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ORIGINAL ARTICLE

Impact of recipient and donor smoking in living-donor kidney transplantation: a prospective multicenter cohort study

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SUMMARY

The smoking status of kidney transplant recipients and living donors has not been explored concurrently in a prospective study, and the synergistic adverse impact on outcomes remains uncertain. The self-reported smoking status and frequency were obtained from recipients and donors at the time of kidney transplantation in a prospective multicenter longitudinal cohort study (NCT02042963). Smoking status was categorized as "ever smoker" (current and former smokers collectively) or "never smoker." Among 858 eligible kidney transplant recipients and the 858 living donors, 389 (45.3%) and 241 (28.1%) recipients were considered ever smokers at the time of transplant. During the median follow-up period of 6 years, the rate of death-censored graft failure was significantly higher in ever-smoker recipients than in never-smoker recipients (adjusted HR, 2.82; 95% CI 1.01–7.87; $P = 0.048$). A smoking history of >20 pack-years was associated with a significantly higher rate of death-censored graft failure than a history of ≤20 pack-years (adjusted HR, 2.83; 95% CI 1.19–6.78; $P = 0.019$). No donor smoking effect was found in terms of graft survival. The smoking status of the recipients and donors or both did not affect the rate of biopsy-proven acute rejection, major adverse cardiac events, all-cause mortality, or post-transplant diabetes mellitus. Taken together, the recipient's smoking status before kidney transplantation is dose-dependently associated with impaired survival.

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Key words
graft survival, kidney transplantation, living donors, smoking, transplant recipient

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Introduction

Despite modifiable, smoking increases the risk of cancer [1], cardiovascular disease [2], and kidney dysfunction [3] in the general population. In particular, smoking promotes the progression of diabetic nephropathy [4], hypertensive kidney disease [5], and primary glomerular nephropathies [6]. The exact mechanisms underlying smoking-associated kidney injury remain only partially understood and may be multifactorial. Kidney transplant recipients may experience the deleterious effects of smoking. The Kidney Disease Improving Global Outcome clinical practice guidelines recommend recipient candidates abstain from tobacco use for a minimum 1 month before wait-listing or living-donor transplantation [7] and donor candidates to quit smoking 4 weeks before donor nephrectomy [8].

Smoking by kidney transplant recipients has been significantly associated with impaired graft and patient survival and increased cardiovascular events [9–15]. Relatively few studies have demonstrated that the smoking status of donors is a significant risk factor for decreased graft and recipient survival, as well as decreased post-transplant kidney function [13,16,17]. For studies on smoking and its effect, the major strength of a prospective cohort study compared with a retrospective study is an increased accuracy of the data collection with regard to smoking exposures, confounding variables, and outcomes. Better quality data can provide more reliable results and conclusions. However, the smoking status of kidney transplant recipients and living donors has not been explored concurrently in a prospective study, and the synergistic adverse impact on transplant outcomes remains uncertain.

The aim of this prospective, multicenter, longitudinal cohort study was to compare outcomes based on the smoking status of the recipients and donors.

Materials and methods

Study participants

A total of 1080 *de novo* kidney transplant recipients were enrolled from the Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT) between 2012 and 2016 and followed up until 2020 (clinicaltrial.gov identifier: NCT02042963). After excluding deceased-donor kidney transplant recipients and 27 kidney transplant recipients who had insufficient information on smoking history, 858 kidney transplant recipients were included in this study (Fig. 1). The Institutional Review Committee of each participating center approved the KNOW-KT study protocol [18]. All patients provided written informed consent before participation. All clinical investigations were conducted in accordance with the guidelines of the 2008 Declaration of Helsinki and Good Clinical Practice.

