



Framingham risk score is a useful indicator of posttransplant cardiovascular events and survival among Korean kidney transplant recipients: a nationwide, prospective cohort study

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Background: Cardiovascular disease is an important risk factor for mortality among kidney transplant recipients. In this study, we aimed to investigate the association between cardiovascular risk score at kidney transplantation and long-term outcomes of patients.

Methods: In this prospective, observational cohort study, we enrolled kidney transplant recipients who participated in the Korean Organ Transplantation Registry and underwent transplantation between April 2014 and December 2019. The cardiovascular risk status of kidney transplant recipients was assessed using the Framingham risk score. All-cause mortality, major adverse cardiovascular events, allograft failure, estimated glomerular filtration rates (eGFRs), and composite outcomes were evaluated after kidney transplantation.

Results: Of the 4,682 kidney transplant recipients, 96 died during 30.7 ± 19.1 months of follow-up. The Kaplan-Meier survival analysis results showed that high Framingham risk scores were associated with all-cause mortality, major adverse cardiovascular events, and composite outcomes. According to the multivariable Cox analysis, high Framingham risk scores were associated with an increased risk of mortality (hazard ratio [HR], 3.20; 95% confidence interval [CI], 1.30–7.91), major adverse cardiovascular events (HR, 8.43; 95% CI, 2.41–29.52), and composite outcomes (HR, 2.05; 95% CI, 1.19–3.46). The eGFRs after transplantation were significantly higher among patients in the low Framingham risk score group ($p < 0.001$). However, Framingham risk scores were not associated with graft loss or rapid decline in eGFRs.

Conclusion: The Framingham risk score is a useful indicator of cardiovascular events, mortality, and kidney function after kidney transplantation.

Keywords: Cardiovascular disease, Framingham risk score, Glomerular filtration rate, Kidney transplantation, Major adverse cardiovascular event, Mortality

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Introduction

Cardiovascular disease is one of the most common complications of chronic kidney disease (CKD) and a leading cause of mortality among patients with CKD [1]. Patients with CKD who experience progression to end-stage kidney disease (ESKD) require renal replacement therapy including hemodialysis, peritoneal dialysis, and kidney transplantation [2]. The survival outcomes of these patients are significantly poor compared with those of patients with CKD who are not on dialysis and those of the general population [3]. In the United States, the 1-year mortality rate after the initiation of dialysis is approximately 30% [4]. The risks of mortality and cardiovascular events increase with the progression of CKD [5], and cardiovascular disease is the leading cause of death in patients on dialysis [6].

Kidney transplantation, which can reduce complications and improve the patients' quality of life and prognosis, is generally preferred over other dialysis modalities. One cohort study found that the relative risk of death for kidney transplant recipients (KTRs) decreased by approximately 47% compared with that of patients with ESKD on the kidney transplantation waiting list [7]. This reduction in cardiovascular events and improvement in survival after kidney transplantation are mainly related to the improvement in kidney function [8]. However, the risks of cardiovascular disease and death remain high even after kidney transplantation; KTRs have an approximately 50-fold greater risk of cardiovascular disease than the general population [9]. The increased risk of cardiovascular disease among KTRs is responsible for their increased mortality and worsening prognosis. According to the United States Renal Data System (1996–2014) report, death from cardiovascular disease (24.7%) was the main cause of death in KTRs [10].

Efforts have been made to reduce the risk of cardiovascular disease before transplantation. The Framingham risk score is the most commonly used index for predicting the risks of cardiovascular disease and death among KTRs [11–13]. However, studies on the implications of the Framingham risk score with regard to cardiovascular events and mortality after transplantation in Asian KTRs are still lacking. In addition, there have been few studies on the effect of cardiovascular disease risk as assessed using the Framingham risk score on kidney function after transplan-

tation. In this study, we aimed to investigate the association of cardiovascular risk status before transplantation as assessed using the Framingham risk score with all-cause mortality, major cardiovascular events (MACEs), graft failure, and estimated glomerular filtration rates (eGFRs) after transplantation among Asian KTRs.

Methods

Participants and study design

This longitudinal, prospective, observational cohort study enrolled a total of 6,129 adults (19 years or older) who had undergone kidney transplantation between April 2014 and December 2019 and were screened using a nationwide prospective transplantation registry (Korean Organ Transplantation Registry, KOTRY). In April 2014, the prospective KOTRY began enrolling patients from 30 kidney transplantation centers in South Korea [14]. KTRs without baseline clinical information regarding systolic blood pressure ($n = 28$), total cholesterol levels ($n = 442$), and high-density lipoprotein cholesterol levels ($n = 1,228$) were excluded. A total of 4,682 KTRs were included in the final analysis (Fig. 1).

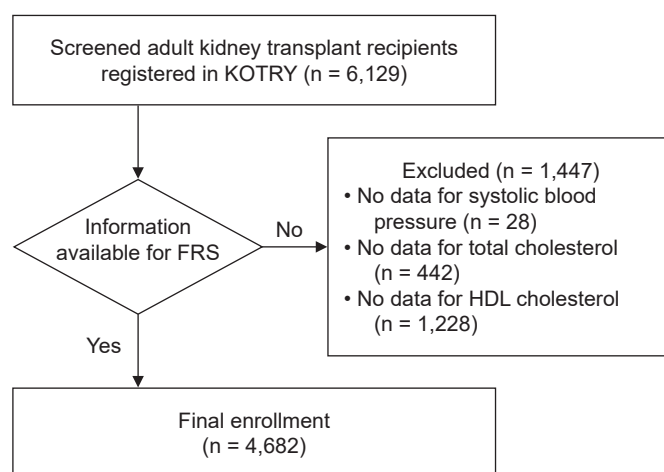


Figure 1. Flowchart of enrolled patients. A total of 6,129 adult kidney transplant recipients (KTRs) were screened for the nationwide prospective Korean Organ Transplantation Registry (KOTRY). A total of 4,682 KTRs were included in the final analysis. FRS, Framingham risk score; HDL, high-density lipoprotein.

