Influence of donors' cigarette smoking on recipients' postoperative survival and complications after simultaneous pancreas-kidney transplantation

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Research article

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Abstract

Background

Many pancreatic transplant donors have smoking history. We aimed to evaluate the effect of donors' smoking on recipient survival rates and postoperative complications.

Methods

Patients(N=6564) from the Scientific Registry of Transplant Recipients database who underwent simultaneous pancreas-kidney transplants (SPK) were divided into a cigarette group (n=5465) and non-cigarette group (n=799) based on their donors' smoking history. Patients' rates of overall and graft survival were compared and analyzed using the log-rank test. Hazard ratios were estimated using Cox proportional hazards models, and postoperative complications and dialysis times were evaluated using logistics analysis.

Results

The overall survival and graft survival of the patients in the non-cigarette group were significantly higher compared to those in the cigarette group ($P < 0.05$ for both log-rank tests). Cigarette smoking among the donors was associated with a significant difference in the recipients' rate of pancreas graft survival and kidney graft survival ($P < 0.05$ for both log rank-tests). However, multivariate analyses indicated that donors' smoking history was not an independent factor, while the donors' age was associated with reduced survival (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.93-1.28; $P = 0.287$). The cigarette group had a higher postoperative infection rate than the non-cigarette group (HR, 1.45; 95% CI, 1.02-2.06; $P = 0.038$).

Conclusions

Donors' smoking history has no overall effect on rates of overall or graft survival of SPK transplant recipients. However, it should be evaluated before transplantation because of its higher rate of postoperative complications.

Background

Cigarette smoking has been deemed a societal problem due to its harm to smokers and second-hand smokers. Tobacco smoke and involuntary smoking have been confirmed by research to be important pre-tumor factors[1], which cause multiple chronic diseases, especially cardiovascular and pulmonary damage. Based on the prediction of Jha, approximately 450 million adults will die from the effects of smoking between 2000 and 2050[2]. Governments and societies have been raising taxes, enforcing stricter regulations on smoking and supplying more information for consumers to decrease its prevalence. However, many factors also entice people to smoke. To some degree, citizens must cope with higher social anxiety because of the widening wealth gap and faster pace of life. The experience of peer-

victimization, depression and social marginalization has been reported to be associated with an increase some individuals' tendency to indulge in drug and tobacco use[3]. The prevalence of smoking has been gradually decreasing because of the efforts of governments and societies, according to the National Survey on Drug Use and Health, in 2016. Nevertheless, 24.6 percent of interviewees who were older than 15 years of age admitted current tobacco use. 30.6% were male and 18.9% were female[4]. Thus, a considerable portion of the population has a history of smoking.

Simultaneous pancreas-kidney transplants (SPK) have been recommended for patients with type I diabetes mellitus (DM) and for some with type II DM[5]. SPK have a higher survival rate compared with pancreas transplants alone and pancreas transplants after kidney. From 2009 to 2015, SPK had a first-year overall survival rate of 95.8% for type II DM and 91.1% for a three-year survival rate[5]. For an entire SPK follow-up cohort, the adjusted 10-year survival rate was 67% and the 15-year actuarial patient survival rate was 56%[6]. Therefore, pancreatic transplants has been regarded as the gold standard of therapy for DM. Compared with liver and heart transplants, patients with DM could survive longer wait-list times for pancreatic transplants with the help of insulin and dialysis, and they had confidence in their ability to meet the stricter criteria for pancreas transplantation. Thus, SPK related risk factors have been receiving increased attention in the research literature to promote better prognoses and preclinical decision-making.

It has been reported that transplantation recipients who smoke before or after a transplant show a significant decrease in survival rates and an increase in surgery complications[7]. There is also a substantial number of donors with a history of cigarette use. For kidney transplants, some research supports the premise that donors who smoke cigarette increase recipients' overall death rates[8] and reduce their graft survival[9], while others predict higher rates of peri-operative complications[10]. For liver transplants, donor smoking has been reported to have a risk ratio as high as 1.249 for overall survival but no effect on graft survival[11]. However, there is paucity of research on the effects cigarette smoking on pancreas and SPK. Thus, we collected and analyzed clinical data, aiming to estimate the effect of donors' history of cigarette smoking on recipients' rate of overall and graft survival.

Method

Data on patients (N = 6264) from the Scientific Registry of Transplant Recipients (SRTR) were retrieved for analysis. The SRTR's data from the Organ Procurement and Transplantation Network has important information about all donors, wait-list candidates and transplant recipients in the United States. Patients who underwent SPK from January 1, 2004 to December 31, 2013. All of these patients received the organs from deceased donors. Cases with a history of malignancy of the donor or recipients, or pre-transplant history were deleted from the cohort. Patients' records with missing survival data were excluded from the study, as well as the records with missing information on cigarette history. This study was exempt from institutional review board approval at our institution.

Data from the 6264 patients were divided into two study groups: the cigarette group(n = 5465) and non-cigarette group(n = 799) based on their donor's cigarette-use history. The donor cigarette-use history was defined as smoking more than 20 packs of cigarettes per year. The recipients' and donors' characteristics are represented in Table 1.

