Transplantation

Cigarette Smoking, Kidney Function, and Mortality After Live Donor Kidney Transplant

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Background: The role of smoking as a risk factor for adverse renal outcomes after kidney transplant has not been well studied. We therefore undertook this investigation to assess the association of smoking with transplant outcomes.

Study Design: Retrospective cohort study.

Setting & Participants: 997 consecutive laparoscopic live donor kidney transplant recipients at a tertiary-care transplant center.

Predictor: Smoking at the time of the transplant evaluation.

Outcomes & Measurements: Primary outcome is transplant survival.

Results: At the time of pretransplant evaluation, 329 participants had ever smoked and 668 participants had never smoked. Transplant survival was worse in ever smokers compared with never smokers (adjusted HR, 1.47; 95% CI, 1.08-1.99; $P = 0.01$), as was patient survival (adjusted HR, 1.60; 95% CI, 1.06-2.41; $P = 0.02$). First-year rejection-free survival was substantially worse (adjusted HR, 1.46; 95% CI, 1.05-2.03; $P = 0.03$) and risk of rejection on or before posttransplant day 10 was much higher (adjusted HR, 1.8; 95% CI, 1.10-2.94; $P = 0.02$) in ever smokers compared with never smokers. Glomerular filtration rate (estimated using the Modification of Diet in Renal Disease Study equation) at 1 year posttransplant was lower and poor early transplant function was more common in ever smokers on univariate, but not multivariate, analysis.

Limitations: Lack of quantitation of smoking exposure and uncertainty about whether patients were still smoking at the time of transplant.

Conclusions: Our results suggest that any history of smoking before transplant is associated with impaired transplant and patient survival and increases the risk of early rejection after live donor kidney transplant. Further study is needed to determine whether smoking may impart immunomodulatory and perhaps nephrotoxic effects.

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INDEX WORDS: Kidney transplantation; smoking; acute rejection.

Editorial, p. 817

In the general population, smoking may be an important modifiable risk factor for the development of chronic kidney disease.[1-3] Several studies have suggested an association between smoking and risk of microalbuminuria and macroalbuminuria/proteinuria.[4-7] Some studies also suggest that smoking may promote a decrease in kidney function, particularly in those with hypertension,[8] diabetes mellitus,[9] and primary renal diseases.[10-13] Two recent systematic reviews suggested that the overall evidence for cigarette smoking as a remediable risk factor for incident chronic kidney disease is strong.[3]

The mechanisms of smoking-related kidney injury are not entirely clear, and the pathophysiologic process likely is multifactorial. Many have hypothesized direct vascular effects that could lead to both small- and large-vessel disease.[14-18] Others have suggested that activation of the sympathetic nervous system may aggravate hypertension, increase oxidative stress, and result in endothelial dysfunction.[19,20] Smoking-induced alterations in intrarenal hemodynamics also may be at play.[13,21,22] Cigarette smoking also may affect the immune system in ways that could alter the risk

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of progression of immune-mediated native kidney disease[23] or perhaps even affect tolerance-rejection balance in organ transplant.[24]

Prior retrospective studies of kidney transplantation suggest that active smoking may be an important risk factor for transplant loss[24-26] and mortality.[25,27] A retrospective review of 1,334 renal transplant recipients performed by Kasiske and Klinger[25] at Hennepin County Medical Center between 1963 and1997 found that a smoking history of $>$ 25 pack-years was associated with a 30% higher risk of transplant failure ($P = 0.021$), whereas lesser magnitudes of smoking did not show significant associations with transplant survival. Their data showed that stopping smoking 5 years before transplant abrogated some of the risk of smoking. The study also suggested that the higher rate of transplant loss in heavy smokers was caused by an increase in deaths because higher mortality was noted in smokers and return to dialysis therapy and 1-year serum creatinine levels were not different in smokers.[25]

A second study by Sung et al[26] analyzed a cohort of 645 kidney transplant recipients from 1958-1995 and found that pretransplant smoking was a strong and independent risk factor for transplant loss during follow-up of ~10 years (adjusted relative risk, 2.3; $P < 0.005$). In contrast to the study by Kasiske and Klinger,[25] they did not show a statistically significant difference in patient survival between smokers and nonsmokers. Similar to the Kasiske and Klinger[25] study, they noted that those who stopped smoking pretransplant were not at higher risk of transplant loss compared with those who never smoked. Additionally, they noted no difference in risk of acute rejection between smokers and nonsmokers.[26] Thus, the limited available data suggest that current smoking at the time of transplant appears to be associated with worse transplant survival, but the mechanism for this apparent association is unclear.