Data collection, definitions, classifications, and outcomes

We determined each patient's cardiovascular risk before transplantation using the Framingham risk score (American College of Cardiology/American Heart Association 2013 atherosclerotic cardiovascular disease risk score) [15]. In brief, the Framingham risk score is derived from a regression equation for calculating the 10-year risk of atherosclerotic cardiovascular disease (first occurrence of nonfatal myocardial infarction or coronary heart disease death, or fatal or nonfatal stroke) identified in a number of large cohort studies and includes a number of key variables including age, sex, ethnicity, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (including treated or untreated status), diabetes mellitus, and current smoking status. Framingham risk scores were categorized into quartiles. Mortality, MACEs, and graft failure of the KTRs were evaluated after transplantation by an independent researcher who was blinded to the cardiovascular risk scores before transplantation. Data regarding mortality of the KTRs (date and cause of death) were collected by merging the Statistics Korea data with data from the KOTRY. A MACE was defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization because of heart failure, and revascularization including percutaneous coronary intervention or coronary artery bypass graft [16]. Graft failure was defined as the need for permanent dialysis, allograft nephrectomy, or repeat transplantation, excluding the patient's death [17]. Additionally, we evaluated composite outcomes of mortality, MACEs, and graft failure. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation at 6, 12, 24, and 36 months after kidney transplantation [18].

In the KOTRY data set, key clinical parameters such as comorbidities are defined based on the patient's medical history, medications, and laboratory results are registered by a physician, trained clinical coordinators based on history taking or medical record review. Hypertension is defined as an average systolic blood pressure of higher than 140 mmHg or diastolic blood pressure of higher than 90 mmHg measured at least twice, a history of hypertension, or currently taking antihypertensive medications. Diabetes mellitus is defined as fasting glucose level of higher than 126 mg/dL, random glucose level of higher than 200 mg/dL, hemoglobin A1c level of higher than 6.5%, history of

diabetes mellitus, or currently taking anti-diabetes medications. Donor type is categorized into liver or deceased donor. Primary kidney diseases are classified as diabetes mellitus, hypertension, glomerulonephritis, tubulointerstitial disease, autosomal dominant polycystic kidney disease (ADPKD), hereditary diseases other than ADPKD, obstructive nephropathy, and others.

Statistical analysis

Categorical variables are expressed as frequencies with percentages, and continuous variables are expressed as means $\pm$ standard deviations. Variables were visualized using histograms for normal distributions that were tested using the Kolmogorov-Smirnov test. Variables of baseline characteristics were compared using an analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables based on the Framingham risk score quartile categories. The *post hoc* Bonferroni correction was applied in the ANOVA. The cardiovascular risk status of KTRs at transplantation, as represented by the Framingham risk score, was calculated using the R package "CVrisk" (<https://github.com/vcastro/CVrisk>). The effects of the cardiovascular risk score before transplantation on outcomes, including mortality, MACEs, graft failure, and composite outcomes, were evaluated using the Kaplan-Meier analysis. Multivariable Cox proportional hazard models were used to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes. In the multivariable model, the following baseline characteristics affecting kidney function were adjusted: donor type, primary renal disease, body mass index, desensitization, serum phosphate levels, and donor-specific antibodies. The risk of outcomes according to the increase in cardiovascular risk before transplantation was visualized using restricted cubic splines adjusted with covariates included in the multivariable Cox analysis. The statistical difference in eGFR after transplantation according to the Framingham risk score before transplantation was evaluated by performing a multivariable analysis of covariance and adjusting for covariates included in the multivariable Cox analysis and repeated measures ANOVA. Statistical analyses were performed using SPSS version 27.0 (IBM Corp.) and R version 4.0.3 (R Foundation for Statistical Computing). A p-value of <0.05 was considered statistically significant.

Ethical considerations

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Boramae Medical Center (No. 30-2019-64). Informed consent was obtained at the time of enrollment in the KOTRY study; however, this requirement was waived for the present secondary analysis.

Results

Baseline clinical characteristics according to cardiovascular risk before transplantation

A total of 4,682 KTRs were enrolled in this study. The mean age of the patients was 49.8 ± 11.6 years, and 59.8% of the patients were male (Table 1). The prevalences of hypertension and diabetes mellitus were 89.5% and 31.1%, respectively. The mean systolic blood pressure and body mass index were 138.4 ± 20.3 mmHg and 23.1 ± 3.5 kg/m²,

Table 1. Baseline characteristics according to cardiovascular risk assessed using the Framingham risk score