Table 1
Comparison of the baseline characteristics of recipients and donors

Recipient characteristic	**0 (n = 5465)**	**1(n = 799)**	**P**
Age (years)	41.56 ± 8.8	41.33 ± 8.6	0.488
Male	3434 (62.8)	522 (65.3)	0.092
Ethnicity			0.000
White	3792 (68.2)	610(76.3)	
Black	970 (17.7)	133(16.6)	
Asian	84 (1.5)	4(0.5)	
Hispanic	603(11.0)	46(5.8)	
Other	79(1.4)	6(0.8)	
BMI	25.13 ± 4.1	25.40 ± 4.2	0.090
Exocrine drainage			0.000
Bladder drainage	477 (8.7)	125 (15.6)	
Enteric drainage	4781 (87.5)	651 (81.5)	
Others	207 (3.8)	861 (3.8)	
Endocrine drainage			0.007
Systemic system	4291 (78.5)	664 (83.1)	
Portal system	1133(20.7)	133(16.6)	
Other	40 (0.7)	2(0.3)	
HLA mismatch > 2/6	5210 (95.4)	756 (94.6)	0.198
PRA% > 20%	443 (8.5)	40 (5.2)	0.001
Recent serum creatinine	6.77 ± 3.1	6.68 ± 2.9	0.463
DM duration	26.69 ± 8.8	26.38 ± 8.9	0.386
Follow-up in months	85.38 ± 41.3	94.48 ± 46.0	0.000
Donor characteristic	0 (n = 5465)	1 (n = 799)	P
Age (years)	24.26 ± 9.1	33.84 ± 10.4	0.000
Male	3833 (70.1)	501(62.7)	0.000
Ethnicity			0.000

Recipient characteristic	0 (n = 5465)	1(n = 799)	P
White	3396 (62.1)	665(78.3)	
Black	1045 (19.1)	104(12.2)	
Asian	117 (2.1)	7(0.8)	
Hispanic	855 (15.6)	65(7.7)	
Other	52 (1.0)	8(1.0)	
BMI (kg/m^2)	24.02 ± 4.0	24.30 ± 3.8	0.056
Cause of death			0.000
Anoxia	847(15.5)	105(13.1)	
Cerebrovascular accident	778(14.2)	233(29.2)	
Head trauma	3721(68.1)	443(55.4)	
Other	119(2.2)	18(2.3)	
STROKE	815(14.9)	245(30.7)	0.000
DDAVP	1223(22.4)	237(29.7)	0.000
Expanded kidney criteria	11(0.2)	12(1.5)	0.000
Hypertension	237(4.3)	124(15.6)	0.000
Serum creatinine > 1.5	470(8.6)	66(8.3)	0.405
WIT (min)	37.08 ± 21.0	40.67 ± 23.1	0.000
CIT (h)	11.75 ± 5.8	11.81 ± 5.9	0.780

Recipients

The recipients' variables included age (years), gender, ethnicity, body mass index (BMI) before the transplant, exocrine and endocrine drainage, human leukocyte antigen (HLA) mismatch, panel-reactive antibody (PRA), recent serum creatinine before the transplant, time since the onset of DM to the surgery date (DM duration), and date of the surgery to the final follow-up date (Follow-up). Ethnicity was classified as White, Black, Asian, Hispanic, and Other. Exocrine drainage was classified as bladder drainage, enteric drainage, and other. Endocrine drainage was grouped according to the systemic system, portal system, and other.

Donors

The donors' characteristics were also compared between groups, including age, gender, ethnicity, BMI, cause of death, death from stroke, desmopressin acetate (DDAVP) before the transplant, expanded kidney criteria, history of hypertension, serum creatinine, warm ischemia time (WIT) and cold ischemia time

(CIT). Ethnicity was classified using the same categories as those used for the recipients. Cause of the donor's death was classified as anoxia, cerebrovascular accident, head trauma, and others. Hypertension was defined as a systolic pressure greater than 160 mmHg or a diastolic pressure greater than 90 mmHg. Serum creatinine level were retrieved from the participants' most recent records before surgery.

Statistical analysis

Continuous and categorical variables were compared using Student's t-test and the chi-square test, respectively. The results were reported as mean ± standard deviation unless otherwise indicated. An alpha level of 0.05 indicated statistical significance. The Kaplan-Meier method was used to compare patients' overall and graft survival. Log-rank tests and multivariate Cox proportional hazard regression analyses were performed to obtain survival curves and for multivariate analyses. Univariate and multivariate Cox proportional hazards regressions of the entire cohort were performed to identify the predictors. A p value < 0.05 was considered statistically significant in univariate analysis as showed in Table 1. All factors with p values < 0.1 in the univariate analysis were selected for inclusion in the multivariate model. All statistical analyses were performed using SPSS 20.0 (IBM Corp, Armonk, NY).

Results

Data from 6264 patients were analyzed (cigarette group = 5465 and non-cigarette = 799). Few significant differences were found between the two groups of recipients (cigarette and non-cigarette groups). Except for ethnicity ($P < 0.01$), exocrine/endocrine drainage ($P < 0.01$) and PRA% > 20% ($P < 0.01$), there were no significant differences between the groups (i.e., age, gender, BMI, HLA mismatch > 2/6, recent serum creatinine or DM duration).

A significant difference was found between two groups of donors (smokers and non-smokers) by age, gender, ethnicity, cause of death, stroke, DDVAP, expanded kidney criteria, hypertension and WIT. However, no significant difference in BMI or Serum creatinine > 1.5 was found between the two groups. These findings might be related to the epidemiology of the donors' cigarette use and selection bias. Since we defined the cigarette group as those who smoked more than 20 packs of cigarette per year, the average age should have been older than those of the non-cigarette group, which had more teenagers. Males are more likely to smoke whereas females find it harder to quit[12], but in our study, there were more males in the non-cigarette group ($P < 0.01$). Differences in gender between the two groups might be related not only to gender bias in the prevalence of smoking but also to donor pairing and selection bias. Though smoking is usually associated with a higher body weight[13], the criteria for donors might have offset this association because over-weight donors were not selected for transplants. Thus, no differences were found between two groups. Furthermore, the cigarette use can also lead to hypertension, a higher resting heart rate[14], worse kidney function[15] and harm to the cardiovascular system[12]. Thus, in the cigarette group, there were higher proportions of deaths by stroke and other cardiovascular accident, which also led to the more frequent use of DDAVP for the treatment of donors. Given the characteristics of the cigarette group, the differences in cause of death, stroke, DDAVP, expanded kidney criteria and hypertension might have been related to or caused by cigarette smoking, thus, these variables were not included in the multivariate analysis. In this study, only the donors' age, and the donors' and recipients'

gender, BMI, exocrine and endocrine drainage, PRA > 20%, and ethnicity were included in the multivariate analysis.

