kidney recipients according to pre-transplant diabetes status and transplant era are shown in Table S3.

Figure 2c and d show the adjusted survival curves for all-cause mortality and four-point MACE according to diabetes status and recipient age. Recipient age did not significantly affect the incidences of all-cause mortality and four-point MACE in either recipient group. Thus, the associations between diabetes status and all-cause mortality and four-point MACE were not modified by recipient age (*P*-values for interaction = 0.542 and 0.696, respectively).

DISCUSSION

The present long-term retrospective cohort study compared all-cause mortality and four-point MACE between kidney transplant recipients with and without pre-transplant diabetes. Diabetes is associated with poor patient outcomes after renal

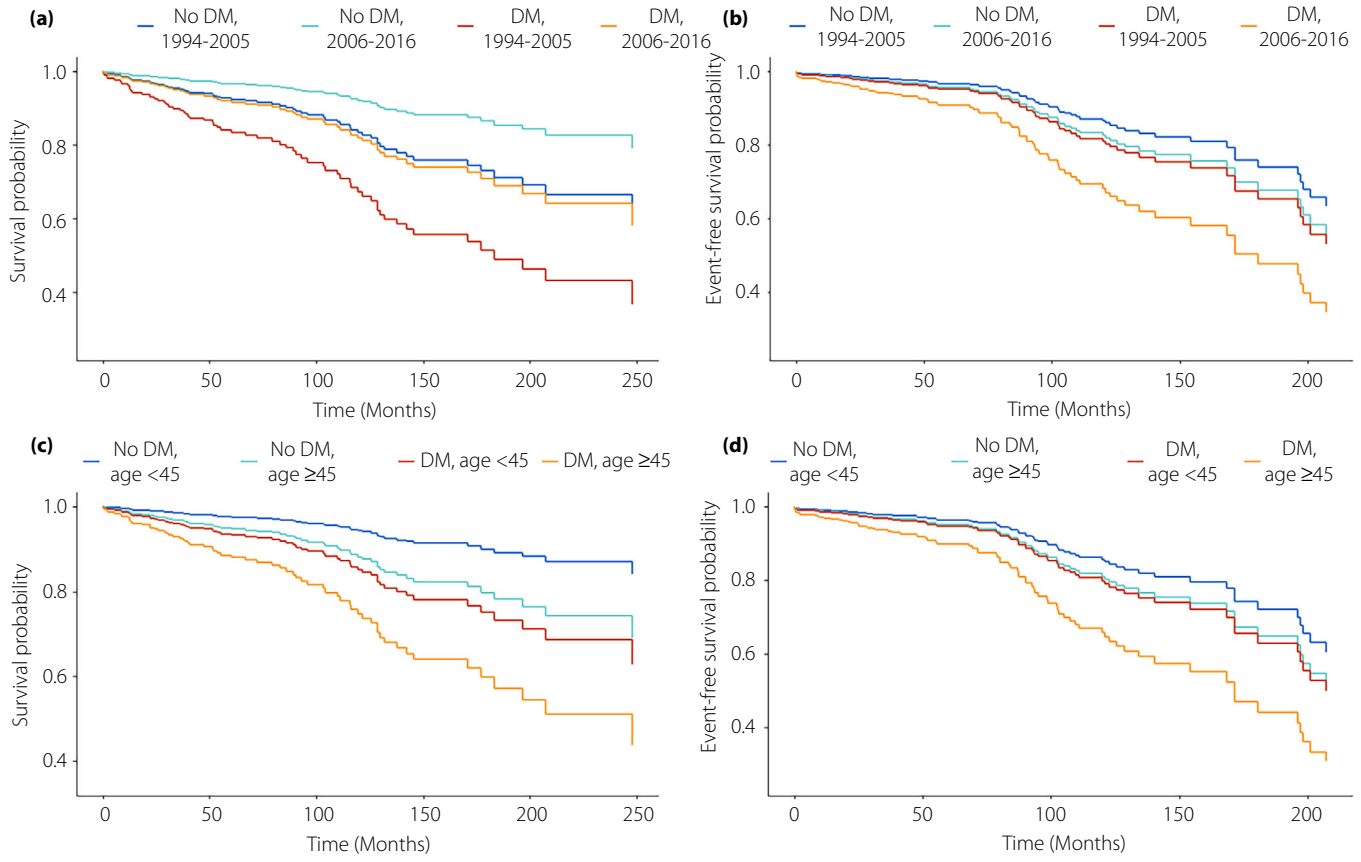

Figure 2 | Adjusted survival curves for all-cause mortality and four-point major adverse cardiovascular events according to diabetes status stratified by (a,b) transplant era and (c,d) recipient age. The adjusted survival curves were generated by Cox proportional hazards models adjusted for age, sex, smoking status, body mass index, hypertension, history of cardiovascular disease, donor age and donor type. (a) All-cause mortality according to diabetes status and transplant era. (b) Four-point major adverse cardiovascular events according to diabetes status and transplant era. (c) All-cause mortality according to diabetes status and recipient age. (d) Four-point major adverse cardiovascular events according to diabetes status and recipient age. DM, diabetes.

transplantation. Although survival in kidney transplant recipients has improved in recent years, pre-transplant diabetes remains an independent risk factor for post-transplant mortality and cardiovascular events regardless of transplant era and recipient age. Overall graft loss was similar between recipients with and without pre-transplant diabetes; however, we observed a trend toward fewer incidences of death-censored graft failure in patients with diabetes.

The present findings confirm those of previous studies that reported a negative impact of diabetes on patient survival and cardiovascular risk after renal transplantation[11,12,20,21]. Although a few previous studies found comparable outcomes between kidney transplant recipients with and without diabetes, the studies were limited by a relatively small sample size or the inclusion of only living-donor or cadaveric transplantation[15,16,18].