Characteristic	Total	Framingham risk score				p-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
No. of patients	4,682	1,174	1,167	1,171	1,170	
Age (yr)	49.8 ± 11.6	37.6 ± 8.3	46.7 ± 8.8	54.2 ± 7.2	60.7 ± 6.6	<0.001
Male sex	2,799 (59.8)	440 (37.5)	590 (50.6)	774 (66.1)	995 (85.0)	<0.001
Hypertension	4,189 (89.5)	904 (77.0)	1,049 (89.9)	1,094 (93.4)	1,142 (97.6)	<0.001
Diabetes mellitus	1,458 (31.1)	54 (4.6)	196 (16.8)	386 (33.0)	822 (70.3)	<0.001
Systolic blood pressure (mmHg)	138.4 ± 20.3	131.4 ± 18.7	137.1 ± 20.0	139.1 ± 20.6	146.3 ± 20.1	<0.001
Body mass index (kg/m ²)	23.1 ± 3.5	21.7 ± 3.6	23.1 ± 3.5	23.7 ± 3.5	24.2 ± 3.1	<0.001
Primary kidney disease						<0.001
Diabetes mellitus	1,144 (24.4)	44 (3.7)	150 (12.9)	301 (25.7)	649 (55.5)	
Hypertension	707 (15.1)	137 (11.7)	191 (16.4)	226 (19.3)	153 (13.1)	
Glomerulonephritis	1,504 (32.1)	586 (49.9)	448 (38.4)	327 (27.9)	143 (12.2)	
Tubulointerstitial disease	12 (0.3)	7 (0.6)	1 (0.1)	2 (0.2)	2 (0.2)	
ADPKD	233 (5.0)	53 (4.5)	73 (6.3)	74 (6.3)	33 (2.8)	
Hereditary diseases other than ADPKD	63 (1.3)	39 (3.3)	15 (1.3)	4 (0.3)	5 (0.4)	
Obstructive nephropathy	19 (0.4)	12 (1.0)	1 (0.1)	2 (0.2)	4 (0.3)	
Other	44 (0.9)	14 (1.2)	13 (1.1)	10 (0.9)	75 (6.6)	
Unknown	956 (20.4)	282 (24.0)	275 (23.6)	225 (19.2)	174 (14.9)	
Comorbidities						
Myocardial infarction	60 (1.3)	0 (0)	4 (0.3)	18 (1.5)	38 (3.2)	<0.001
Angina	245 (5.2)	5 (0.4)	33 (2.8)	60 (5.1)	147 (12.6)	<0.001
Heart failure	68 (1.5)	6 (0.5)	11 (0.9)	24 (2.0)	27 (2.3)	<0.001
Other cardiovascular diseases	2020 (4.3)	21 (1.8)	28 (2.4)	67 (5.7)	86 (7.4)	<0.001
Medication use						
Aspirin	954 (20.4)	104 (8.9)	163 (14.0)	289 (24.7)	398 (34.0)	<0.001
Statin	1,365 (29.2)	279 (23.8)	321 (27.5)	340 (29.0)	425 (36.3)	<0.001
Smoking status						<0.001
Never	3,586 (76.6)	1,062 (90.5)	972 (83.3)	849 (72.5)	703 (60.1)	
Current smoker	399 (8.5)	9 (0.8)	54 (4.6)	118 (10.1)	218 (18.6)	
Former smoker	659 (14.1)	92 (7.8)	135 (11.6)	193 (16.5)	239 (20.4)	
Unknown	38 (0.8)	11 (0.9)	6 (0.5)	11 (0.9)	10 (0.9)	
Total cholesterol (mg/dL)	155.1 ± 42.1	156.3 ± 35.1	160.8 ± 43.8	154.0 ± 44.5	149.4 ± 43.5	<0.001

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Table 1. Continued

Characteristic	Total	Framingham risk score				p-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
HDL cholesterol (mg/dL)	47.9 ± 16.9	57.1 ± 17.8	48.9 ± 16.2	44.8 ± 15.6	40.5 ± 13.2	<0.001
Phosphorus (mg/dL)	5.2 ± 1.6	5.3 ± 1.6	5.3 ± 1.6	5.1 ± 1.6	4.8 ± 1.4	<0.001
Donor type						<0.001
Living donor	3,135 (67.0)	876 (74.6)	795 (68.1)	763 (65.2)	701 (59.9)	
Deceased donor	1,547 (33.0)	298 (25.4)	372 (31.9)	408 (34.8)	469 (40.1)	
Type of dialysis before transplantation						<0.001
Hemodialysis	3,308 (70.7)	802 (68.3)	802 (68.7)	820 (70.0)	884 (75.6)	
Peritoneal dialysis	560 (12.0)	130 (11.1)	139 (11.9)	159 (13.6)	132 (11.3)	
Kidney transplantation	60 (1.3)	17 (1.4)	15 (1.3)	18 (1.5)	10 (0.9)	
Preemptive transplantation	754 (16.1)	225 (19.2)	211 (18.1)	174 (14.9)	144 (12.3)	
Duration of dialysis (mo), n = 3,923	51.5 ± 62.6	48.3 ± 61.6	58.8 ± 70.0	56.0 ± 65.8	43.4 ± 50.7	<0.001
No. of kidney transplantations						0.01
First kidney transplantation	4,324 (92.4)	1,072 (91.2)	1,063 (91.1)	1,077 (92.0)	1,113 (95.1)	
Second kidney transplantation	344 (7.3)	98 (8.3)	102 (8.7)	91 (7.8)	53 (4.5)	
Third kidney transplantation	12 (0.3)	4 (0.3)	2 (0.2)	3 (0.3)	3 (0.3)	
Fourth kidney transplantation	2 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
No. of HLA mismatch						<0.001
0	359 (7.7)	116 (9.9)	90 (7.7)	83 (7.1)	70 (6.0)	
1	172 (3.7)	40 (3.4)	47 (4.0)	51 (4.4)	34 (2.9)	
2	380 (8.1)	115 (9.8)	89 (7.6)	80 (6.8)	96 (8.2)	
3	1,000 (21.4)	344 (29.3)	231 (19.8)	219 (18.7)	206 (17.6)	
4	988 (21.1)	244 (20.8)	259 (22.2)	220 (18.8)	265 (22.6)	
5	1,097 (23.4)	198 (16.9)	290 (24.9)	313 (26.7)	296 (25.3)	
6	686 (14.7)	117 (10.0)	161 (13.8)	205 (17.5)	203 (17.4)	
HLA class I PRA (%), n = 2,518	10.7 ± 23.3	12.7 ± 24.9	13.7 ± 26.2	9.5 ± 22.4	6.4 ± 17.1	<0.001
HLA class II PRA (%), n = 2,500	10.8 ± 23.6	11.7 ± 24.3	13.5 ± 26.3	9.8 ± 22.7	7.6 ± 19.9	<0.001
Desensitization	1,100 (23.5)	313 (26.7)	281 (24.1)	271 (23.1)	235 (20.1)	0.002
Donor-specific antibodies						<0.001
Negative	2,515 (53.7)	652 (55.5)	616 (52.8)	616 (52.6)	631 (53.9)	
Positive	510 (10.9)	147 (12.5)	167 (14.3)	117 (10.0)	79 (6.8)	
Unknown	1,657 (35.4)	375 (31.9)	384 (32.9)	438 (37.4)	460 (39.3)	
Immunosuppressants						
Steroid	4,608 (98.4)	1,162 (99.0)	1,150 (98.5)	1,146 (97.9)	1,150 (98.3)	0.26
Steroid dose (mg/day)	18.8 ± 8.9	18.9 ± 9.4	18.9 ± 8.5	18.8 ± 8.3	18.5 ± 9.1	0.72
Tacrolimus	4,539 (97.0)	1,149 (97.9)	1,131 (96.9)	1,134 (96.8)	1,125 (96.2)	0.11
Tacrolimus dose (mg/day)	6.1 ± 3.5	6.8 ± 3.6	6.2 ± 3.6	5.9 ± 3.4	5.6 ± 3.3	<0.001
Cyclosporine	110 (2.3)	18 (1.5)	28 (2.4)	30 (2.6)	34 (2.9)	0.16
Cyclosporine dose (mg/day)	260.4 ± 96.9	280.4 ± 105.7	265.0 ± 93.5	265.9 ± 97.8	244.1 ± 96.7	0.64
Mycophenolate	4,326 (92.4)	1,078 (91.8)	1,081 (92.6)	1,078 (92.1)	1,089 (93.1)	0.56
Mycophenolate dose (mg/day)	1,132 ± 382	1,110 ± 407	1,140 ± 378	1,157 ± 369	1,117 ± 371	0.02
Mizoribine	44 (0.9)	15 (1.3)	12 (1.0)	9 (0.8)	8 (0.7)	0.58
Azathioprine	2 (0.0)	2 (0.2)	0 (0)	0 (0)	0 (0)	0.24
Framingham risk score	7.55 ± 9.11 3.84 (1.37–10.14)	1.05 ± 0.10 1.00 (1.00–1.02)	2.40 ± 0.70 1.80 (2.32–2.95)	6.47 ± 1.77 6.28 (4.92–7.84)	20.3 ± 9.81 17.06 (13.09–24.44)	<0.001