Figure 1 shows the results of the Kaplan-Meier analysis of overall survival, graft survival (including grafts of the kidney and pancreas) and kidney and pancreas survival. The four survival curves revealed significant differences between the two groups; all of the log-rank Ps were all < 0.05, suggesting the smoking history of the donors might have harmed the recipients and reduced graft survival.

The results of the Cox analysis, which was performed to identify the independent effect of cigarettes, are presented showed in Table 2. Although the univariate analysis showed significant differences between the two groups in their overall, graft, kidney and pancreas survival, the multivariate analysis showed that the donors' cigarette usage had no significant effect on the recipients' overall, graft, pancreas and kidney survival (P > 0.05). We thought the differences between the two groups were mainly caused by their different ages. The significant difference in age between the two groups of donors was due to the study's criteria for cigarette use (20 packs of cigarette smoked per year). Donors who were non-smokers were much younger than those who smoked and the curve of the smokers showed a bimodal distribution (Fig. 2). To control for bias of donors' age, the survival rates of the two groups were analyzed by their age categories (Fig. 3A-F, 4 A-F,5 A-F and 6 A-F). No meaningful findings emerged from the Kaplan-Meier analysis, confirming the small survival effect of the donor cigarette history.

Table 2
Cox proportional hazard regression analyses

Variable	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Donor smoking for overall survival	1.18	1.03–1.37	0.020	1.09	0.93–1.28	0.287
Donor smoking for kidney survival	1.23	1.06–1.43	0.005	1.14	0.97–1.35	0.125
Donor smoking for pancreas survival	1.30	1.13–1.50	0.000	1.16	0.99–1.36	0.073
Donor smoking for graft survival	1.25	1.11–1.41	0.000	1.11	0.97–1.27	0.113

The recipients in the cigarette group had a longer hospital stay than those in the non-cigarette group (P < 0.05), as seen in Fig. 7.

The frequency of each variable and results of the multivariate analysis of the recipients' complications, including rejection, pancreatitis, infection, leaks, thrombosis and bleeding are showed in Table 3. The morbidities of infection and thrombosis were significant different between the two groups. However, due to the large amount of missing data (90%) on thrombosis (thrombosis data for only 384 individuals were

found in the database), the difference between the groups was not meaningful. However, our findings suggest the cigarette smoking was a risk factor for a higher infection rate after the transplant.

Table 3
Postoperative complications of two groups

Variable	Groups		Logistics
	Non-Cig	Cig	p
Rejection(324/65)	10(3.1)	1(1.5)	.426
Pancreatitis(5429/793)	149(2.7)	28(3.5)	.130
Infection(5419/793)	185(3.4)	64(8.1)	.000
Leak(5415/788)	102(1.9)	15(1.9)	.527
Thrombosis (319/65)	262(82.1)	42(66.2)	.004
Bleeding(318/63)	33(10.4)	63(16.5)	.426

Discussion

Smoking has been confirmed to be a primary cause of disease, especially diseases of the cardiovascular system. Cigarette smoking could impact all phases of atherosclerosis leading to acute clinical events, which are largely thrombotic[16]. Blood supply is one of the key factors in graft survival, thus, we surmise that the organs from donors who smoked cigarettes might have been inferior for post-transplant survival. Furthermore, people's tendency to become addicted to cigarette smoking[3], might explain the considerable portion of donors who had a cigarette smoking history. Thus, it is necessary to examine the survival rates of patients who receive organs from smoking donors.

In our study, the multivariable analysis showed donors' cigarette history had no effect on overall or graft survival. However, post-transplant complications increased due to the donors' cigarette history. The results of a kidney transplant, study on living donors supported a higher death rate among smoking donors[17]. When deceased donors were included, the effect of donors' smoking history decreased[18]. Our results found little difference between the two groups, which might have been due to the donor source for the SPK. The organs donated for SPK, which are usually from deceased donors, are more likely to have been exposed to longer ischemia times and other potential injuries compared to the organs of living donor transplants, and SKP have stricter criteria for donors than do kidney and other types of pancreas transplants[19]. Thus, it is possible that the stricter criteria for donors also excluded most injured organs, decreasing the risk for death related to cigarette smoking history.

The significant differences in overall, graft and kidney survival found in the Kaplan-Meier analysis were mainly related to donors' age, which has been confirmed as a risk factor for death[20, 21]. However, only a

small difference between the smoking and non-smoking donors was found when the donors' age was analyzed by subgroups. For the different age groups, no significant difference between any two groups was found until data from donors older than 50 years old were analyzed. Perhaps these results are related to the chronic damage caused by cigarette smoking, as older smokers are more likely to have a much longer history than younger smokers are, which is a worthwhile issue for further investigation.