We undertook this study to examine whether ever smoking is predictive of impaired patient and transplant survival after kidney transplant. Importantly, we also evaluated acute rejection risk and renal function parameters in hopes of providing information about the possible mechanisms through which smoking may impact on transplant survival. Additionally, we limited our analysis to living donor kidney recipients, for whom there would be less variability in the quality of the transplant to confound interpretation of short- and long-term outcomes.

METHODS

Participants

The study population included 997 consecutive recipients of laparoscopically procured living donor renal transplants at our major university hospital transplant center, and transplants were performed between March 1996 and November 2005. The laparoscopic surgical technique was described previously.[28]

Immunosuppression

During the study period, our immunosuppression protocol of choice evolved. Lymphocyte-depleting agents, including lymphocyte immune globulin, antithymocyte globulin (equine) sterile solution (Atgam; Pfizer, www.pfizer.com), muromonab-CD3 (OKT3; Centocor Ortho Biotech Inc, www.centocor.com), rabbit antithymocyte globulin (Thymoglobulin; Genzyme Corporation, www.genzyme.com), were used as induction in recipients who had a prior transplant or panel reactive antibody level $>$ 40%. In others, basiliximab was used routinely for induction since February 2002. The maintenance immunosuppression regimen initially consisted of microemulsion cyclosporine, mycophenolate, and prednisone. In October 1997, tacrolimus replaced cyclosporine. In the absence of a prior transplant or panel reactive antibody level $>$ 40%, corticosteroid dosage was tapered off within 3 weeks in non–African American recipients since February 2002 and in African American recipients since August 2005. Sirolimus was used sporadically since 2002. Percutaneous renal transplant biopsies were performed in recipients with poor transplant function every 7-14 days in the early posttransplant period, and later biopsies were performed as clinically indicated to evaluate transplant dysfunction. Acute rejection was treated with high-dose corticosteroids or a course of lymphocyte-depleting agents.

Study Procedures

After approval from The University of Maryland Institutional Review Board (Baltimore, MD), donor and recipient data were retrieved for study participants. Patient demographic, clinical, and laboratory data, as well as transplant and patient survival status, were compiled primarily from our transplant database, with review of transplant clinic and hospital records when appropriate. Hemodialysis unit billing records for the first postoperative week were reviewed for all recipients.

Smoking status was determined at the time of the pretransplant evaluation. Ever smokers were defined as past or current smokers. Never smokers were defined as those who had negative responses to queries about prior and current smoking. Current smokers were defined as those who admitted to current smoking at the time of pretransplant evaluation, and ex-smokers are defined as those who had quit smoking by the time of the pretransplant evaluation. Quantitation of either past or current smoking history was not consistently available.

Outcomes and Analyses

Failure of the renal transplant was defined as return to another form of renal replacement therapy (dialysis or repeated kidney transplant) or patient death with a functioning transplant. Follow-up time and survival analyses were censored at the time of the most recent follow-up with our center. Poor early transplant function was defined as the need for hemodialysis on posttransplant day 1-7 or serum creatinine level $\geq$ 3.0 mg/dL on posttransplant day 5. Need for dialysis was determined by identifying which patients generated an inpatient hemodialysis unit bill during the first postoperative week. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[29] Identification of acute rejection episodes during the first posttransplant year was achieved using manual review of pathology reports for all recipients by the first author. Acute rejection was defined as biopsy-proven acute cellular or humoral rejection according to prevailing Banff criteria.[30,31] Findings similar to or more severe than Banff 1A rejection were required to qualify as acute cellular rejection. Very early rejection was defined as acute rejection diagnosed on or before posttransplant day10. The primary outcome was renal transplant survival, and our primary analysis of interest was the comparison of ever smokers with never smokers.