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

ADPKD, autosomal dominant polycystic kidney disease; HDL, high-density lipoprotein; HLA, human leukocyte antigen; PRA, panel reactive antibody.

respectively. The causes of ESKD were glomerulonephritis (32.1%), diabetes mellitus (24.4%), hypertension (15.1%), and others. Additionally, 8.5% and 14.1% of patients were current and former smokers, respectively. The rates of living-related and deceased donor transplantations were 67.0% and 33.0%, respectively. The mean baseline total cholesterol level was 155.1 ± 42.1 mg/dL, and the mean high-density lipoprotein cholesterol level was 47.9 ± 16.9 mg/dL. The mean Framingham risk score at transplantation was 7.55 ± 9.11 (median, 3.84; interquartile range, 1.37–10.14).

The baseline clinical characteristics were compared based on the Framingham risk score before transplantation (Table 1). KTRs who were older and those who were male were at high cardiovascular risk ($p < 0.001$). Additionally, their systolic blood pressure, body mass index, and prevalences of hypertension and diabetes mellitus were high (all $p < 0.001$). These KTRs also had a higher prevalence of diabetes mellitus and a lower prevalence of glomerulonephritis as the primary cause of ESKD ($p < 0.001$). KTRs who were current smokers and those with lower high-density lipoprotein cholesterol levels were at a high cardiovascular risk ($p < 0.001$). Serum phosphorus levels were lower among patients in the high Framingham risk score group ($p < 0.001$). Deceased donor transplantation was associated with a higher cardiovascular risk ($p < 0.001$); however, desensitization and donor-specific antibodies were associated with a lower cardiovascular risk ($p = 0.002$ and $p < 0.001$, respectively).

Cardiovascular risk at transplantation and major adverse cardiovascular events, all-cause mortality, and graft failure

During the mean follow-up of 30.7 ± 19.1 months, outcomes of rejection, graft loss, all-cause mortality, cardiovascular mortality, and MACEs occurred in 976, 106, 96, 11, and 116 KTRs, respectively (Supplementary Table 1, available online). According to the Kaplan-Meier analysis, high cardiovascular risk, as represented by the Framingham risk score, was associated with a high probability of MACE and all-cause mortality ($p < 0.001$ for both) (Fig. 2A, B). KTRs at high cardiovascular risk were at higher risk for mortality and MACEs according to the multivariable Cox analysis (Table 2). However, KTRs at high cardiovascular risk did not have a high probability of graft failure according to the

Kaplan-Meier analysis (Fig. 2C). Additionally, high cardiovascular risk among KTRs was not associated with the risk of graft failure according to the univariable and multivariable analyses (HR, 0.51; 95% CI, 0.21–1.28; $p = 0.15$ [quartile 4 vs. quartile 1, overall $p = 0.32$]). The composite outcomes of all-cause mortality, MACEs, and graft failure were significantly associated with high cardiovascular risk according to both the Kaplan-Meier ($p < 0.001$) (Fig. 2D) and multivariable analyses (HR, 2.05; 95% CI, 1.19–3.46; $p = 0.01$ [quartile 4 vs. quartile 1, overall $p = 0.004$]).

We analyzed the risks of outcomes according to the Framingham risk score and visualized those risks using multivariable restricted cubic spline curves (Fig. 3). The risks of all-cause mortality and MACEs showed continuously increasing trends over all Framingham risk score ranges (Fig. 3A, B, respectively); however, the risk of graft failure did not increase according to the Framingham risk score (Fig. 3C).