Though donors' cigarette smoking history had no effect on graft or overall survival, it did influence post-transplant complications. Our research suggests donors' history of cigarette smoking increase the risk for postoperative infection. The results of other studies also support the findings that cigarette smoking can cause dysfunction, functional delays, infection and other postoperative complications of liver, kidney and lung transplants[9, 22, 23]. Therefore, although there is controversy about whether donors' cigarette history influence recipients' survival, smoking should be discouraged and quitting smoking encouraged before surgery, with the aim of increasing the benefits of survival and decreasing the risk of complications through smoking cessation.

Some factors were independent predictors of overall and graft survival of SPK recipients. Our results suggest that cigarette smoking history of donors should have no significant effect on overall or graft survival. However, it does predict higher morbidity rates due to postoperative complications. Hence, the potential risks for recipients should be evaluated before transplants.

Declarations

Ethics approval and consent to participate: With Data Release Agreement with the Scientific Registry of Transplant Recipients database, all data in this study were released from SRTR. And no additional patient consent was required for the measurements in the data analysis.

Consent for publication: Not applicable

Availability of data and material: The data that support the findings of this study are available from the Scientific Registry of Transplant Recipients database, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Scientific Registry of Transplant Recipients database.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Y.J.G contributed to this paper as first author. G.Y.J and J.Z performed the statistical analysis. Y.J.G wrote the first draft of the manuscript. Y.J.G, Z.W.L and X.J contributed intellectual content and all authors contributed to critical revisions to the manuscript. Z.H.H and S.S.Z are the corresponding author. All authors approved the final manuscript.

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Figures

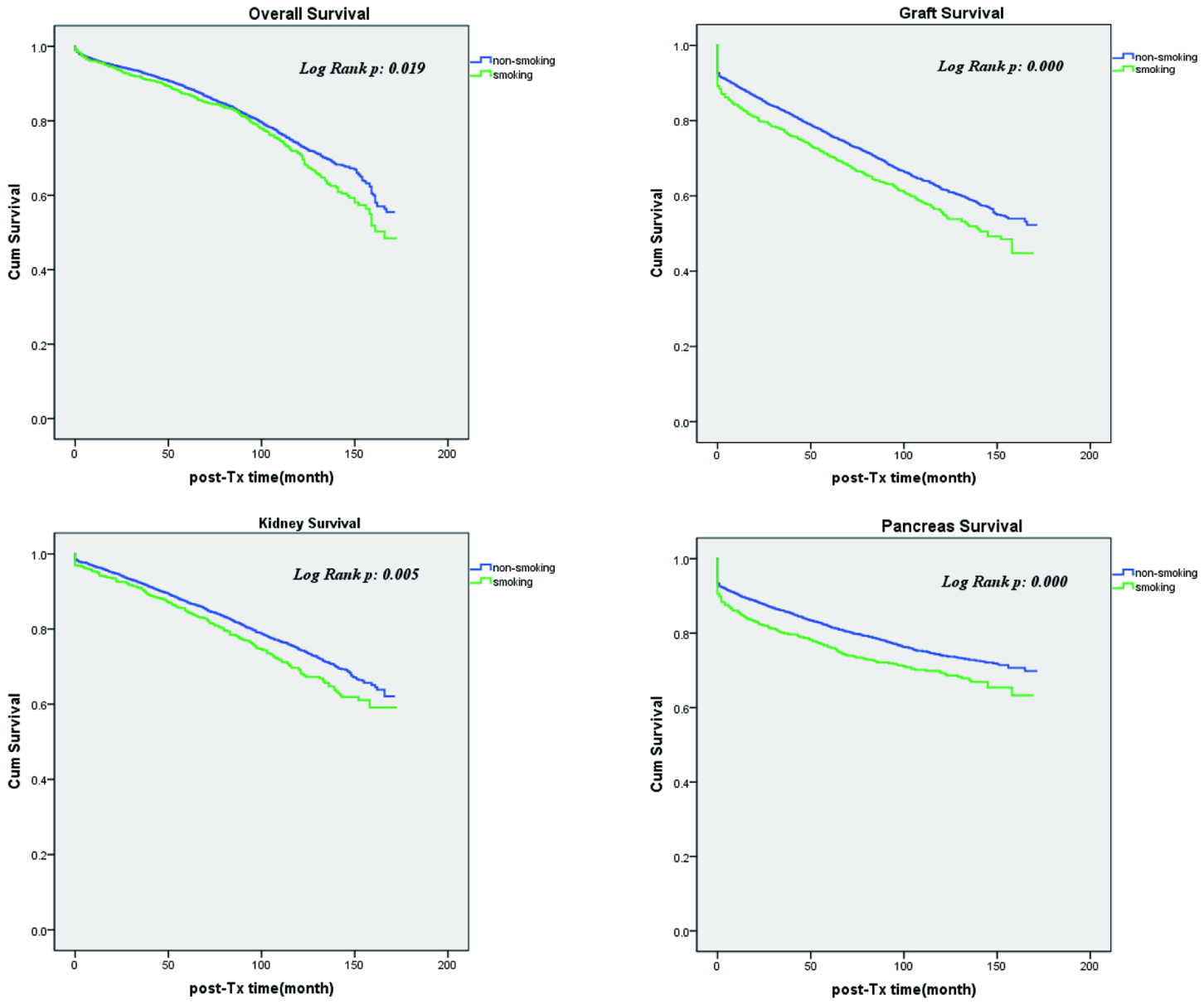

Figure 1

Kaplan-Meier analysis of overall survival, graft survival, kidney and pancreas survival.

