ORIGINAL ARTICLE

Former smoking and early and long-term graft outcome in renal transplant recipients: a retrospective cohort study

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SUMMARY

Smoking is associated with unfavourable outcome in solid-organ transplant recipients. Nicotine may predispose to kidney injury by increasing oxidative stress. We hypothesized that former smoking negatively affects graft outcome in kidney transplant recipients and especially those with delayed graft function (DGF). We included adult recipients of a kidney transplant between 1 January 2003 and 1 October 2015 at Ghent University Hospital and recorded outcomes until 31 October 2015. We used Kaplan–Meier and multivariable Cox proportional hazard analysis to examine the relationship between former smoking at the time of transplantation and the incidence of 10-year graft loss with and without censoring for death in 1013 participants. We evaluated mean differences in eGFR over time by a random intercept and slope model, considering a linear time effect. After adjusting for potential confounders, a history of smoking was associated with an increased hazard of graft loss (adjusted hazard ratio (aHR) 1.60; 95% CI: 1.17–2.17; $P = 0.003$) and death-censored graft loss (aHR 2.29; 95% CI: 1.41–3.72; $P = 0.001$). The linear time trend of eGFR was different between former and never smokers ($P = 0.001$). To conclude, former smoking exerts long-lasting negative effects on graft outcome and this independent of DGF.

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Key words
delayed graft function, graft survival, nicotine, previous smoking, rejection

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Introduction

We have known for decades that smoking causes chronic vascular damage. In people with diabetes, hypertension and polycystic kidney disease, active smoking is associated with accelerated progression of chronic kidney disease and faster decline in kidney function [1,2]. In kidney transplant recipients, smoking is associated with decreased graft survival [1,3–5].

But smoking does not just kill off the kidneys in the long run, it also seems to predispose for acute injury after heart transplantation and cardiac surgery [6,7]. In mice, chronic nicotine exposure potentiates acute kidney injury by potentiating ischaemia/reperfusion-related oxidative stress [8]. Other proposed mechanisms include stimulation of renal nicotinic acetylcholine receptors and the renin–angiotensin system, increased sympathetic activity and finally direct hemodynamic effects leading to reduced glomerular filtration rate and renal plasma flow [1,9,10].

Not only current smoking seems to matter. In lung transplant recipients, former smoking was

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independently associated with faster decline of kidney function than in recipients who never smoked [11]. In rats, previous exposure to nicotine aggravated cyclosporine-induced nephrotoxicity [12]. As such, not only current but also former smoking may sensitize the kidney to ischaemic insults and predispose to delayed graft function (DGF) and faster decline of kidney function. We speculated that a smoking history could amplify the negative effects of DGF on long-term graft function.

Materials and methods

We designed a retrospective observational cohort study to examine the association between previous smoking before transplantation and both immediate graft function and long-term graft survival. We included all men and women aged 18 years or older, who received a single of combined graft kidney at Ghent University Hospital between 1 January 2003 and 1 October 2015. Outcomes were recorded until 31 October 2015 after which data were censored for administrative reason. We extracted patient characteristics and outcome data from a compiled database which prospectively records patient characteristics and graft outcome including date of patient and graft loss of all transplanted participants at Ghent University Hospital.

The primary variable of interest was smoking history. We categorized people into former and never smoker according to their status, which was recorded at the pretransplantation visit. Former smoking was defined as active smoking at any time before transplantation. Smoking cessation for at least three months is a prerequisite for enlisting for kidney transplantation in our centre. We additionally recorded smoking after transplantation as a dichotomous covariate and defined it as active smoking at any time after transplantation. The primary outcome was graft loss, which was defined as the need for renal replacement therapy for at least one month or due to patient death. The secondary outcome was kidney function, assessed by estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI formula [13] at year one, three and five, recorded the closest date one month (year one and three) or two months (year five) before or after these time points. We recorded DGF defined as need for renal replacement therapy the first week after transplantation. We performed a secondary analysis to ascertain robustness of the findings across subgroups and analysed whether smoking status would have a different effect on graft outcome in specified subgroups: age $<$ or $\geq$60 years, DGF, extended criteria donor (ECD) kidney and rejection. We checked for an interaction between smoking status and DGF which could affect graft outcome and stratified graft outcome according to DGF and former smoking. We recorded the occurrence of rejection, which was biopsy-proven by definition.