Smoking history

The self-reported smoking status and frequency of the recipients and donors were obtained at the time of

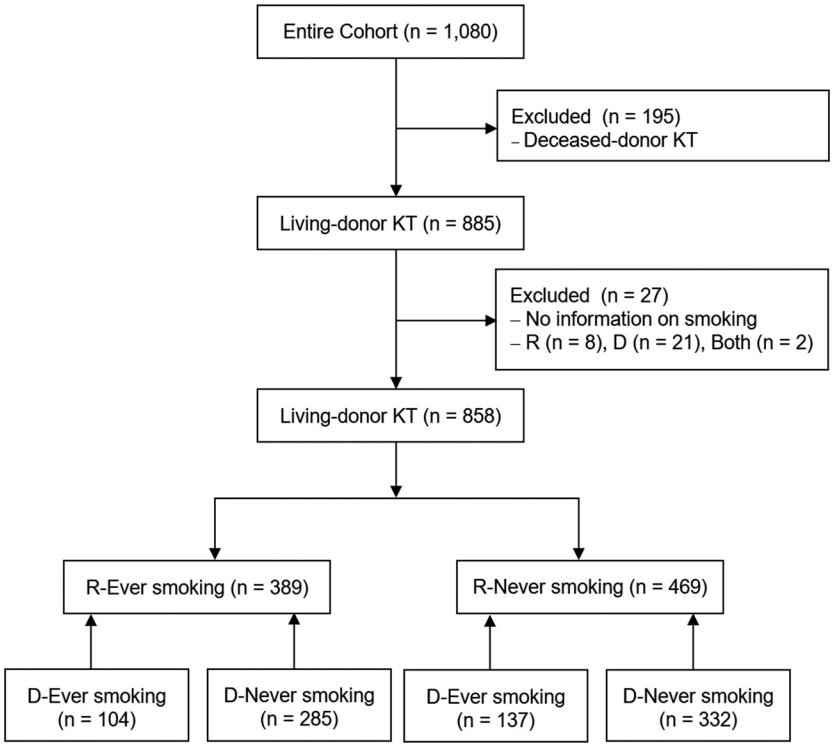

Figure 1 Flow chart of study inclusion. Of 1,080 kidney transplant recipients, 885 were living-donor kidney transplant recipients. Twenty-seven living-donor kidney transplant recipients had insufficient information on the smoking status of the recipients (n = 8), donors (n = 21), or both (n = 2) and were excluded. Finally, 858 kidney transplant recipients were included in this study. D, donors; KT, kidney transplantation; R, recipients.

living-donor kidney transplantation. Participants were asked whether they were current, former, or never smokers. Current and former smokers were collectively referred to as "ever smokers." Ever smokers were also asked the total number of packs (20 cigarettes per package) smoked per day and total years smoking at the time of kidney transplantation (pack-years).

Outcomes

The primary outcome was death-censored graft failure, which was defined as a new return to regular long-term dialysis or new kidney transplantation. Secondary outcomes included all-cause graft failure, biopsy-proven acute rejection, major adverse cardiac events, cardiac events, all-cause mortality, and post-transplant diabetes mellitus. Biopsy-proven acute rejection was defined as biopsy-proven acute T-cell-mediated rejection or acute antibody-medicated rejection. Major adverse cardiac events included cardiovascular death, sudden cardiac death, myocardial infarction, unstable angina, percutaneous coronary intervention, and coronary artery bypass grafting. Cardiac events included myocardial infarction, unstable angina, percutaneous coronary intervention, and coronary artery bypass grafting. Outcomes were compared between the two groups based on the smoking status of recipient, donor, or both and the smoking frequency.

Other variables

Possible confounders for death-censored graft failure, all-cause graft failure, or biopsy-proven acute rejection included recipient age, donor age, recipient sex, donor sex, recipient body mass index (BMI), diabetes, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, high-density lipoprotein (HDL), re-transplantation, desensitization, total number of human leukocyte antigen (HLA) mismatches, and antithymocyte globulin induction. Possible confounders for major adverse cardiac events, cardiac events, or all-cause mortality included recipient age, recipient sex, recipient BMI, diabetes, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, HDL, re-transplantation, and desensitization.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Intergroup differences were assessed by independent sample t-tests for continuous variables and chi-squared tests for categorical variables. The Cox regression model was used to analyze the association between smoking status and the development of death-censored graft failure, all-cause graft failure, biopsy-proven acute rejection, major adverse cardiac events, cardiac events, and all-cause death. Differences in the cumulative incidences of outcomes were

Transplant International 2021; 34: 2794–2802

compared according to the smoking status using Gray's test. The Aalen-Johansen estimator was used as an estimator for the cumulative incidence functions. Logistic regression analysis was used to examine the association between smoking status and the development of post-transplant diabetes mellitus, because post-transplant diabetes mellitus was recorded at the annual follow-up after kidney transplantation and the exact date and year of occurrence could not be specified. Statistical analyses were performed using the SAS system for Windows, version 9.4 (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Significance was set as $P < 0.05$.