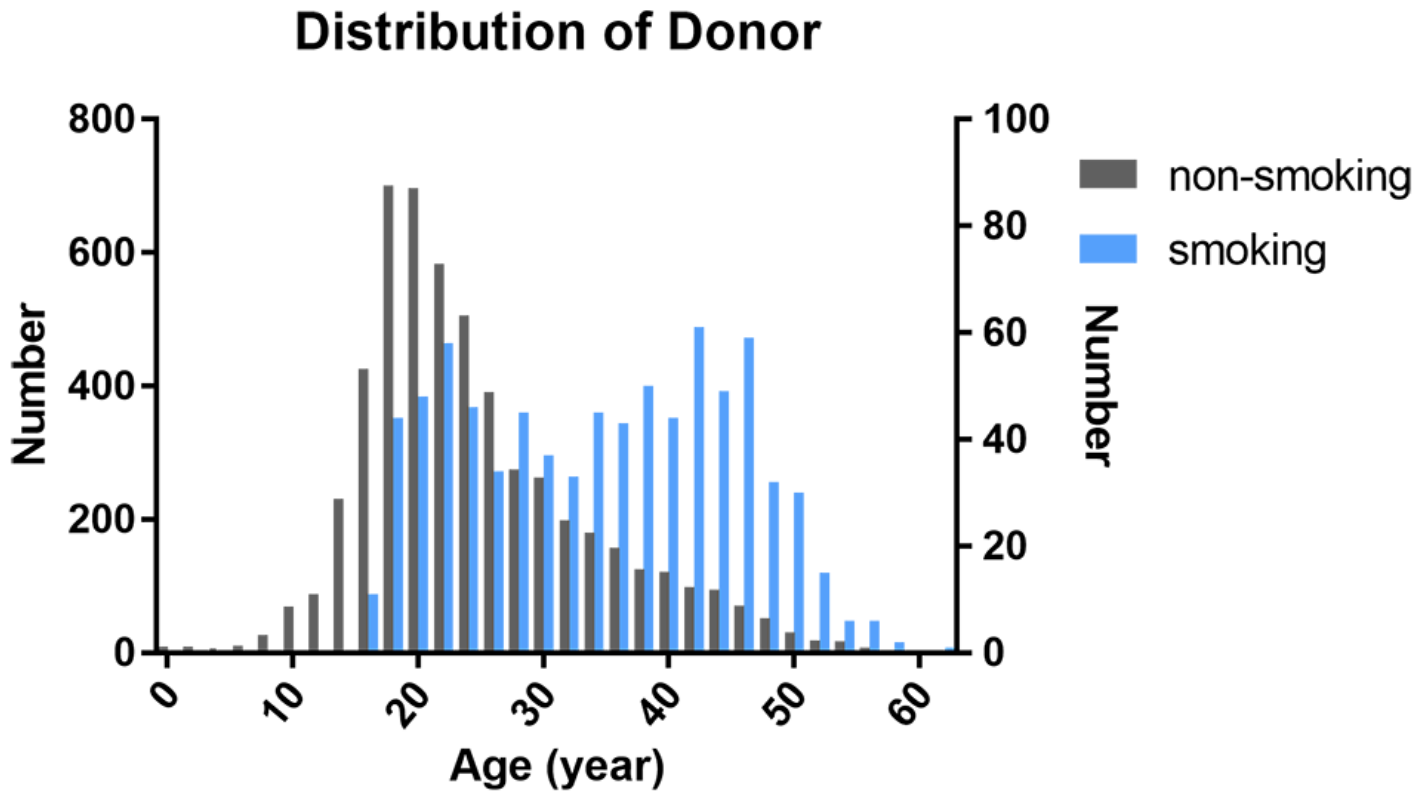

Figure 2

Distribution of donors according to their age.