We retrieved covariates from the medical files and our transplant database which possibly affect graft and recipient outcome based on literature data: donor criteria, body mass index (BMI), diabetes, dialysis modality, dialysis vintage, hypertension, cardiovascular disease, immunosuppression, induction treatment, donor age, race, retransplantation, combined transplantation, human leucocyte antibodies (HLA) and panel-reactive antibodies (PRA).

Donor characteristics including donation after cardiac death (DCD) are recorded in our transplant database. ECD was defined by donor age>60 year or donor age of more than 50 years with at least two of the following additional criteria of history of hypertension, cerebrovascular accident as cause of death or serum creatinine>1.5 mg/dl. BMI was calculated as weight in kilograms divided by the square of height in metres. Diabetes was defined according to the American Diabetes Association criteria [14] or as intake of glucose-lowering drugs according to the patient records. The dialysis modality was coded into three categories: haemodialysis, peritoneal dialysis or preemptive transplantation. The immunosuppressive regimen comprised use of corticosteroids, mycophenolate mofetil combined with cyclosporine, tacrolimus or mammalian target of rapamycin (mTOR) inhibitors. Induction treatment included polyclonal antibodies in immunized recipients or basiliximab. We dichotomized people with previous immunization according to the presence of antibodies (positive PRA) or not. Hypertension was defined as the intake of antihypertensive drugs before transplantation. Cardiovascular disease was defined as a history of percutaneous coronary stenting, myocardial infarction, coronary revascularization, transient ischaemic attack, stroke or peripheral arterial disease.

The study protocol was approved by the ethical committee of Ghent University Hospital and all authors adhered to the Declaration of Helsinki.

Statistical analysis

We used Kaplan–Meier and Cox proportional hazard analysis to examine the relationship between baseline smoking status and the incidence of graft loss with and without censoring for death. We summarized baseline

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characteristics as mean ± standard deviation for normally distributed continuous variables or median with interquartile range (IQR) for skewed distributions. We compared characteristics of former smokers with never smokers by the chi-square test or analysis of variance (ANOVA) for parametric variables and the Kruskal–Wallis test for nonparametric variables. We used a *post hoc* Scheffé test in case of multiple comparisons. We compared mean differences in eGFR over time between former smokers and never smokers by a random intercept and slope model, considering a linear time effect. We compared differences in Kaplan–Meier cumulative-event curves according to smoking status by the Mantel (log-rank) test. Because of the well-known effect of DGF on graft survival, this variable was used for further stratification in univariate Kaplan–Meier analysis. As the primary interest of the study was how the covariates affect the event of interest, we preferred a cause-specific hazard model over a competing risk approach, as the former seems more valid for medical decision-making [15]. We designed the multivariable Cox proportional hazard regression model with backward elimination including covariates associated with graft outcome based on existing literature such as ECD, age and BMI or on the univariate association with graft loss (P-value <0.1) in our analysis. We tested proportional hazards assumption using plots of the scaled Schoenfeld residuals against time. We searched for interactions with former smoking by stratifying for *a priori* chosen covariates: receptor age < or > 60 years, DGF, ECD donor and rejection. A two-sided P value of <0.05 was considered to indicate statistical significance for all analyses. We conducted all statistical analyses using SPSS® (version 22, IBM, New York, NY, USA).

Results

Baseline characteristics

We included 1013 adult kidney transplant recipients, 636 men (63%), and 474 (47%) with a history of smoking and excluded 28 paediatric recipients. The mean time of follow-up was 4.4 years. Baseline characteristics are summarized in Table 1. Seventy-one patients smoked after transplantation (7%). Overall 119 people (11.7%) died within the first 10 years after transplantation and 128 (12.7%) of the study population had rejection during follow-up. DGF occurred in 137 people (13.5% of the overall study population). Former smokers vs. never smokers were more often male, had a higher prevalence of diabetes, were more likely transplanted with a kidney from a DCD donor, had a higher BMI, more often used tacrolimus, had a shorter waiting time for transplantation and had more hypertension and cardiovascular disease and a lower PRA. There were no missing data for any covariate of interest.