Results

Baseline characteristics

Table 1 shows the baseline characteristics according to the smoking status of recipients. Among 858 eligible living-donor kidney transplant recipients, 389 (45.3%) were categorized as ever smokers [58 (14.9%) current smokers and 331 (85.1%) former smokers] and 469 (54.7%) as never smokers at the time of kidney transplantation. Among the 858 donors, 241 (28.1%) and 617 (71.9%) were categorized as ever and never smokers, respectively, at the time of kidney donation. Recipients who were ever smokers were significantly younger, tended to be men and have a male donor, had a lower BMI, had a higher proportion of diabetes, hypertension, and coronary artery disease, were less likely to have received desensitization, and had higher total cholesterol and HDL levels than those who were never smokers.

Smoking status of recipients and donors and outcomes

During the median follow-up of 6.0 years, 35 death-censored graft failures (IQR 4.9–7.0) and 55 all-cause graft failures (IQR 4.9–7.0) occurred. A total of 97 biopsy-proven acute rejections (IQR 4.6–6.9) occurred during the median follow-up of 5.9 years. Multivariate Cox regression analysis demonstrated that the rate of death-censored graft failure was significantly higher in ever-smoker recipients than in never-smoker recipients (adjusted hazard ratio [HR] = 2.82; 95% confidence interval [CI] 1.01–7.87; $P = 0.048$; Table 2). No significant intergroup difference in the rate of all-cause graft failure and biopsy-proven acute rejection was observed. The cumulative incidence curve was consistent (Fig. 2). No significant differences were found in the development of death-censored graft failure, all-cause graft failure, or biopsy-proven acute rejection between recipients with donors who were ever or never smokers. Compared with cases in which both recipients and donors were never smokers, cases in which both recipients and donors were ever smokers had no significant differences in the rate of death-censored graft failure, all-cause graft failure, or biopsy-proven acute rejection.

During the median follow-up of 6.0 years, 28 major adverse cardiac events (IQR 4.9–6.9), 27 cardiac events (IQR 4.9–6.0), and 20 all-cause deaths (IQR 5.0–7.0) occurred. No significant differences in the rate of major adverse cardiac events, cardiac events, or all-cause deaths were observed between ever- and never-smoker recipients or between recipients with donors who were ever or never smokers. Compared with cases in which both recipients and donors were never smokers, cases in which both recipients and donors were ever smokers did not have an increased rate of major adverse cardiac events, cardiac events, or all-cause death (Table 3). No significant differences in the development of all-cause graft failure, biopsy-proven acute rejection, a major adverse cardiac event, cardiac event, or death were observed between ever-smoker and never-smoker recipients in the cumulative incidence curve (Fig. 2).

Among 635 kidney transplant recipients without pre-transplant diabetes mellitus, post-transplant diabetes mellitus occurred in 110. The risk of the development of post-transplant diabetes mellitus was not significantly associated with the recipient's and donor's smoking status (Table 4).

Smoking frequency and death-censored graft failure

Multivariate Cox regression analysis showed that among the ever-smoker recipients, a smoking history of >20 pack-years was associated with a significantly higher rate of death-censored graft failure compared with a smoking history of ≤20 pack-years (adjusted HR = 2.83; 95% CI 1.19–6.78; $P = 0.019$; Table 5). The sum of the smoking frequency of ever-smoker recipients or ever-smoker donors being >20 pack-years was not associated with a significantly higher rate of death-censored graft failure compared with a total smoking history of ≤20 pack-years.

Discussion

In this prospective longitudinal cohort study including 858 pairs of living donors and recipients, the smoking history of recipients at the time of living-donor kidney transplantation was associated with a 2.8-times higher rate of impaired death-censored graft survival during the median follow-up of 6 years after transplantation. The detrimental effect of smoking on graft survival presented dose-dependent effects, with a cutoff of 20

Table 1. Baseline characteristics according to the smoking status of recipients.