Statistical Methods

Continuous variables were reported as mean $\pm$ standard deviation and compared using analysis of variance and *t* tests. Categorical variables were reported as absolute number of patients and/or percentage of the particular group and compared using χ^2 tests. Adjustments for multiple covariates, as detailed in the Results section, were made using linear regression for continuous outcomes and logistic regression for categorical outcomes. Survival analyses were performed using Kaplan-Meier techniques, compared using log-rank tests, and adjusted for potential confounders using Cox proportional hazard regression. Proportionality assumptions were tested using Schoenfeld tests and log-minus-log survival plots. The assumption of linearity of the relationship was examined using component plus residual plotting for continuous variables and comparing subgroup residuals for binary covariates. $P < 0.05$ is considered statistically significant. Potential confounding variables were chosen a priori for inclusion in the multivariate analysis from baseline factors that were asymmetrically distributed between the groups, for which data were available from a sufficient number of participants (>95%), and for which an independent effect on the outcomes was believed to be reasonably expected, even if a statistically significant effect was not shown in univariate analysis. SPSS version 8.0 (SPSS Inc, www.spss.com) and Stata SE 9.1 (Stata Corp, www.stata.com) software were used for statistical analyses.

RESULTS

At the time of transplant evaluation, there were 668 participants who never smoked and 329 who had ever smoked, 96 of whom were current smokers and 233 were ex-smokers. The lapse of time from initial pretransplant evaluation (at which time smoking history was routinely obtained) to transplant was 265 $\pm$ 273 days, with 79% $<$ 1 year and 94% $<$ 2 years. Baseline demographic and clinical parameters of participants and duration of follow-up are listed in Table 1. Some important differences between groups existed, including older recipient age and higher proportion of male recipients, diabetes mellitus, and steroid-free initial maintenance immunosuppression regimen in ever smokers. Based on the a priori criteria discussed, the following covariates were used in regression analyses: recipient age, recipient sex, diagnosis of diabetes mellitus, steroid-sparing initial maintenance immunosuppression regimen, and history of illegal drug use. We found no evidence for interactions among smoking and the predicting covariates (analyses not shown).

Overall renal transplant survival was worse in ever smokers compared with never smokers, as shown in Fig 1A. Patient survival was worse in ever smokers, as shown in Fig 1B. Table 2 lists cumulative events and event rates for the ever- and never-smoker groups. These differences persisted on multivariate analysis, and Table 3 lists details of univariate and multivariate analyses.

Figure 2A and B show these survival analyses (transplant and patient survival, respectively) with the ever-smoker group separated into current smokers and ex-smokers. On multivariate analysis of transplant survival in the ex-smoker and current-smoker subgroups of ever versus never smokers, we found that ex-smokers were marginally more likely (adjusted hazard ratio [HR], 1.37; 95% confidence interval [CI], 0.97-1.94; $P = 0.07$) and current smokers were significantly more likely (adjusted HR, 1.76; 95% CI, 1.14-2.7; $P = 0.01$) to experience transplant loss compared with never smokers. On multivariate analysis of patient survival in the ex- and current-smoker cohorts of ever versus never smokers, we found that ex-smokers were more likely (adjusted HR, 1.61; 95% CI, 1.02-2.53; $P = 0.04$) and current smokers were marginally more likely (adjusted HR, 1.77; 95% CI, 0.99-3.17; $P = 0.06$) to die compared with never smokers.