Graft survival

In univariate stratified Kaplan–Meier analysis, former smoking and the occurrence of DGF both were associated with an increased risk of 10-year graft loss during follow-up. Graft survival was shortest in people who were previous smokers (overall $P < 0.001$) (Figure 1). When stratifying patients according to DGF and smoking status, the subgroup of former smokers with DGF demonstrated the poorest graft and death-censored graft survival (Figure 1) (overall $P < 0.001$).

According to the Cox model, former smokers had a 65% higher 10-year risk of graft loss than those who never smoked with a HR of 1.65 (95% CI: 1.23–2.21; $P = 0.001$) (Table 2). After adjustment for polyclonal induction, diabetes, BMI, gender, ECD donor, age, retransplantation, cardiovascular disease, hypertension and HLA mismatches, former smoking remained associated with a higher graft loss with an adjusted hazard ratio (aHR) of 1.60 (95% CI: 1.17–2.17; $P = 0.003$). Further adjustment for intermediate outcomes rejection and DGF did not alter the association with an aHR of 1.73 (95% CI: 1.27–2.37; $P = 0.001$) for former smokers vs. never smokers. PRA and donor age were not included as parameter in the multivariable model considering the collinearity with polyclonal induction and ECD, respectively, while we did not include DCD considering the collinearity with DGF and the absence of an association in univariable analysis. In comparison with never smokers, patients who smoked after transplantation had a higher graft loss with an aHR of 2.54 (95% CI: 1.56–4.13; $P < 0.001$) and patients who smoked before but not after transplantation still had a higher graft loss with an aHR of 1.40 (95% CI: 1.01–1.95; $P = 0.046$) vs. never smokers.

Death-censored graft survival

Former smokers had a 110% higher hazard of death-censored 10-year graft loss than those who never smoked with a HR of 2.1 (95% CI; 1.35–3.27; $P = 0.001$). Also associated with death-censored graft survival were retransplantation, rejection, higher BMI,

Table 1. Baseline characteristics study population (n = 1013).

		Previous Smokers (n = 472)	Never smokers (n = 541)	P value
Combined transplantation	n = 70 (6.9%)	n = 27	n = 43	0.16
Retransplantation	n = 40 (3.9%)	n = 18	n = 22	0.84
Male gender	n = 637 (62.8%)	n = 351	n = 286	<0.001
Age (years)	52.2 ± 12.6	52.3 ± 11.9	52.1 ± 13.2	0.77
Non-Caucasian Race	n = 52 (5.1%)	n = 20	n = 32	0.23
Diabetes	n = 172 (17%)	n = 96	n = 76	0.008
BMI	25.4 ± 4.4	25.8 ± 4.5	25.0 ± 4.3	0.008
Polyclonal induction	n = 94 (9.3%)	n = 41	n = 53	0.54
Hypertension	n = 922 (91.0%)	n = 445	n = 477	0.001
Cardiovascular history	n = 107(18.5%)	n = 107	n = 80	0.001
DCD donor	n = 91 (9.1%)	n = 55	n = 36	0.006
ECD donor	n = 155 (15.1%)	n = 74	n = 81	0.76
Living donor	n = 86 (8.5%)	n = 45	n = 41	0.27
Immunosuppressive regimen				
Cyclosporine	n = 234 (23.1%)	n = 93	n = 141	0.001
Tacrolimus	n = 735 (72.6%)	n = 367	n = 368	
mTOR inhibitors	n = 44 (4.3%)	n = 12	n = 32	
Cold ischaemia time (min)	761 ± 337	741 ± 343	778 ± 331	0.07
HLA mismatches	3 (1)	3 (1)	3 (1)	0.20
PRA>0%	113 (11.2%)	40	73	0.01
Waiting time (days)	572 (846)	532 (758)	625 (937)	0.001
Donor age (years)	44.2 ± 14.5	44.9 ± 14.0	43.6 ± 14.8	0.16
Dialysis modality				
Pre-emptive	n = 98 (9.7%)	n = 50	n = 48	0.29
Haemodialysis	n = 691 (68.2%)	n = 327	n = 364	
Peritoneal dialysis	n = 224 (22.1%)	n = 95	n = 129	

BMI, body mass index; DCD, donation after cardiac death; ECD, extended criteria donor; mTOR, mammalian target of rapamycin; HLA, human leucocyte antigen; PRA, panel-reactive antibodies.