We also performed a subgroup analysis (Supplementary Table 2–7, available online). When KTRs were divided into those under 50 and those over 50 years old, the increased risk of MACEs with Framingham risk score was significant in those under 50 years old. In nondiabetic patients, the risk of MACEs increased significantly with increasing Framingham risk scores but was not significant in diabetic patients. Framingham risk scores for MACEs were also significant in the living-related donor transplant subgroup (not significant in the deceased donor transplant subgroup).

Cardiovascular risk at transplantation and subsequent kidney function

The eGFRs of KTRs were compared according to the Framingham risk scores (Table 1, Fig. 4). The baseline eGFRs were comparable among groups. KTRs recovered kidney function at discharge after kidney transplantation, but patients with high Framingham risk scores had a relatively low GFR. At 6 months after kidney transplantation, the eGFR at quartile 4 of the Framingham risk score was the lowest (61.2 ± 18.2 mL/min/1.73 m² vs. 70.2 ± 21.2 mL/min/1.73 m² [quartile 1] vs. 67.8 ± 19.4 mL/min/1.73 m² [quartile 2] vs. 65.2 ± 18.2 mL/min/1.73 m² [quartile 3]; overall $p < 0.001$ in the ANOVA). This significant association was maintained during follow-up ($p < 0.001$ at 1, 2, and

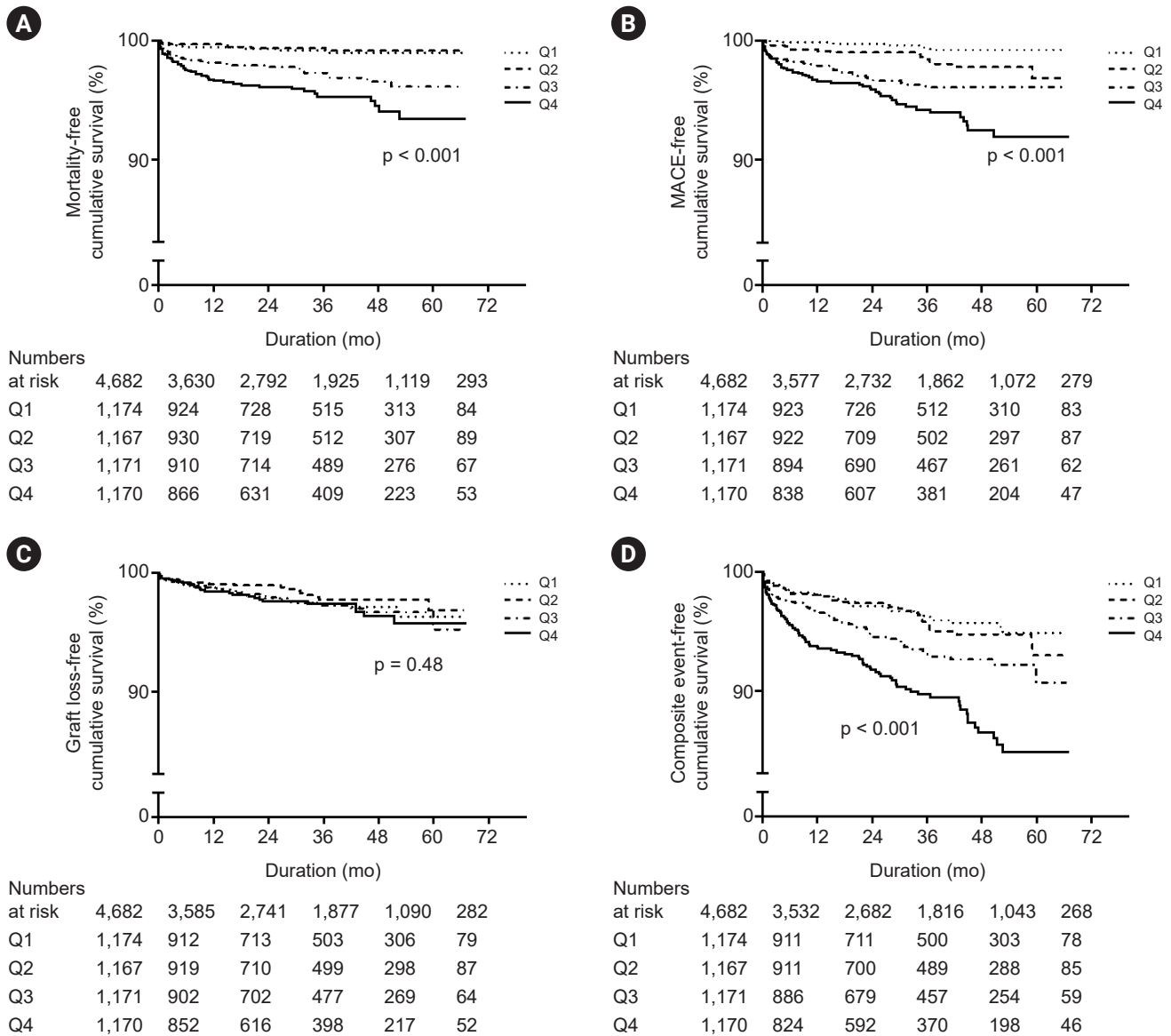


Figure 2. Kaplan-Meier survival analysis of event-free survival for each clinical outcome. (A) All-cause mortality. (B) Major adverse cardiovascular events (MACEs). (C) Graft failure. (D) Composite outcomes of all-cause mortality, MACEs, and graft failure. Q, Framingham risk score quartile.