We had information about cause of death for 22 of 50 participants who died in the ever-smoker group, and these included 8 cardiovascular, 11 septic, and 3 oncologic deaths. We had information

Table 1. Baseline Factors of Groups

	Entire Group (N = 997)	Smoking Status: Ever (n = 329)	Smoking Status: Never (n = 668)	Data Completeness (%)	*P* (ever vs never)
Duration of follow-up (y)					
Mean ± SD	3.49 ± 2.57	3.46 ± 2.55	3.51 ± 2.59	100	0.8
Median	3.27	3.17	3.30	100	NS
Recipient factors					
Male (%)	58.5	63.2	56.2	100	0.03
Age at transplant (y)	46.2 ± 13.9	50.6 ± 12.2	44.1 ± 14.2	99.8	<0.001
African American (%)	27.4	26.7	27.7	100	0.8
Body mass index (kg/m^2)	26.7 ± 5.8	27.1 ± 6.6	26.5 ± 5.9	99.5	0.1
Diabetes mellitus (%)	32.4	41.3	28.0	100	<0.001
Prior transplant (%)	6.5	6.1	6.7	100	0.7
History of illegal drug use (%)	5.2	11.9	1.9	100	<0.001
Zero HLA mismatch with donor (%)	8.9	9.2	8.7	99.5	0.8
HLA mismatch (no. of loci)	3.04 ± 1.59	2.99 ± 1.59	3.06 ± 1.59	99.7	<0.001
Donor factors					
Male (%)	42.7	41.8	43.2	100	0.7
Age at transplant (y)	40.2 ± 11.3	40.1 ± 11.2	40.0 ± 11.4	99.6	0.8
African American (%)	26.2	25.0	26.8	99.2	0.5
Genetically unrelated to recipient (%)	30.1	31.8	29.2	99.8	0.4
Immunosuppression factors					
LDA induction (%)	21.9	20.2	22.7	95.3	0.4
Anti–interleukin 2 antibody induction (%)	26.9	29.7	25.5	95.5	0.4
Tacrolimus in initial maintenance IS regimen (%)	83.1	82.5	83.3	94.2	0.2
Sirolimus in initial maintenance IS regimen (%)	5.8	7.7	4.9	95.5	0.08
Steroid-free maintenance IS regimen (%)	15.0	19.2	12.9	95.2	0.01
Pretransplant desensitization (%)	3.9	4.3	3.7	100	0.7

Abbreviations: HLA, human leukocyte antigen; IS, immunosuppression; LDA, lymphocyte depletion antibody; NS, not significant.

about cause of death in 23 of 58 participants who died in the never-smoker group, and these included 13 cardiovascular, 8 septic, and 2 oncologic deaths. There were no statistically significant differences between groups in the proportion of any of these categories of death.

Death-censored renal transplant survival was similar in ever and never smokers, as shown in Fig 1C, with cumulative events and event rates listed in Table 2. There was a trend of worse death-censored transplant survival (graphs not shown) in current compared with never smokers ($P = 0.08$), but there was no apparent difference in ex- compared with never smokers ($P = 0.5$). On multivariate analysis, a trend toward worse death-censored transplant survival was noted in the ever-smoker group (adjusted HR, 1.42; 95% CI, 0.94-2.17; $P = 0.1$).

To explore potential mechanisms that could link smoking to decreased renal survival (in addition to the effect of increased patient mortality), we assessed rejection rates, early kidney function outcomes, and later renal outcomes in the 2 groups. As shown in Fig 1D, rejection-free kidney survival in ever smokers was worse during the first posttransplant year, and this difference persisted on multivariate analysis (Table 3). Figure 2C shows differences in rejection-free survival among current, ex-, and never smokers.

Interestingly, Fig 1D shows that the curves separate early, and very early acute rejection (diagnosed on or before posttransplant day10)