Depicted are absolute numbers (percentages), mean ± standard deviation or median (interquartile range) depending upon the distribution.

ECD donor kidney and DGF (Table 2), while combined transplantation, age, gender, race, diabetes, polyclonal induction, PRA, immunosuppression, DCD donor, living donor, HLA mismatch, dialysis modality and waiting time for transplantation were not. After adjustment for polyclonal induction, diabetes, BMI, gender, ECD donor, age, retransplantation, hypertension, cardiovascular disease and HLA mismatches, former smoking remained associated with graft loss with an aHR of 2.29 (95% CI: 1.41–3.72; P = 0.001). Further adjustment for intermediary outcomes rejection and DGF did not change this association with an aHR of 2.42 (95% CI: 1.48–3.95; P < 0.001) in former vs. never smokers. In comparison with never smokers, patients who smoked after transplantation had a higher 10-years death-censored graft loss with an aHR of 3.79 (95% CI: 1.98–7.27; P < 0.001) and patients who smoked before but not after transplantation still had a higher graft loss with an aHR of 1.82 (95% CI: 1.08–3.07; P = 0.02) vs. never smokers.

Secondary analysis

The linear time trend is different between former smokers and never smokers (P = 0.001). The change in mean eGFR of former smokers was estimated as −1.0 (95% CI: −1.6 to −0.4) mL/min/year (P = 0.001), while in never smokers, it was estimated as 0.3 (95% CI: −0.2 to 0.9) mL/min/year (P = 0.19). Unadjusted mean eGFR was lower in former vs. never smokers at year 3 and 5 after transplantation (55.6 ± 17.9 vs. 60.8 ± 19.4 ml/min/1.73 m^2; P = 0.004 and 54.5 ± 18.8 vs. 62.4 ± 19.0 ml/min/1.73 m^2; P < 0.001, respectively); while the difference at year one was not statistically