3 years). In the multivariable analysis of covariance, high Framingham risk scores were significantly associated with decreased eGFRs after transplantation at 6 months and 1 year ($p < 0.001$ for both), and eGFRs showed a decreasing trend at 2 and 3 years ($p = 0.07$ and $p = 0.09$, respectively). In the repeated measures ANOVA, the eGFR according to the Framingham risk score was lower for patients in the high cardiovascular risk group ($p < 0.001$). However, when we compared the change in eGFR between follow-up peri-

ods, KTRs with low Framingham risk scores did not exhibit a favorable outcome in terms of maintaining GFR.

Changes in cardiovascular risk scores after kidney transplantation

We also examined the Framingham risk score changes after transplantation ([Supplementary Figure 1](#), available online). The Framingham risk scores of the entire sample showed

Table 2. HRs for all-cause mortality, MACEs, graft failure, and composite outcomes according to the Framingham risk scores

Outcomes	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause mortality		<0.001		0.002
Q1	Reference		Reference	
Q2	0.90 (0.35–2.32)	0.82	0.58 (0.18–1.84)	0.35
Q3	3.41 (1.62–7.19)	0.001	2.17 (0.89–5.30)	0.09
Q4	5.87 (2.88–11.94)	<0.001	3.20 (1.30–7.91)	0.01
MACEs		<0.001		0.003
Q1	Reference		Reference	
Q2	3.66 (1.36–9.96)	0.01	3.13 (0.87–11.32)	0.08
Q3	7.54 (2.96–19.21)	<0.001	4.85 (1.38–17.01)	0.01
Q4	12.82 (5.14–31.99)	<0.001	8.43 (2.41–29.52)	0.001
Graft failure		0.47		0.32
Q1	Reference		Reference	
Q2	0.76 (0.43–1.33)	0.33	0.51 (0.23–1.15)	0.11
Q3	0.99 (0.58–1.68)	0.98	0.75 (0.35–1.60)	0.46
Q4	1.18 (0.71–1.98)	0.53	0.51 (0.21–1.28)	0.15
Composite outcomes		<0.001		0.004
Q1	Reference		Reference	
Q2	1.14 (0.75–1.75)	0.54	0.87 (0.49–1.53)	0.62
Q3	1.70 (1.15–2.52)	0.008	1.23 (0.65–1.97)	0.67
Q4	3.05 (2.12–4.39)	<0.001	2.05 (1.19–3.46)	0.01

Multivariable analysis included the following covariates: donor type, primary causes of kidney disease, body mass index, desensitization, serum phosphorus levels, and donor-specific antibodies.

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; Q, quartile of Framingham risk scores.

a decreasing trend until 1 year after kidney transplantation. Subsequently, the Framingham risk scores gradually increased. The Framingham risk score trends of KTRs who underwent living-related donor transplantation were similar to those of the overall sample. The Framingham risk scores of the KTRs who underwent deceased donor transplantation were significantly higher than those of KTRs who underwent living-related donor transplantation. Although Framingham risk scores of deceased donor KTRs decreased after 6 months following the transplant, they remained significantly higher than in living-related donor KTRs.

Discussion

Cardiovascular disease is one of the most notable causes of death among KTRs, making it imperative to assess and manage cardiovascular risk to improve prognosis. In this context, several studies have investigated KTRs' prognosis according to the status of cardiovascular risk. The Framingham risk score is widely used for predicting the risk of

cardiovascular events, and it has also been tested in the prediction of cardiovascular disease development among KTRs. However, because previous studies have been conducted in the Western context, the effects of cardiovascular risk as assessed by the Framingham risk score on the prognosis of KTRs cannot be easily generalized to Asian populations. In general, as the risk of cardiovascular disease is lower among Asians, the impact of pretransplant cardiovascular risk on the overall prognosis can be different in Asian KTRs. In addition, studies on the effects of cardiovascular risk factors on kidney function after transplantation in KTRs are insufficient. In this study, we performed a large-scale, nationwide, prospective investigation of Asian KTRs and determined that the cardiovascular risk as evaluated by the Framingham risk score is associated with the risks of overall mortality, cardiovascular events, and subsequent kidney function after kidney transplantation.

Traditional cardiovascular risk factors are significant among KTRs. Hypertension and blood pressure status have significant effects on the incidence of cardiovascular