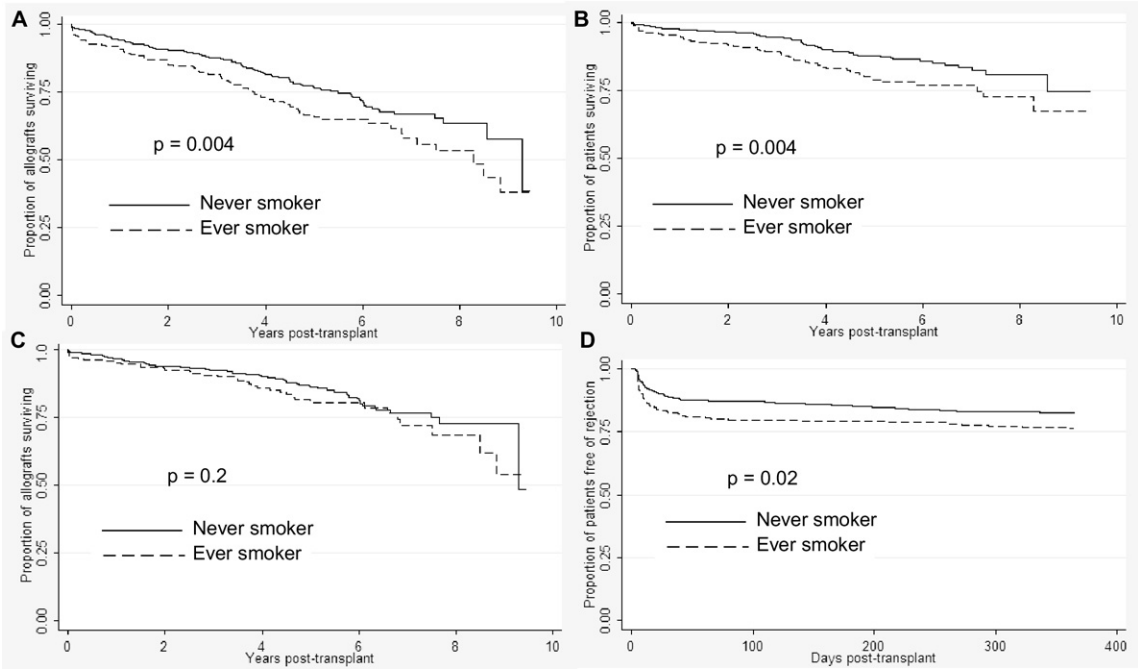

Figure 1. Survival outcomes for ever versus never smokers. (A) Renal transplant survival (non–death censored). (B) Patient survival for ever smokers. (C) Death-censored renal transplant survival. (D) Rejection-free renal survival.

was much more common in ever than never smokers (12.5% and 6.6%, respectively; $P = 0.002$), even on multivariate analysis (Table 3).

Table 2. Cumulative Event Rates for Various Survival Outcomes

	Smoking Status	
	Ever	**Never**
Graft loss		
Events	86	121
Person-years	2,162	4,902
Event rate/100 person-years	4.0	2.5
Death		
Events	50	59
Person-years	2,546	5,589
Event rates/100 person-years	2.0	1.1
Death-censored graft loss		
Events	45	74
Person-years	2,530	5,376
Event rates/100 person-years	1.8	1.4
Acute rejection in first year		
Events	75	109
Person-years	261	667
Event rates/person-year	0.29	0.19

We also found that the incidence of very early acute rejection was higher in the ex-smoker subset of ever smokers compared with never smokers (28 of 233 [12%] and 44 of 666 [6.6%], respectively; $P = 0.009$). We likewise found significantly higher rates of very early rejection in the current-smoking cohort compared with never smokers (13 of 96 [13.5%] and 44 of 666 [6.6%], respectively; $P = 0.02$). In the subgroup that experienced very early rejection, there were no statistically significant differences in baseline factors listed in Table 1 for ever smokers compared with never smokers (data not shown). Additionally, we did not find differences in outcomes based on smoking status in this group, including eGFR at 1 year (48.7 ± 15.4 mL/min/1.73 m^2 in ever smokers vs 53.1 ± 19.8 mL/min/1.73 m^2 in never smokers; $P = 0.3$), transplant survival (log-rank $P = 0.8$), death-censored transplant loss (log-rank $P = 0.9$), and patient survival (log-rank $P = 0.7$).