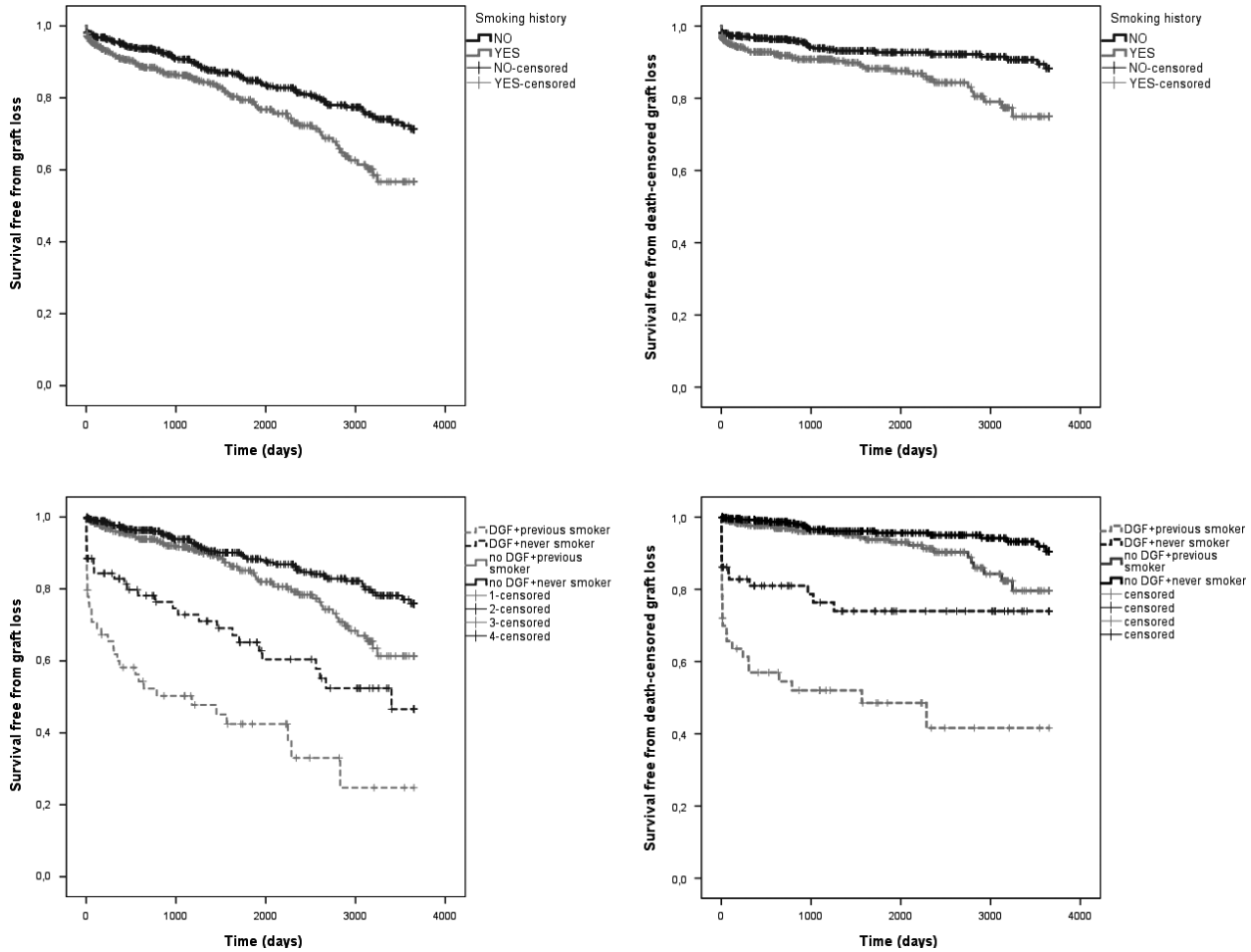

Figure 1 Ten-year graft and death-censored graft loss in subjects according to smoking history and/or delayed graft function. Ten-year graft and 10-year death-censored graft survival according to delayed graft function (DGF) and smoking status. The 10-year graft survival (upper left) and death-censored graft survival (upper right) are better in subjects who never smoked vs. former smokers (log-rank $P = 0.001$ in both analyses). Considering 10-year graft survival (down left), survival is significantly better in those with no DGF who never smoked than former smokers without DGF (log-rank $P = 0.007$) and both groups with DGF (both log-rank $p < 0.001$). The survival is significantly better in subjects with DGF who never smoked vs. former smokers ($P = 0.004$). Considering 10-year death-censored graft survival (down right), survival is significantly better in those with no DGF who never smoked than former smokers without DGF (log-rank $P = 0.014$) and both groups with DGF (both log-rank $p < 0.001$). The survival is significantly better in subjects with DGF who never smoked vs. former smokers ($P = 0.004$). Pooled log-rank *P*-value <0.001 in both analyses.

significant (57.2 ± 17.9 vs. 59.5 ± 18.1 ml/min/1.73 m^2; $P = 0.09$).

According to the Cox model, former smokers had a 58% higher 10-year mortality than those who never smoked with an aHR of 1.58 (95% CI: 1.09–2.23; $P = 0.015$) after adjustment for age, gender, diabetes, BMI, hypertension, cardiovascular disease and immunosuppression. They had a 87% higher hazard of rejection with an aHR of 1.85 (95% CI: 1.26–2.70; $P = 0.002$) after adjustment for age, gender, BMI, PRA, ECD, DCD, ATG, retransplantation and immunosuppression. The incidence of DGF in former smokers (12.5%) did not differ from people who never smoked (14.4%) ($P = 0.37$).

Subgroup analysis

There were no significant interactions between historical smoking and other predictors of graft loss or death-censored graft loss including rejection although we could observe a trend towards an interaction between DGF and historical smoking with graft survival as dependent variable only but not death-censored graft survival (Table 3, Figure 2).

Discussion

In our study sample of >1000 kidney transplant recipients, former smoking was associated with increased

Table 2. Cox proportional hazard regression model for 10-year graft loss and death-censored graft loss.