Comparisons of mortality in kidney transplant recipients with and without pre-transplant diabetes according to transplant era have yielded conflicting results[19,20]. A single-center study of 1,688 kidney recipients carried out at the Mayo Clinic between 1996 and 2007 found that mortality and cardiovascular events declined progressively in recipients with diabetes, but not in patients without diabetes. Furthermore, the 5-year mortality rate was not significantly different between groups from 2004 to 2007. The authors suggested that the increased survival of recipients with diabetes reflected, in part, improved post-transplant care[19]. By contrast, a recent large cohort study of 10,714 patients from the Australian and New Zealand registry for the period between 1994 and 2012 found that survival rates in kidney transplant recipients with diabetes did not improve over time compared with those without diabetes[20], which is consistent with the present findings.

In a study by the same group, recipient age modified the association between diabetes status and all-cause mortality and cardiovascular disease mortality, such that younger recipients were at increased risk of adverse outcomes[20]. By contrast, we did not find an interaction between diabetes status and recipient age for all-cause mortality or four-point MACE. The impact of diabetes on all-cause mortality and four-point MACE was not significantly different in older (≥45 years) and younger (<45 years) kidney transplant recipients. This disparity might be explained by differences in participant characteristics, including ethnicity, proportion of patients with diabetes included in the study, selection criteria for transplantation and differences in pre- or post-transplant management.

The unadjusted Kaplan–Meier curve showed that the recent transplant era (2006–2016) was associated with an increased risk of four-point MACE compared with the 1994–2005 transplant era (log–rank test, $P = 0.004$, data not shown). However, after adjusting for the potential confounding factors age, sex, smoking status, body mass index, diabetes, HTN, history of cardiovascular disease, donor age and donor type, there was no significant difference between the 1994–2005 and 2006–2016 transplant eras (Table 2). These findings were influenced by the differences in baseline characteristics of recipients between the transplant eras. Recipients in the 2006–2016 transplant era had more risk factors for four-point MACE, such as old age, diabetes, HTN, cardiovascular disease and smoking, compared with those in the 1994–2005 transplant era (all P-values <0.05). Since the early 2000s, studies reporting good outcomes of older kidney transplant recipients and improved survival after kidney transplantation might have indirectly increased the number of potential recipients[22,23]. The increasing prevalence of cardiovascular disease, and the improvements in mortality associated with the initial cerebrovascular disease event, are in accordance with those in the general population, although few studies have analyzed cardiovascular disease trends in kidney recipients alone[24,25].