The ever-smoker group was more likely to experience poor early transplant function than never smokers (19.8% vs 14.5%, respectively; $P = 0.04$). One year posttransplant, the ever-smoker group also had lower eGFRs than the

Table 3. Univariate and Multivariate Analyses for Primary Outcome and Selected Secondary Outcomes

Outcomes With Covariates	Univariate Model		Multivariate Model	
	HR or OR (95% CI)	*P*	HR or OR (95% CI)	*P*
Graft failure				
Ever smoker	1.50 (1.14-1.98)	0.004	1.47 (1.08-1.99)	0.01
Male recipient	0.80 (0.61-1.06)	0.1	0.81 (0.61-1.08)	0.2
Recipient age (/decade)	1.07 (0.97-1.19)	0.2	1.02 (0.92-1.14)	0.7
Diabetes mellitus	1.43 (1.09-1.91)	0.01	1.37 (1.03-1.85)	0.03
Ever use of illegal drugs	1.16 (0.66-2.03)	0.6	1.09 (0.60-1.97)	0.8
Steroid-free maintenance regimen	1.06 (0.64-1.73)	0.2	1.04 (0.63-1.71)	0.9
Patient death				
Ever smoker	1.73 (1.19-2.54)	0.004	1.60 (1.06-2.41)	0.02
Male recipient	0.86 (0.59-1.25)	0.4	0.77 (0.52-1.14)	0.2
Recipient age (/decade)	1.51 (1.30-1.76)	<0.001	1.45 (1.23-1.70)	<0.001
Diabetes mellitus	1.22 (0.82-1.80)	0.3	1.15 (0.76-1.74)	0.5
Ever use of illegal drugs	0.65 (0.23-1.75)	0.4	0.84 (0.30-2.36)	0.7
Steroid-free maintenance regimen	1.16 (0.59-2.25)	0.7	1.05 (0.54-2.05)	0.9
Acute rejection during first posttransplant year				
Ever smoker	1.43 (1.07-1.92)	0.02	1.46 (1.05-2.03)	0.03
Male recipient	0.97 (0.72-1.3)	0.8	0.88 (0.65-1.19)	0.4
Recipient age (/decade)	0.91 (0.82-1.01)	0.08	0.89 (0.79-0.99)	0.04
Diabetes mellitus	1.15 (0.85-1.56)	0.4	1.11 (0.81-1.52)	0.5
Ever use of illegal drugs	2.17 (1.35-3.5)	0.001	1.86 (1.10-3.14)	0.02
Steroid-free maintenance regimen	0.98 (0.64-1.49)	0.9	0.98 (0.64-1.50)	0.9
Very early acute rejection				
Ever smoker	2.02 (1.29-3.16)	0.002	1.8 (1.1-2.94)	0.02
Male recipient	0.67 (0.43-1.04)	0.08	0.56 (0.35-0.90)	0.02
Recipient age (/decade)	1.07 (0.91-1.26)	0.4	1.06 (0.88-1.27)	0.5
Diabetes mellitus	1.15 (0.72-1.84)	0.6	1.07 (0.66-1.73)	0.8
Ever use of illegal drugs	2.39 (1.12-5.10)	0.02	2.33 (1.07-5.37)	0.05
Steroid-free maintenance regimen	1.53 (0.87-2.69)	0.1	1.44 (0.81-2.57)	0.2

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

never smoker group (51.1 ± 18.7 vs 54.6 ± 20.5 mL/min/1.73 m^2, respectively; $P = 0.03$). However, neither of these findings retained statistical significance on multivariate analysis. Current smokers had an 18.3% risk of poor early transplant function ($P = 0.3$ vs never smokers) and eGFR of 45.4 ± 16.6 mL/min/1.73 m^2 ($P = 0.001$ vs never smokers), and ex-smokers had a 20.3% risk of poor early transplant function ($P = 0.04$ vs never smokers) and eGFR of 53.3 ± 19.1 mL/min/1.73 m^2 ($P = 0.5$ vs never smokers). When we excluded participants who experienced very early acute rejection from analysis, the incidence of poor early transplant function was similar in ever and never smokers (43 of 282 [15%] and 77 of 617 [12%], respectively; $P = 0.3$), and eGFR was not significantly worse in never compared with ever smokers (51.4 ± 19.1 vs 54.8 ± 20.6 mL/min/1.73 m^2, respectively; $P = 0.06$).