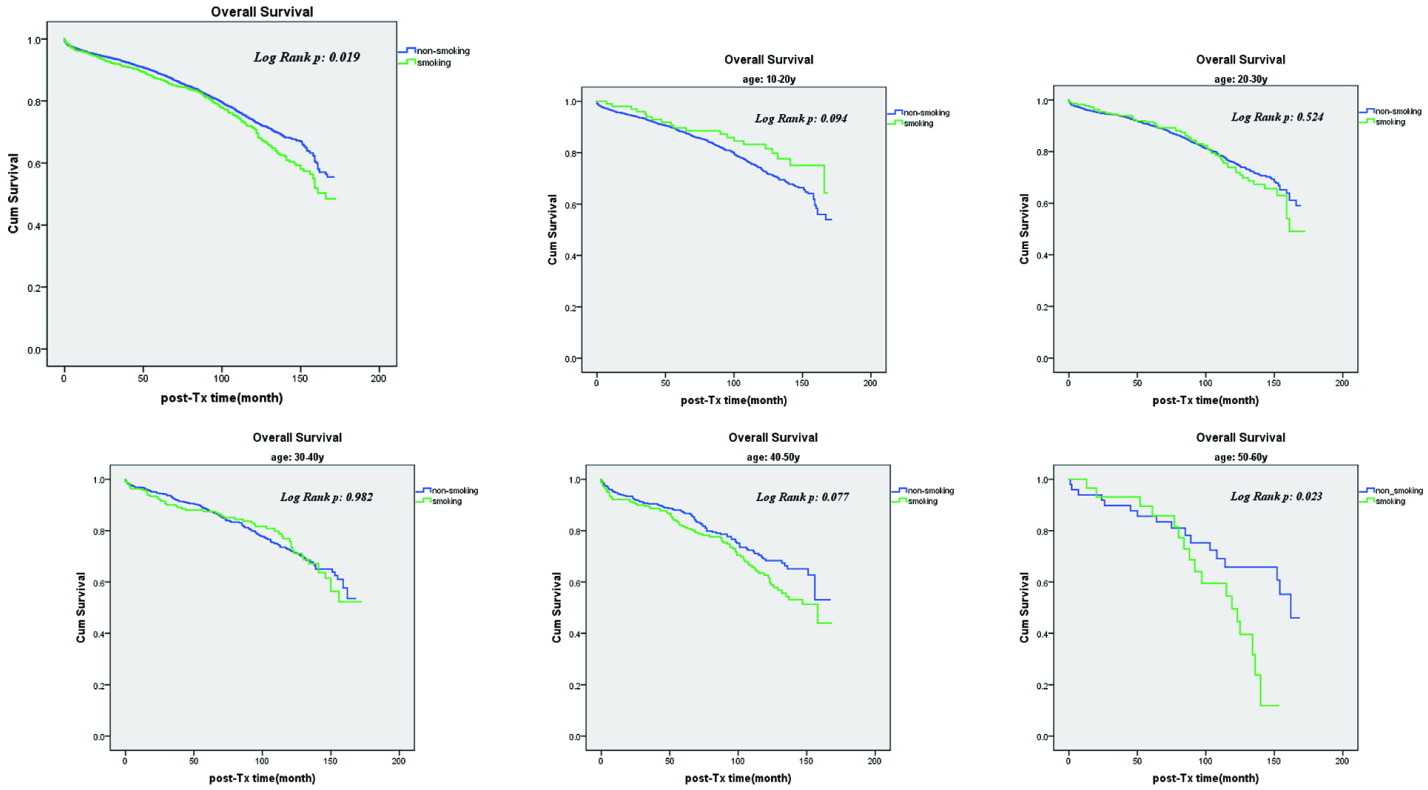

Figure 3

Survival curves of the two groups by their age categories (patient).

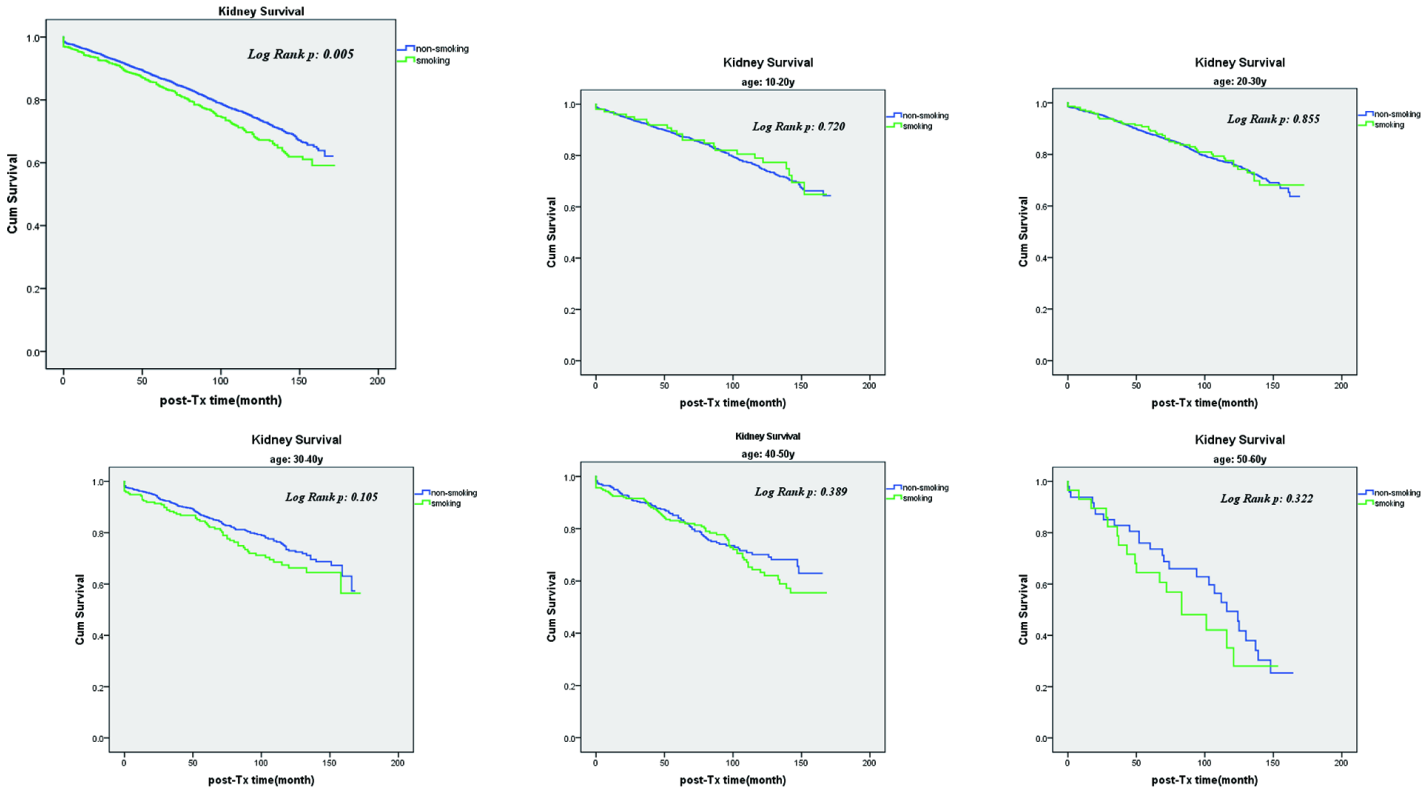

Figure 4

Survival curves of the two groups by their age categories (kidney).