	Univariable			Multivariable		
	HR	95% CI	*P* value	AHR	95% CI	*P* value
Graft loss						
Diabetes (yes vs. no)	1.87	1.34–2.26	<0.001	1.39	0.93–2.08	0.011
Previous smoking (yes vs. no)	1.65	1.23–2.21	0.001	1.60	1.17–2.17	0.003
Polyclonal induction (yes vs. no)	1.55	1.03–2.35	0.04	1.79	1.16–2.77	0.009
ECD donor (yes vs. no)	2.40	1.71–3.35	<0.001	1.86	1.28–2.70	0.001
Age (per year)	1.03	1.02–1.04	<0.001	1.03	1.01–1.04	0.002
Cardiovascular disease (yes vs. no)	2.02	1.48–2.76	<0.001	1.53	1.09–2.16	0.01
DGF (yes vs. no)	4.16	3.06–5.64	<0.001	3.35	2.40–4.66	<0.001
BPAR (yes vs. no)	1.87	1.18–2.42	0.005	1.97	1.36–2.86	<0.001
Death-censored graft loss						
Retransplantation (yes vs. no)	2.44	1.18–5.05	0.02	3.31	1.49–7.38	0.003
BMI (per unit)	1.07	1.02–1.13	0.004	1.07	1.02–1.13	0.004
ECD donor (yes vs. no)	2.03	1.20–3.43	0.008	2.37	1.34–4.20	0.03
Cardiovascular disease (yes vs. no)	1.72	1.06–2.80	0.03	1.65	0.92–2.96	0.09
Previous smoking (yes vs. no)	2.10	1.35–3.27	0.001	2.29	1.41–3.72	0.001
DGF (yes vs. no)	7.84	5.11–12.04	<0.001	6.96	4.35–11.13	<0.001
BPAR (yes vs. no)	2.57	1.59–4.16	<0.001	2.76	1.68–4.53	0.001

ECD, extended criteria donor; DGF, delayed graft function; BMI, body mass index; BPAR, biopsy-proven acute rejection.

Table 3. Secondary analyses stratified by age, delayed graft function, rejection and extended criteria donor in former smokers.

	HR	95% CI	*P* for HR	*P* for interaction
Graft loss				
Recipient age>60 years	1.24	0.73–2.11	0.42	0.14
Recipient age ≤60 years	2.11	1.36–3.26	0.001	
DGF	2.13	1.10–4.12	0.03	0.07
No DGF	1.75	1.17–2.60	0.006	
BPAR	0.96	0.46–2.00	0.91	0.30
No BPAR	1.73	1.19–2.52	0.004	
ECD	0.78	0.39–1.58	0.49	0.06
No ECD	1.96	1.35–2.86	<0.001	
Death-censored graft loss				
Recipient age>60 years	2.57	1.09–6.07	0.03	0.95
Recipient age ≤60 years	2.23	1.26–4.13	0.006	
DGF	2.72	1.31–5.62	0.007	0.47
No DGF	2.46	1.29–4.70	0.007	
BPAR	1.02	0.39–2.66	0.97	0.44
No BPAR	2.29	1.27–4.15	0.006	
ECD	0.84	0.30–2.40	0.75	0.15
No ECD	2.87	1.63–5.04	<0.001	

DGF, delayed graft function; BPAR, biopsy-proven acute rejection; ECD, extended criteria donor.

long-term graft and death-censored graft loss independently from DGF. This association was even stronger in those recipients who restarted or continued smoking after transplantation. Moreover, kidney function as measured by eGFR declined significantly over time the first years after transplantation in former but not in never smokers.

Mechanistically, our study corroborates findings in lung transplant recipients, where previous smoking seemed to prime for a faster decline in GFR after