DISCUSSION

This study of nearly 1,000 live donor kidney transplant recipients shows that ever smoking is independently associated with worse long-term kidney transplant survival. Other important findings are that smoking independently predicts worse patient survival, higher very early acute rejection risk, and worse first-year rejection-free survival. Additionally, we showed possible associations with higher risk of poor early transplant function and worse 1-year kidney function. In general, current smoking was associated with more robust differences in outcomes; but ex-smokers also showed worse transplant survival, worse patient survival, and higher very early acute rejection risk.

Our findings of worse renal transplant and patient survival in ever smokers contribute to the

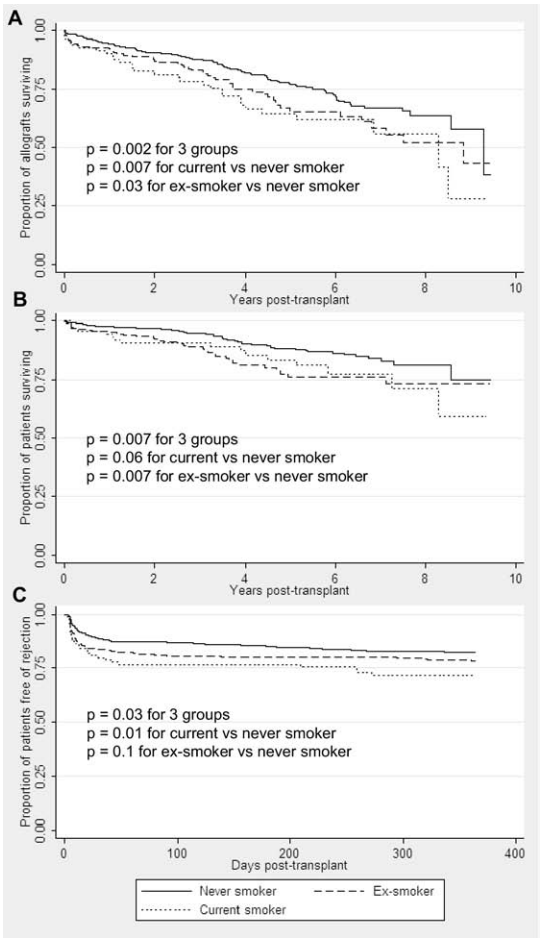

Figure 2. Survival outcomes in current, ex-, and never smokers. (A) Renal transplant, (B) patient, and (C) rejection-free survival.

literature by corroborating previously reported findings from the other studies discussed. More importantly, our study supplies the intriguing and previously unreported finding of a higher incidence of acute rejection in ever smokers, with differences in rejection rates that are clinically relevant and supported by compelling statistical strength. Importantly, the independent association of smoking with a markedly higher rate of very early acute rejection argues that smoking imparts a true biological risk, rather than being simply a marker of psychosocial factors that increase the risk of rejection precipitated by lack of treatment adherence. It is very unlikely that medication adherence would be problematic in the first 10 days, during which most patients with a malfunctioning transplant would still be hospitalized. Furthermore, a recent study found that pretransplant tobacco exposure in a rat model of heart transplant produced accelerated transplant rejection, thus providing experimental support for our epidemiologic findings of higher risk of rejection in smokers.[32]

We suspect that the higher risk of transplant loss in ever smokers is mediated primarily by both patient deaths and effects of acute rejection. The association of smoking with worsened patient survival and the lack of statistically significant impairment of death-censored transplant survival are consistent with higher mortality as a major cause of worse transplant survival in ever smokers. Furthermore, this explanation is consistent with conclusions of the Kasiske and Klinger[25] study and is intellectually palatable given the known mortality risks of smoking. Our data suggest that acute rejection–induced kidney dysfunction likely also contributes to the worsened transplant survival in ever smokers, to the higher rate of poor early transplant function (which includes delayed and slow transplant function), and to the worse 1-year eGFR that we observed in ever smokers.