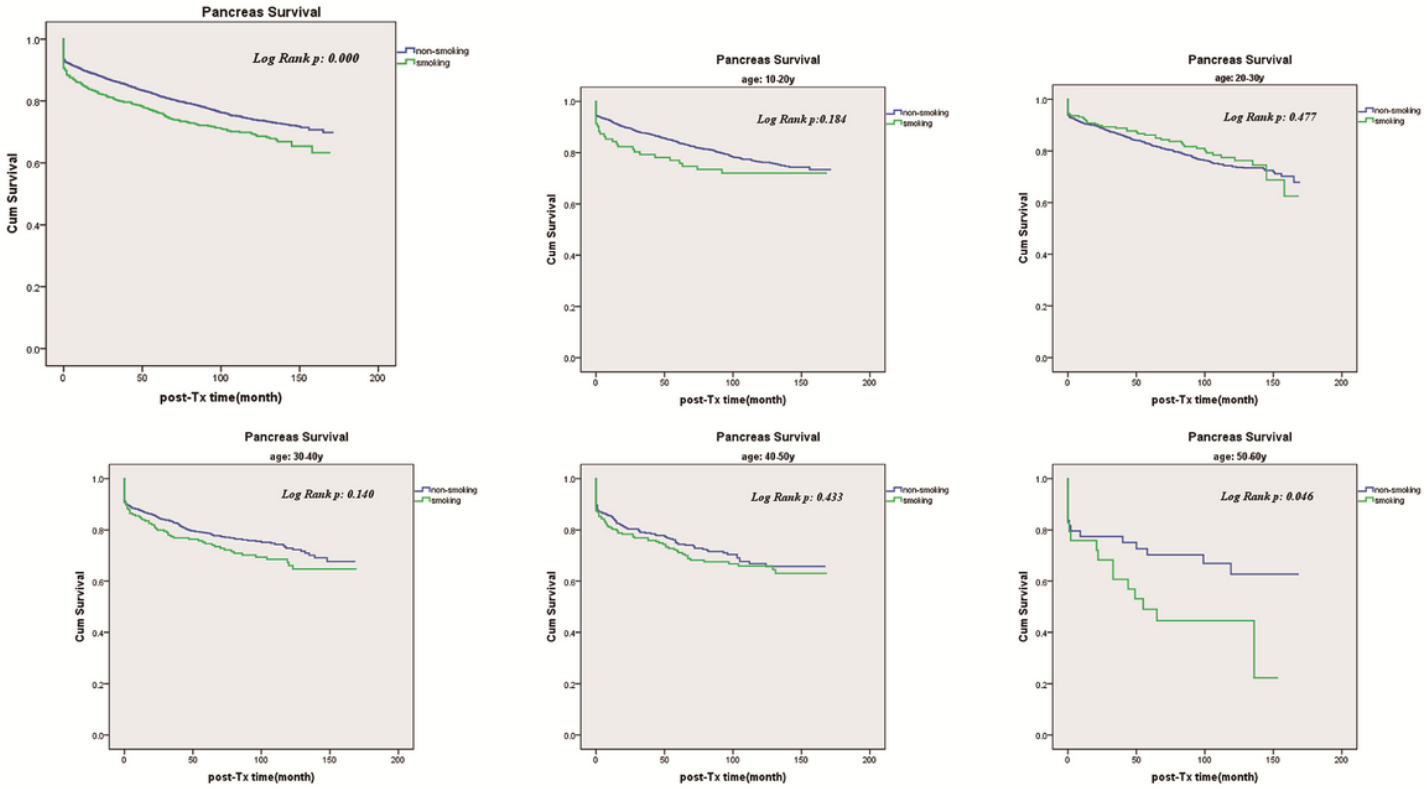

Figure 5

Survival curves of the two groups by their age categories (pancreas).