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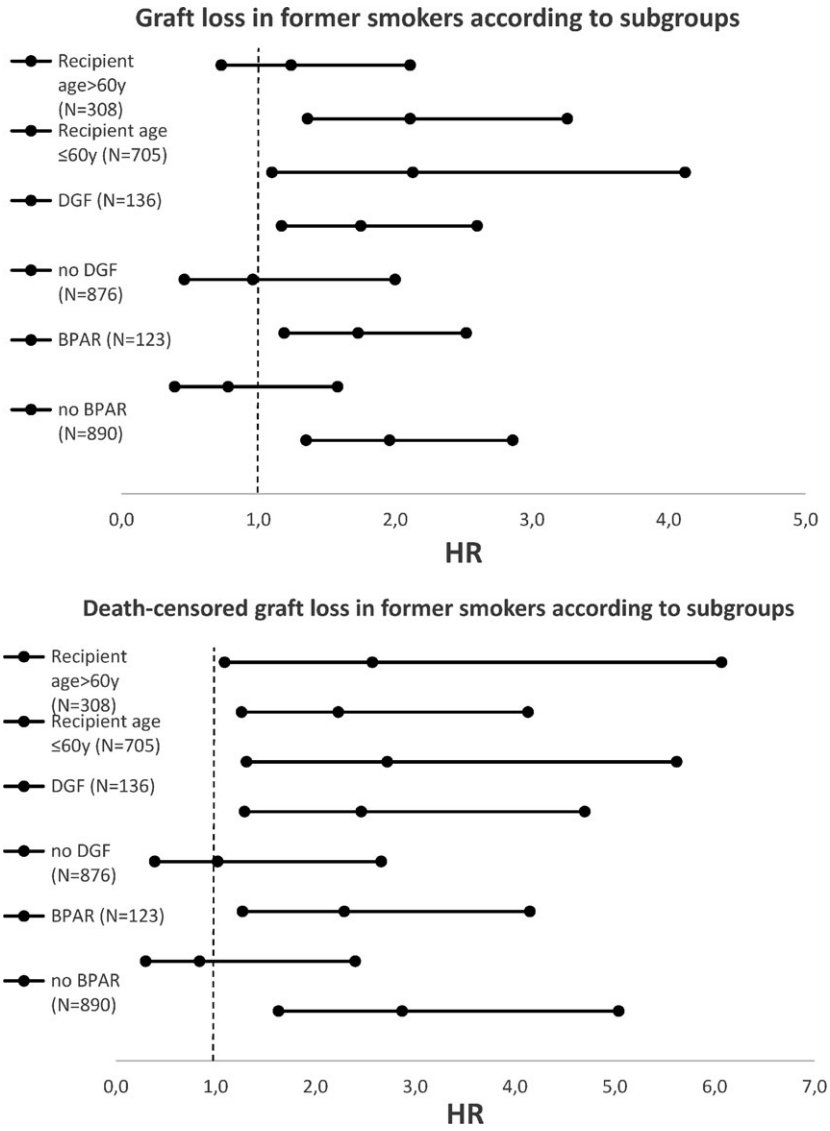

Figure 2 Forest plot demonstrating the adjusted hazard ratio of 10-year graft loss and death-censored graft loss for former smokers according to subgroups. BPAR, biopsy-proven rejection; ECD, extended criteria donor; DGF, delayed graft function.

transplantation [11]. In a retrospective study in 997 kidney transplant recipients from exclusively living donors, former smoking was associated with worse patient and graft survival but not death-censored graft survival (aHR 1.42 with 95% CI of 0.94–2.17; $P = 0.1$) despite higher rejection rates in former smokers vs. never smokers [16]. Data on the role of DGF and its potential interaction with former smoking are lacking in the latter analysis. Our cohort study is thus the first to demonstrate an independent association between former smoking and death-censored graft loss and to integrate DGF into the analysis. We postulated that adverse renal outcome might be driven by an increased risk for DGF in former smokers or that the presence of DGF in former smokers might amplify the decline of kidney function in these people.

However, the data do not support this hypothesis. We did not observe a higher risk of DGF in former smokers. In addition, the effect of former smoking was not different in patients with or without DGF although this absence of any interaction seemed more obvious for death-censored graft loss (Figure 2, Table 3). Of note, our findings support recent findings suggesting that DGF is an independent predictor of long-term graft outcome [15].

In addition to the higher risk of graft loss, former smoking was also associated with a faster decline in transplant kidney function as evidenced by the increasing difference in eGFR over time compared to never smokers. In people with DGF, the inverse seemed true and the difference in eGFR at year one got smaller at year three and five. All these observations point out that chronic profibrotic or vascular effects rather than immunological effects might play a role in previous smokers. In rats, nicotine stimulates the epithelial–

mesenchymal transition (EMT) and connective tissue growth factor (CTGF) expression in kidney epithelium and induces neonatal kidney fibrosis after exposure to pregnant animals [9]. In line with this, despite comparable kidney function, native kidney biopsies of current or historical smokers show a higher degree of glomerulosclerosis and arteriolar hyalinosis than in people who never smoked [17]. Also, former smoking is associated with increased fibrous intimal thickening of small arteries [18]. Hence, histological changes in former smokers in our study population might have preceded the faster decline of kidney function over time.