If there truly are pertinent pathophysiologic differences between smokers and nonsmokers in this setting, it could be hypothesized that they could be caused by short-term effects of nicotine and/or long-lasting or permanent sequelae of prior smoking. Our data suggest that the latter may be a major component of the association. Making the seemingly conservative assumption that participants did not resume smoking in the interim between the pretransplant evaluation and subsequent living donor kidney transplant, the exclusion of current smokers would ensure that very few active smokers were included in this subgroup of ever smokers and thus would eliminate short-term nicotine effects from the picture. After this manipulation, differences in transplant survival, patient survival, and very early acute rejection risk persisted. Thus, it could be conjectured that carryover effects of smoking impact negatively on posttransplant outcomes. Whether this association is biological or related to other unidentified confounders is not known, and further study is needed to make this assessment. Further study also is needed to determine the pathophysiologic mechanisms that explain these epidemiologic associations. For example, it will

be important to determine whether smoking-related effects on the immune system or the vascular system, which could range from endothelial function to problems with large-vessel integrity, could impart renal injury and perhaps mediate the apparent increased rejection risk.

Similar to prior reports, our study also shows substantial impairment of long-term patient survival in ever smokers, even after adjustment for potential confounders and excluding current smokers. However, no obvious explanation of this difference in patient survival was found in our data because no statistical differences in causes of death (including oncologic or cardiovascular) between the 2 groups were identified. Acceleration of cardiovascular disease in smokers and increased risk of malignancies would be expected to be important mediators of mortality in kidney transplant patients who smoked. Although this determination was well beyond the scope of our study given the relatively small number of participants whose cause of death was known to us, septic deaths seemed to account for a slightly higher (albeit statistically insignificant) relative proportion of causes of death in ever smokers than never smokers (54% and 35%, respectively). This raises the concern that smoking may have mediated some of its effects on mortality through its tendency to increase acute rejection and thereby increase level of immunosuppression and possibly risk of infections, which could result in septic deaths.

There are significant limitations to our study. Most importantly, we did not quantitate smoking exposure in terms of either intensity (cigarettes per day) or duration and therefore could not assess whether there is dose response or a threshold level at which smoking becomes a risk factor. We also do not know how many patients were still smoking at the time of transplant and how many continued to smoke after transplant because our assessment of smoking status was made at the time of pretransplant evaluation. This severely limits our ability to distinguish effects of remote versus recent smoking. Our data provide no direct information about whether smoking cessation before or at the time of transplant may be beneficial in decreasing the incidence of acute rejection, transplant failure, or death after transplant. An additional limitation to this study is the inability to adequately incorporate the many confounding psychosocial and medical conditions that may accompany a history of smoking, even if they are not the result of this exposure. Additionally, accompanying medical conditions that may increase incentive to quit and character-related factors associated with the ability to break a strongly addictive habit could be pertinent to these outcomes. Despite adjusting for several confounding factors included in our database (such as illegal drug use, diabetes mellitus, etc) by using regression techniques, unmeasured confounding factors are still plausible. Nevertheless, the impressive difference in acute rejection by posttransplant day 10, before behavioral factors would be expected to have an impact, strongly suggests that smoking is pathogenic and not just a marker of psychosocial risk.

A final limitation is that we did not know the smoking status of the donors. It may be expected that recipients who smoked may be more likely to have a donor who is/was a smoker or who had a strong secondhand smoke exposure. Certainly, kidneys from such donors may have preexisting vascular and endothelial damage that could be problematic posttransplant.

In conclusion, our study shows that patients with either a past or current smoking history at the time of pretransplant evaluation who receive a live kidney donor transplant show impaired transplant survival and higher mortality, which may be mediated in part by early transplant rejection and consequent injury. Our study also suggests there is likely a carryover effect of prior smoking exposure on these outcomes. More work is required to fully elucidate the pathogenesis of the association of ever smoking and adverse posttransplant outcomes and whether any interventions could attenuate this risk, such as closer vigilance for rejection or more intensive immunosuppression in smokers. It also will be important to know whether smoking in a living kidney donor may be associated with impaired recipient outcomes, even in a nonsmoking recipient. Ultimately, these observations may be important in kidney recipient and donor selection and management.

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