In terms of allograft-specific outcomes, overall graft failure and death-censored graft failure rates were similar between groups. In the recipients with pre-transplant diabetes, overall graft failure was most often caused by death with a functioning kidney. No grafts failed due to diabetic nephropathy in the present study. Other than death with a functioning graft, the main cause of graft failure was chronic allograft rejection, which is not affected by diabetes[12,26].

The mortality rates of kidney transplant recipients with and without diabetes (3.28 vs 9.09 per 100 recipients at 5 years, respectively) in the present study are consistent with those reported in recent studies[11,18,27,28]. The two major causes of death in our patients with pre-transplant diabetes were infection and cardiovascular disease. The major causes of death after renal transplantation in Korean recipients are slightly different from those reported in Western countries. Since the 1990s, atherosclerotic cardiovascular disease has replaced infection as the leading cause of post-transplant death in the USA[29]. Infection-related death is still the most common cause of death in Korean kidney recipients, and cardiovascular mortality is the second-highest cause of post-transplant death[30]. Infection-related and cardiovascular mortality was higher in recipients with pre-transplant diabetes than in those without diabetes; however, the difference disappeared after adjusting for confounding factors due to a small number of events.

We investigated long-term outcomes in kidney transplant recipients with and without pre-transplant diabetes in an Asian population. To our knowledge, the present study is the first to identify an association between diabetes status and mortality and four-point MACE, and investigate the modifying effects of transplant era and age. Our study had several limitations. We could not control for unmeasured potential confounding factors, such as the effects of glycemic control and drugs used to treat cardiovascular disease, that might affect survival and four-point MACE. We did not assess glycemic control before and after transplantation; therefore, we could not assess the contribution of glycemic control to the increased risk of adverse events in recipients with pre-transplant diabetes. However, previous studies have reported conflicting findings on the impact of glycemic control on clinical outcomes in diabetic kidney

transplant recipients[12,31,32]. Additionally, our single-center retrospective cohort study might not represent the wider transplant recipient population. Large, multicenter prospective studies are required to confirm the present findings. As our cohort comprised only Korean kidney recipients, our findings might not be generalizable to other populations. The rates of use of calcineurin inhibitors differed between the diabetes and non-diabetes groups. Cyclosporin and tacrolimus have several side-effect profiles, which could in turn affect transplant outcomes[33]. In particular, in terms of glucose metabolism, tacrolimus might worsen glycemic control in patients with pre-existing diabetes, and have a relatively higher risk for developing post-transplant diabetes than cyclosprin[34,35]. However, in further multivariate Cox regression analyses including cyclosporine or tacrolimus use as a confounder, the results regarding all-cause mortality and four-point MACE were similar (data not shown).

In conclusion, we found no evidence to suggest that the rates of mortality and cardiovascular events in kidney recipients with pre-transplant diabetes have improved over the past decades. Furthermore, age did not modify the relationships between diabetes status and mortality and cardiovascular events. Therefore, there is an urgent need to develop strategies to reduce the risk of mortality and adverse cardiovascular events in kidney recipients with pre-transplant diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Patient baseline characteristics according to pre-transplant diabetes status and transplant era. Non-parametric continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers and percentages.

Table S2 | Causes of graft failure in kidney recipients.

Table S3 | Causes of death in kidney recipients according to pre-transplant diabetes status and transplant era.