	Recipients-Ever smoker (n = 389)	Recipients-Never smoker (n = 469)	P-value
Smoking behavior of the recipients, current/former	58 (14.9)/331 (85.1)		-
Pack-years of the recipients	14.5 (5.0–25.0)		-
Smoking behavior of the donors, current/former/never	70 (18.0)/34 (8.7)/285 (73.3)	91 (19.4)/46 (9.6)/332 (70.8)	0.717
Recipient age, years	44.2 ± 12.3	46.5 ± 10.7	0.004
Recipient sex, male	358 (92.0)	169 (36.0)	<0.001
Donor age, years	44.2 ± 11.8	43.2 ± 11.3	0.190
Donor sex, male	243 (62.5)	220 (46.9)	<0.001
Recipient BMI, kg/m^2	22.1 ± 3.6	23.6 ± 3.3	<0.001
Donor BMI, kg/m^2	23.9 ± 2.8	24.0 ± 3.0	0.701
Donor/recipient BMI ratio	1.1 ± 0.2	1.0 ± 0.2	<0.001
Diabetes	115 (29.6)	108 (23.0)	0.030
Hypertension	372 (95.6)	410 (87.4)	<0.001
Coronary artery disease	32 (8.4)	19 (4.4)	0.017
Cerebrovascular disease	17 (4.5)	16 (3.7)	0.565
Total number of HLA mismatches	3.0 (1.0–3.0)	3.0 (1.0–4.0)	0.022
Re-transplantation	20 (5.1)	33 (7.0)	0.251
Desensitization	107 (27.5)	167 (35.6)	0.011
Induction therapy			0.137
IL-2RB	354 (91.0)	412 (87.9)	
ATG	35 (9.0)	57 (12.2)	
Total cholesterol, mg/dl	158.7 ± 42.0	146.8 ± 39.0	<0.001
HDL, mg/dl	49.1 ± 16.8	40.7 ± 13.8	<0.001

ATG, antithymocyte globulin; BMI, body mass index; HDL, high-density lipoprotein; HLA, human leukocyte antigen; IL-2RB, interleukin-2 receptor blocker.

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

pack-years. The smoking status of the recipients and donors did not affect the rate of all-cause graft failure, biopsy-proven acute rejection, major adverse cardiac events, cardiac events, all-cause mortality, or post-transplant diabetes mellitus.

Smoking history was significantly associated with death-censored graft failure but not with all-cause graft failure, biopsy-proven acute rejection, major adverse cardiac events, or patient death, even after adjusting for considerable transplant-related recipient and donor factors. Previous retrospective studies have demonstrated that recipient smoking history before transplant is associated with a higher rate of graft loss, but not with a higher rate of death-censored graft failure [9,10]. However, similar to our results, one prospective study [12] including 604 kidney transplant recipients and 133 smokers, and a retrospective study [11] including 645 kidney transplant recipients and 156 smokers reported that smoking is significantly associated with an increased rate of death-censored graft failure. However, this was not related to patient death or rejection. Our findings contribute to the evidence that smoking increases the rate of transplant loss via another independent mechanism rather than patient death or immunological rejection. Although the main histological allograft lesion associated with smoking is vascular intimal fibrous thickening [19], the mechanisms underlying vascular renal damage caused by smoking remain unclear. Smoking-associated vasotoxicity could be related to its role in direct toxicity to endothelial cells, atherosclerosis, and increased thickness of the renal artery [20,21]. Further research will be needed to identify the main mechanism by which smoking causes allograft loss.

Another important finding of our study is that the detrimental effect of smoking on graft survival was dose-dependent, with a cutoff of 20 pack-years. Previously, Kasiske *et al.* [10] reported that smoking for >25 pack-years was associated with impaired transplant survival, unlike smoking for ≤25 pack-years and never having smoked. Although the present guidelines recommend recipients stop smoking a minimum 1 month before living-donor kidney transplantation [7], considering its dose-dependent effects, a smoking cessation program may be necessary at the start of managing chronic kidney disease.