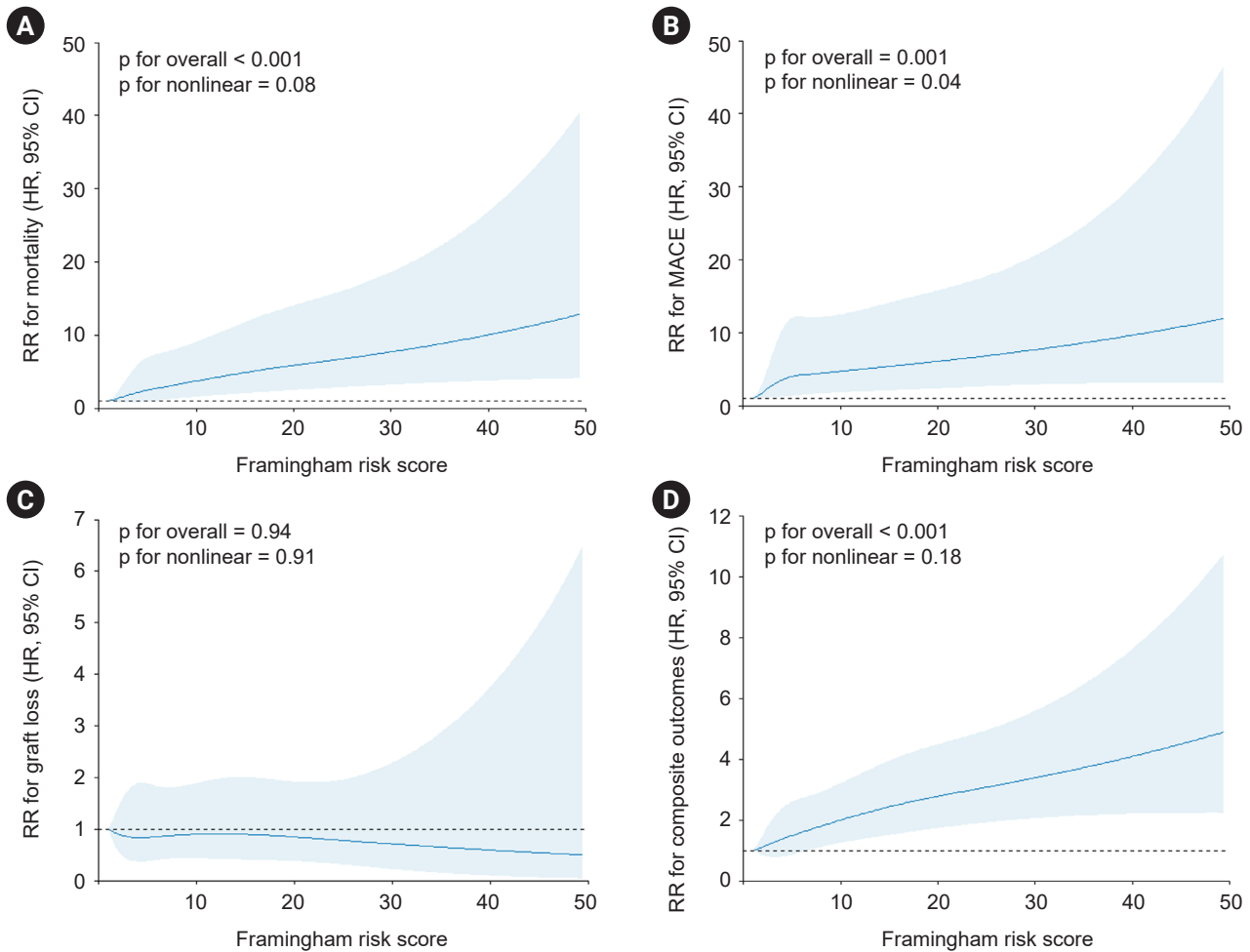


Figure 3. Multivariable restricted cubic splines of Framingham risk scores for outcomes. (A) All-cause mortality. (B) Major adverse cardiovascular events (MACEs). (C) Graft failure. (D) Composite outcomes of all-cause mortality, MACEs, and graft failure. The multivariable analysis included the following covariates: donor type, primary renal disease, body mass index, number of kidney transplantations, desensitization, phosphorus levels, and donor-specific antibodies. CI, confidence interval; HR, hazard ratio; RR, relative risk.

disease after kidney transplantation [19]. Hypertension is the most common comorbidity among KTRs (incidence of 80%–85%) [20]; according to our data, the proportion of patients with hypertension was also high (89.4%). Carpenter et al. [21] reported that a 20-mmHg increase in systolic blood pressure leads to an approximately 43% increase in the cardiovascular disease risk. Immunosuppressants prescribed to KTRs increase the incidence of dyslipidemia by up to 80% [22]. The increase in cardiovascular disease caused by dyslipidemia has been described by epidemiologic studies on both the general population and individuals with CKD. However, the cardiovascular risk associated

with dyslipidemia among patients with advanced CKD and KTRs has not been sufficiently proven [23]. Nevertheless, a randomized controlled trial confirmed that fluvastatin treatment for KTRs lowered low-density lipoprotein cholesterol levels by 32% and the risk of death resulting from cardiovascular disease or myocardial infarction by approximately 35% [24]. Smoking is a major risk factor for cardiovascular disease [25], and this risk has been confirmed for KTRs [26]. Smoking increases the relative risk of ischemic heart disease by 10% to 95% [27,28], and it is significantly associated with increased rates of graft loss and mortality [29]. Additionally, clinical factors such as advanced age,

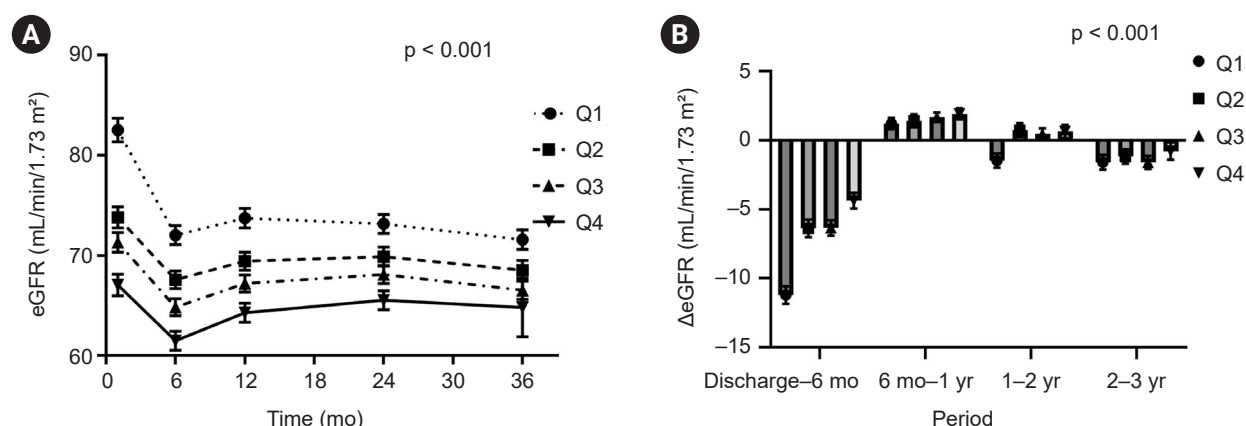


Figure 4. Trends of the changes in the eGFR after kidney transplantation according to Framingham risk score. (A) The eGFR at each time point. (B) The change of eGFR between follow-up intervals. The eGFR at each time point was evaluated using an analysis of variance. Significant differences between Framingham risk score quartile groups were observed ($p < 0.001$). According to the repeated measures analysis of variance, the eGFR according to the Framingham risk score was lower for patients in the high cardiovascular risk group ($p < 0.001$).

eGFR, estimated glomerular filtration rate; Q, Framingham risk score quartile.

male sex, and diabetes mellitus increase the risk of cardiovascular disease in KTRs [30]. Previous studies have reported that, compared with KTRs without diabetes mellitus, KTRs with diabetes mellitus are at increased risk for cardiovascular events by approximately 3 to 3.5 times and have higher all-cause mortality and cardiovascular mortality rates [31,32].