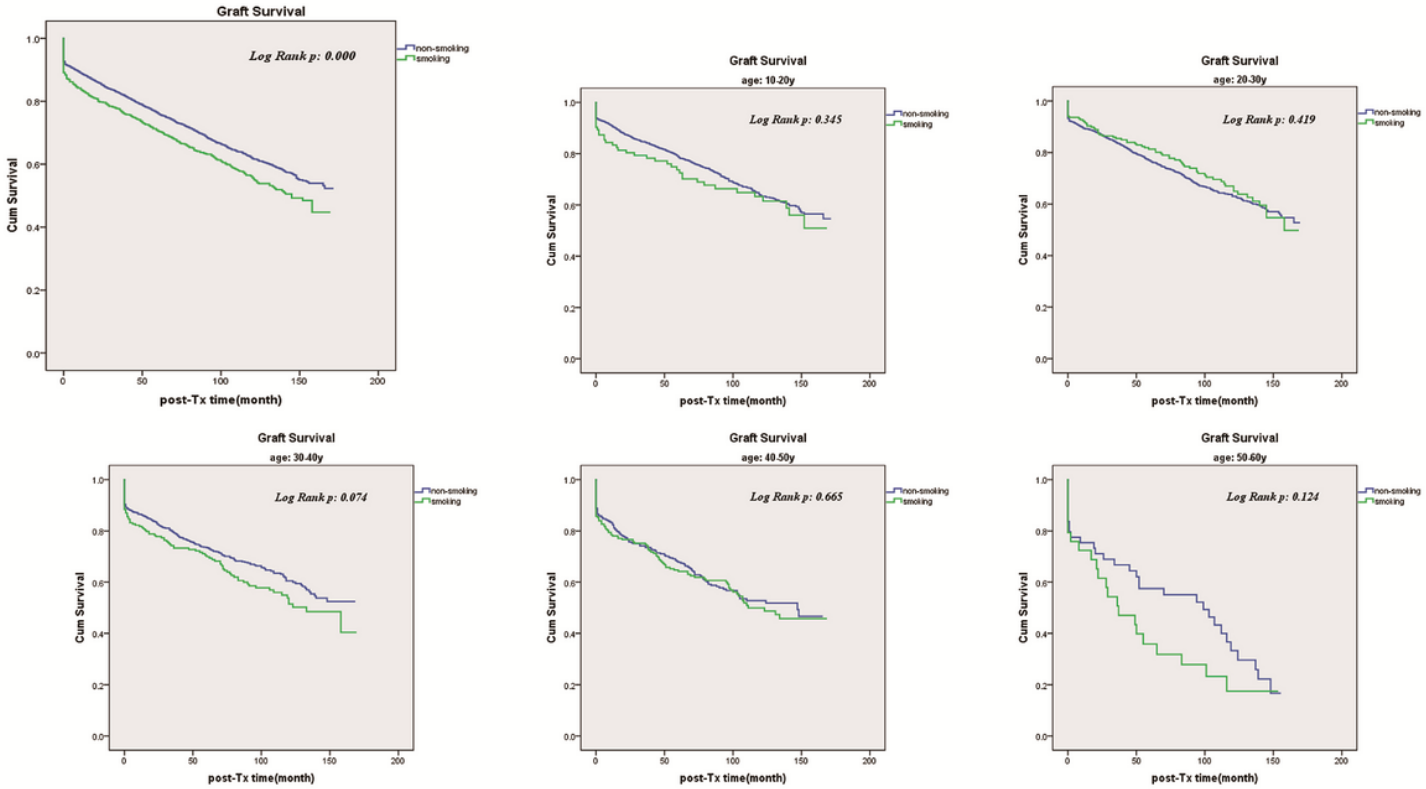

Figure 6

Survival curves of the two groups by their age categories (graft).

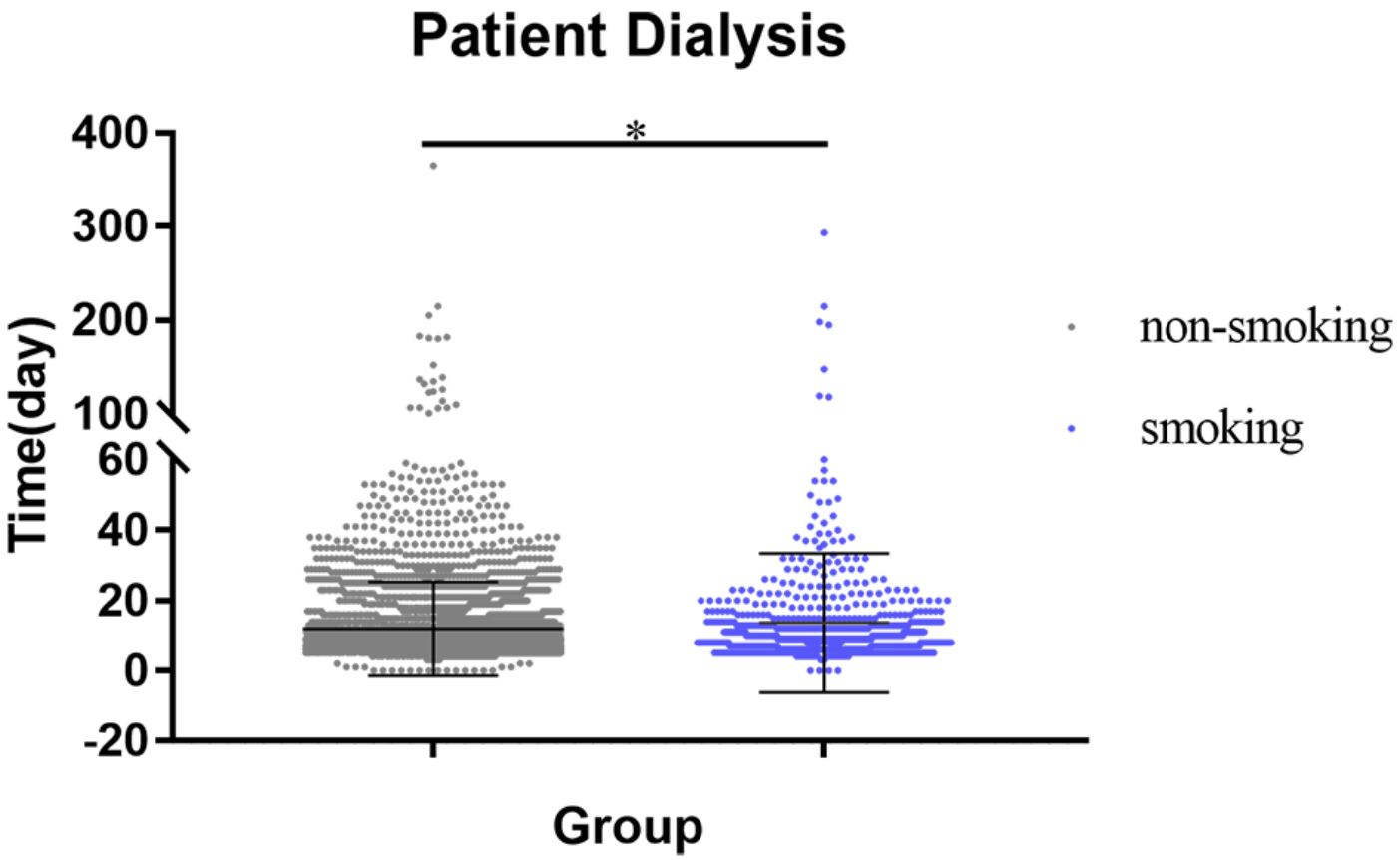

Figure 7

The comparison of hospital stays for cigarette group and non-cigarette group.