Transplant International 2021; 34: 2794–2802

Table 2. Unadjusted and adjusted hazard ratios for death-censored graft failure, all-cause graft failure, and biopsy-proven acute rejection.

	Death-censored graft failure		All-cause graft failure		Biopsy-proven acute rejection	
Unadjusted	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never	2.24 (1.08–4.65)	0.030	1.71 (0.97–3.00)	0.062	1.24 (0.83–1.85)	0.286
Donors-Ever vs. Donors-Never	0.75 (0.34–1.65)	0.476	0.80 (0.42–1.53)	0.499	0.88 (0.56–1.39)	0.596
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	1.43 (0.44–4.66)	0.549	1.29 (0.50–3.32)	0.600	0.96 (0.47–1.95)	0.915
Adjusted	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never*	2.82 (1.01–7.87)	0.048	1.35 (0.65–2.81)	0.420	1.45 (0.84–2.48)	0.180
Donors-Ever vs. Donors-Never†	0.99 (0.33–3.00)	0.986	1.59 (0.63–3.98)	0.324	0.93 (0.52–1.68)	0.811
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	2.76 (0.56–13.54)	0.212	2.42 (0.68–8.59)	0.170	1.13 (0.60–2.12)	0.704

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

Adjusted for recipient age, donor age, recipient sex, donor sex, recipient body mass index, diabetes, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, high-density lipoprotein, re-transplantation, desensitization, total number of human leukocyte antigen mismatches, and antithymocyte globulin induction.

*Also adjusted for the donor's smoking status.

†Also adjusted for the recipient's smoking status.

In this study, there was no difference in the rate of death-censored graft failure between cases in which both recipients and donors were ever smokers (ever-ever) and cases in which both recipients and donors were never smokers (never-never) in both the multivariate and univariate analyses. This may be related to a significant decrease in numbers when constructing the combination of ever–ever and never–never. The possibility of other interactions behind the composition of ever–ever and never–never cannot be excluded completely, and it is difficult to fully explain the results with current data alone.

Smoking results in decreased generation of the vasodilator nitric oxide, increased production of mediators of inflammation and free radicals, and abnormal lipid profile, activation of prothrombotic pathways, and enhanced platelet aggravation, which may contribute to the development of cardiovascular disease and atherosclerosis in smokers [22–24]. We assumed that, compared with cases in which both recipients and donors are never smokers, cases in which both recipients and donors are ever smokers have an increased rate of cardiovascular events and death in the kidney transplant recipients because the recipients are likely to live in the same residence as the living donors and second-hand smoke, in addition to their own smoking, increases the rate of cardiovascular events and death. In contrast to our expectations and the results from previous studies that identified a link between smoking and an increased rate of cardiovascular events and patient death [10,25,26], the outcomes of the current study indicated no association between smoking and cardiovascular events and mortality. Differences between our study and other studies may be attributable to a different ethnic population with different baseline characteristics and lifestyle patterns that could affect cardiovascular events. Furthermore, among the 58 current-smoker recipients in this study, 25 (43.1%) stopped smoking 1 year after kidney transplantation, which may have affected the results.

This study has some limitations. First, this study does not elucidate the association between smoking and outcomes in deceased-donor kidney transplant recipients because the analysis included only living-donor kidney transplant recipients. Second, no information was obtained regarding when former smokers stopped smoking, which would have been more meaningful. Third, the proportion of current smokers among recipients was 6.8%, which is lower than in other studies (approximately 10%–25%) [9–12]. In addition, the analysis of the effect of smoking cessation after transplantation was limited. Fourth, information about smoking may be less reliable because it relies on self-reporting, which is susceptible to inaccurate recall or a desire to give socially acceptable answers. Finally, despite adjusting outcomes for a number of potential confounding factors, there may remain unadjusted variables.