Evaluations of various risk factors have been performed to accurately assess the risk of cardiovascular events through the use of a risk score system. The most representative index used to predict the risk of cardiovascular disease is the Framingham risk score system. During the Framingham Heart Study, this scoring system was developed to estimate an individual's 10-year risk of coronary heart disease, stratified for men and women [33]. The 2008 Framingham Heart Study resulted in an improved score that predicts the risks of various cardiovascular diseases, including cerebrovascular events, peripheral artery disease, and heart failure [34]. Studies have been conducted to predict the cardiovascular risk of KTRs after transplantation by comparing the Framingham risk score with the actual incidence of cardiovascular disease. Kasiske et al. [28] enrolled 1,124 KTRs and compared the ischemic heart disease incidence with the estimated risk calculated using the Framingham risk score. Although the Framingham risk score predicted an increased risk of ischemic heart disease

(relative risk, 1.28; 95% CI, 1.20–1.40), it underestimated the actual risk attributable to the increased prevalence of diabetes mellitus (relative risks of 2.78 for males and 5.40 for females compared with 1.53 and 1.82 for the Framingham Heart Study population, respectively), advanced age, and smoking among KTRs. Ducloux et al. [35] used the Framingham risk score to evaluate the risk of ischemic heart disease of 344 KTRs. Their study also underestimated the actual risk of ischemic heart disease. Kiberd and Panek [12] performed a prospective cohort study of 540 KTRs and compared the actual cardiovascular risk with the value predicted by the Framingham risk score. The risk of stroke was predicted relatively well by the Framingham risk score. However, the actual incidence of cardiovascular disease increased by 64%, revealing that the Framingham risk score underestimated the risk of cardiovascular disease. The cardiovascular risk assessed by the Framingham risk score predicts cardiovascular events after kidney transplantation; however, it relatively underestimates the actual risk. This is probably because the risk of cardiovascular events among KTRs is affected by factors other than those of the general population. KTRs use various immunosuppressive drugs after transplantation, which may increase the risk of cardiovascular disease [36]. Corticosteroids and cyclosporin have the least negative impact on the increased risk of cardiovascular disease because they have the smallest

effect on increased blood pressure, cholesterol levels, and weight gain. However, tacrolimus use may increase the risk of cardiovascular disease owing to the increased risk of diabetes mellitus [12]. There is evidence that the increased inflammatory response in KTRs after kidney transplantation increases the risk of vascular calcification and cardiovascular disease [37]. Additionally, infections such as cytomegalovirus and genetic predispositions related to increased inflammatory responses of KTRs are associated with an increased cardiovascular risk [38,39].

CKD and cardiovascular disease share common risk factors, such as diabetes mellitus, hypertension, hyperlipidemia, advanced age, and male sex [40], and CKD is an independent risk factor for cardiovascular disease [5]. Additionally, evidence has elucidated that more cardiovascular risk factors are associated with the incidence and progression of CKD. Lee et al. [41] reported that the cardiovascular risk, as assessed by the Framingham risk score, can predict CKD development in the general population. Kidney transplantation is a diagnostic factor for CKD [42]; therefore, whether the increased cardiovascular risk of KTRs is related to the deterioration of kidney function as a long-term outcome is of considerable interest. Some studies have reported that cardiovascular risk factors such as blood pressure after kidney transplantation are related to graft failure or survival [43]. Additionally, efforts to reduce cardiovascular risk, such as through exercise or blood pressure control, improve graft survival [44]. However, direct evidence is lacking. In our multivariable analysis, the Framingham risk score was not associated with graft failure. In addition, although the cardiovascular risk categorized by the Framingham risk score was associated with decreased kidney function after kidney transplantation, Framingham risk scores were not associated with rapid eGFR decline.

The cardiovascular disease risk differs according to ethnicity, even in Asian populations. East Asian individuals are known to have a lower risk of cardiovascular disease than individuals of other races [45–47]. A validation study of Framingham risk score predictions for Asian individuals found that the risk of cardiovascular events was overestimated by approximately 10% for both males and females [48]. However, to date, no studies have investigated cardiovascular disease risk or other prognoses according to the Framingham risk scores in Asian KTRs. In this study, we investigated the risk of outcomes including cardiovascular

disease in Asian KTRs. The mean Framingham risk scores were 1.05, 2.40, 6.47, and 20.3 in each quartile, and the relative risks for MACEs were 3.13, 4.85, and 8.43 in the 2nd, 3rd, and 4th Framingham risk score quartiles. This underestimation of Framingham risk scores for MACEs might be due to the relatively lower cardiovascular risk in Asians compared to Westerners.

Attempts such as cardiovascular risk screening and preemptive interventions have been made to reduce the increased risk of cardiovascular disease among KTRs. However, to reduce cardiovascular disease incidence and improve the prognosis, the identification of useful indicators should be prioritized. In this nationwide prospective cohort study, we found that the Framingham risk score is a useful indicator of cardiovascular events, mortality, and kidney function of Asian KTRs after kidney transplantation. Based on the results of our study, actively correcting cardiovascular risk factors of KTRs and improving their prognosis should be emphasized.

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Conflicts of interest

Jeonghwan Lee is the Deputy Editor of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of

interest to declare.

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Funding acquisition, Methodology: JPL

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