Former smokers have an increased rejection rate [3,16], an observation incompletely explained by lower adherence. Smokers have immunological alterations such as disturbed regulatory T-cell generation [3]. In rats, pretransplant exposure to tobacco smoke accelerated cardiac allograft rejection [19]. Yet, in our analysis, despite the confirmation of a relationship between former smoking and rejection already the first year after transplantation (data not shown), previous smoking in patients without rejection during their post-transplant follow-up was associated with unfavourable graft outcome (Table 3, Figure 2).

Our study has some limitations. First, the retrospective character of the analysis implies that confounders such as diabetes might matter. However, adjustment for diabetes, which was overrepresented in the former smoker group, did hardly change the strength of the association between former smoking and graft outcome. Also, in a sensitivity analysis of patients without diabetes, the association between previous smoking and graft loss with and without censoring for death remained. Considering the uncertain effect of new-onset diabetes after transplantation (NODAT) on death-censored graft survival [20], we believe that previous smoking, which is not considered to be a risk factor for NODAT, could flaw the analysis. Nonadherence might be an important confounder. Nevertheless, the stratification for rejection did not alter the observed association. Also, Nogiera and co-workers demonstrated that former smoking was associated with rejection already the first 10 days after transplantation [16]. At this early time point, it seems unlikely that nonadherence already matters, suggesting other mechanisms play a role here [16]. Second and within the limitations of a retrospective data analysis, we were unable to quantify cumulative tobacco exposure or to detect the proportion of cigar vs. cigarette smoking. Also, we lacked information about possible exposure to second-hand or environmental smoke, of which outcome data in kidney transplant recipients are as far as we know not-existing. In a recent questionnaire-based analysis, 20% of all active smokers after kidney transplantation reported additional exposure to second-hand smoke [21]. Of note, self-reporting of smoking exposure is considered particularly inaccurate [22]. Third, subjects accordingly might have incorrectly claimed to have quit smoking so that some patients are active and not former smokers. In lung transplant recipients, despite strong discouragement, 11% of patients had resumed smoking without informing their treating physician [23]. Our active smoking rate of 7% is in line with recent publications in kidney transplant recipients [5,11,21]. Considering the inability to validate patient claims, it might be difficult to distinguish between former and current smoking and some misclassification might occur. Yet, considering the findings of our multivariable model, we believe that this will not dramatically alter the interpretation of the outcome data of former smokers. We do not routinely measure cotinine, which is a metabolite of nicotine with longer half-life of 19 instead of two hours, considering the well-known limitations of its assay, with concerns about costs and informed consent but especially doubtful validity in people without any or very little residual kidney function [3]. In kidney transplant recipients, despite a misclassification rate of 12% according to post-transplantation cotinine sampling, plasma concentrations were predictive of graft outcome and mortality [24]. Fourth, we cannot clearly explain why the difference in kidney function between former smokers and people who never smoked is increasing with time. We could speculate that long-lasting epigenetic changes might play a role here [11]. Also, initial histological damage might have translated in a faster kidney involution with a certain lag time. However, also in recipients who stopped smoking at least five year before transplantation, graft outcome remained worse than in people who never smoked [16,25].

To conclude, we found not only active smoking after but also smoking before transplantation to be independently associated with a poor long-term graft outcome. Although there is a considerable amount of epidemiological data pointing to a negative role of active smoking in the evolution of kidney function particularly in the general population, there are still many open questions. The exact mechanism by which smoking exerts its negative effects largely remains elusive and it remains yet uncertain whether nicotine is the main culprit here. Meanwhile, it seems obvious to scrutinize smoke cessation care in subjects with CKD even long before the development of end-stage kidney disease and waitlisting for transplantation.

Authorship

SVL and WVB: designed the study. SVL: collected the data. SVL, EVN, PP, FV and WVB: analysed and wrote the manuscript.

Conflict of interest

The authors have declared no conflicts of interest.

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