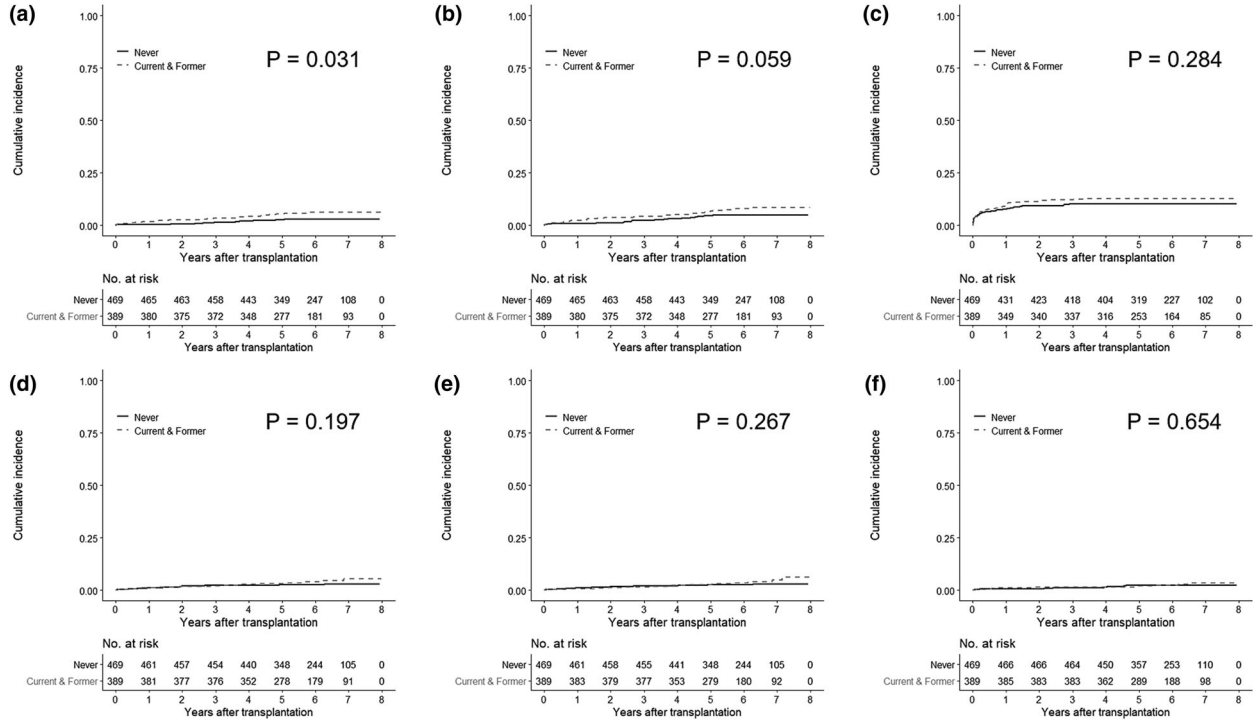

Figure 2 Cumulative incidence curves for death-censored graft failure (a), all-cause graft failure (b), biopsy-proven acute rejection (c), major adverse cardiac events (d), cardiac events (e), and all-cause death (f). Ever-smoker recipients showed a significantly higher rate of death-censored graft failure than never-smoker recipients ($P = 0.031$). Smoking status was not significantly associated with all-cause graft failure, biopsy-proven acute rejection, major adverse cardiac events, cardiac events, or all-cause mortality.

Table 3. Unadjusted and adjusted hazard ratios for major adverse cardiac events, cardiac events, and all-cause death.

	Major adverse cardiac events		Cardiac events		All-cause death	
Unadjusted	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never	1.63 (0.77–3.45)	0.201	1.53 (0.72–3.27)	0.271	1.22 (0.51–2.94)	0.655
Donors-Ever vs. Donors-Never	1.21 (0.55–2.67)	0.644	1.26 (0.57–2.80)	0.573	0.84 (0.31–2.31)	0.734
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	1.80 (0.53–6.14)	0.351	1.80 (0.53–6.14)	0.351	1.18 (0.31–4.45)	0.808
Adjusted	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never*	1.61 (0.60–4.35)	0.347	1.51 (0.55–4.15)	0.421	0.78 (0.28–2.16)	0.634
Donors-Ever vs. Donors-Never†	1.44 (0.62–3.35)	0.391	1.49 (0.64–3.51)	0.359	1.17 (0.41–3.37)	0.767
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	2.01 (0.45–8.89)	0.360	2.01 (0.45–8.89)	0.360	1.01 (0.23–4.44)	0.994

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

Adjusted for recipient age, recipient sex, recipient body mass index, diabetes, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, high-density lipoprotein, re-transplantation, and desensitization.

*Also adjusted for the donor's smoking status.

†Also adjusted for the recipient's smoking status.

Nevertheless, this study has definite strengths. Relatively few smoking-related research studies have been carried out in kidney transplant populations compared with the general population, and most of them are retrospective. Our results were obtained by performing a prospective multicenter study including consecutive

Transplant International 2021; 34: 2794–2802

Table 4. Unadjusted and adjusted odds ratios for post-transplant diabetes mellitus among kidney transplant recipients without pretransplant diabetes mellitus.

	Post-transplant diabetes mellitus	
Unadjusted	OR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never	0.50 (0.33–0.76)	0.001
Donors-Ever vs. Donors-Never	1.17 (0.73–1.87)	0.508
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	0.64 (0.33–1.25)	0.195
Adjusted	aOR (95% CI)	*P*-value
Recipients-Ever vs. Recipients-Never*	0.56 (0.30–1.01)	0.056
Donors-Ever vs. Donors-Never†	1.20 (0.71–2.02)	0.506
Recipients- and Donors-Ever vs. Recipients- and Donors-Never	0.68 (0.30–1.54)	0.353

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

Adjusted for recipient age, recipient sex, recipient body mass index, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, high-density lipoprotein, re-transplantation, and desensitization.

*Also adjusted for the donor's smoking status.

†Also adjusted for the recipient's smoking status.

Table 5. Unadjusted and adjusted hazard ratios for death-censored graft failure according to frequency.

	Death-censored graft failure	
Unadjusted	HR (95% CI)	*P*-value
Recipients		
>10 pack-years vs. ≤10 pack-years	1.88 (0.77–4.62)	0.167
>15 pack-years vs. ≤15 pack-years	2.14 (0.92–5.02)	0.079
>20 pack-years vs. ≤20 pack-years	3.22 (1.58–6.57)	0.001
Adjusted	aHR (95% CI)	*P*-value
Recipients		
>10 pack-years vs. ≤10 pack-years	1.33 (0.49–3.62)	0.583
>15 pack-years vs. ≤15 pack-years	1.90 (0.70–5.20)	0.211
>20 pack-years vs. ≤20 pack-years	2.83 (1.18–6.78)	0.019
Both recipients and donors		
>20 pack-years vs. ≤20 pack-years	2.12 (0.82–5.48)	0.122

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

Adjusted for recipient age, donor age, recipient sex, donor sex, recipient body mass index, diabetes, hypertension, coronary artery disease, cerebrovascular disease, total cholesterol, high-density lipoprotein, re-transplantation, desensitization, total number of human leukocyte antigen mismatches, and antithymocyte globulin induction.

incident living-donor kidney transplant recipients. Furthermore, this study concurrently explored the smoking status of kidney transplant recipients and living donors and its impact on adverse outcomes, which extended our knowledge that recipient smoking status has a stronger effect on transplant outcomes than donor smoking status. Lastly, considering that both the recipients and donors have smoking information, the number of participants involved was considerable, and the median follow-up duration was considerably long.

In conclusion, recipient smoking status before kidney transplantation is dose-dependently associated with impaired kidney transplant survival. However, the donor's smoking status did not affect outcomes or

amplify adverse outcomes. Therefore, these findings should be considered in both recipients and donors before and after kidney transplantation to optimize kidney transplant outcomes. Considering the dose-dependent effects of smoking, a smoking cessation program may be necessary at the start of managing chronic kidney disease.

Authorship

HYJ involved in conceptualization and writing—original draft preparation. HYJ and YJ involved in methodology. HYJ and YJ involved in formal analysis. HYJ, KHH, JBP, CWJ, SL, SH, RH, JY, JHC, SHP, YLK, and CDK involved in investigation. HYJ, KHH, JBP, CWJ, SL, SH, RH, JY, and CA involved in data curation. CA involved in funding acquisition. HYJ and CDK involved in writing—review and editing. All authors involved in the approval of final manuscript.

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Conflict of interest

The authors have declared that no competing interests exist.

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