

The Relationship between Cigarette Smoking and IgA Nephropathy

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Abstract

Background and aim: Regarding that whether cigarette smoking is associated with the progression of IgA nephropathy (IgAN) remains uncertain, we aimed to evaluate the effect of cigarette smoking on the prognosis of IgAN.

Methods: 1239 IgAN patients who meet inclusion criteria from West China Hospital of Sichuan University were divided into smoker and non-smoker group. The endpoint was end stage renal disease (ESRD: eGFR <15 mL/min/1.73 m² or having renal replacement treatment) and/or eGFR decreased >50%. Kaplan-Meier and Cox proportional hazards analyses were performed. Association of cigarette smoking and IgAN was further verified by propensity-score-matched cohort analysis.

Results: During the mean follow-up period of 61 months, 40 out of 209 (19%) patients in smoker group and 110 out of 1030 (11%) in non-smoker group reached study endpoint (p<0.001). Multivariate Cox regression analysis revealed that cigarette smoking (HR=1.58, p=0.043), female gender (HR=2.00, p=0.002), Hypertension (HR=1.50, p=0.029), Serum creatinine (HR=1.01, p<0.001), segmental glomerulosclerosis (HR=1.59, p=0.026), and tubular atrophy/interstitial fibrosis (HR=3.13, p<0.001) were independent risk factors for prediction of poor renal outcome of IgAN. After matching with propensity scores, the significant correlation between cigarette smoking and the renal outcomes of IgAN patients can be seen.

Conclusion: Smoking is an independent risk factor for the progression of IgAN, especially for female subjects.

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis and a leading cause of end-stage renal disease (ESRD). It is diagnosed by renal biopsy which is characterized by the deposition of IgA immune complexes. It is known that 20–40% of IgAN patients reaching ESRD 10–20 years after the first clinical presentation¹. As a result, it is of great importance to identify the risk factors of IgAN to delay the process to ESRD. The prevalence of cigarette smoking is increasing world widely, especially in China². It has been reported that smoking is the risk factor among CKD patients^{3,4}. However, fewer studies have paid attention to the relationship between cigarette smoking and IgAN^{5,6}. A case-control study found that smoking does not have a direct connection with IgAN. However, this study was a small sample study, and unbalanced baseline features may affect the reliability of the result⁶. Another retrospective study showed that smoking was an important predictor of renal outcome in IgAN patients. But this study didn't include renal histologic findings⁵. Our team have explored the predictive role of renal histologic findings for IgAN patients, especially for global glomerulosclerosis and crescent⁷. Therefore, the association of cigarette smoking and IgAN prognosis as well as pathological changes remains uncertain. The aim of this study is to investigate whether cigarette smoking has any effect on the progression of IgAN patients.

Materials And Methods

Patients

1588 adult patients (age >14 years) with renal biopsy proved IgAN from West China Hospital of Sichuan university between January 2009 and December 2018 were recruited. Patients with systemic diseases (including but not limited to systemic lupus erythematosus, diabetes mellitus, Henoch-Schönlein purpura, liver cirrhosis) and those with insufficient pathologic data (renal biopsies < 8 Glomeruli) or missing data during follow up were excluded. All the subjects were followed up for at least 12 months before reaching this study's endpoint. The study was approved by the Ethical Committee of West China Hospital of Sichuan University(2019-33), and all the methods were carried out in accordance with relevant guidelines and regulations.

Clinical and pathological data

Patients enrolled in this study were divided into non-smoker and smoker group. Demographics and baseline clinical data were collected at the time of renal biopsy, including gender, age, serum creatinine, blood pressure and 24h urine protein, eGFR (estimated glomerular filtration rate) was calculated using the CKD-EPI equation. Hypertension was defined as blood pressure >140/90mmHg or using antihypertensive agents. Renal pathology changes were reviewed by experienced pathologists and nephrologists basing on the Oxford classification: mesangial hypercellularity (M0/M1); endocapillary hypercellularity (E0/E1); segmental glomerulosclerosis (S0/S1); tubular atrophy/interstitial fibrosis (T0/T1/T2) and cellular or fibrocellular crescents (C0/C1/C2) ⁸ (Table 1).

Table 1

Demographic and clinicopathological characteristics of 1239 IgAN patients and 497 patients matched by propensity score.

Characteristics	Before PSM		After PSM	
	Non-smokers (1030)	Smokers (209)	Non-smokers(318)	Smokers(179)
Clinical				
Male (%)	351(34.1)	203(97.1)**	299(94)	173(96.6)
Hypertension (%)	252(24.5)	79(37.8)**	98(30.8)	64(35.8)
SBP (mmHg)	127.0±18.2	127.6±16.5	129.2±17.4	128.2±16.2
DBP (mmHg)	83.0±13.2	83.0±13.4	84.9±12.8	83.7±13.1
Serum creatinine (umol/L)	88.3±41.3	116.6±54.2**	108.5±49.3	115.8±55.3
eGFR (mL/min per 1.73m ²)	93.8±31.3	82.8±33.7**	90.7±32.3	85.0±34.3
Urine protein (g/24h)	2.1±2.5	2.7±3.0**	2.3±2.7	2.4±2.6
Pathologic				
	Oxford Classification			
M1 (%)	774(75.2)	116(77)	243(76.4)	137(76.5)
E1 (%)	47(4.6)	12(5.7)	9(2.8)	9(5)
S1 (%)	623(60.5)	130(62.2)	189(59.4)	115(64.2)
T1/T2 (%)	179(17.4)	58(27.8)**	79(24.8)	51(28.5)
C1/C2 (%)	239(23.2)	49(23.4)	77(24.2)	38(21.2)
<p>Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. * stands for p < 0.05, ** stands for p ≤ 0.01.</p> <p>Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; M, mesangial proliferation; E, endocapillary proliferation; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; C, crescents.</p>				

Endpoint

The endpoint was ESRD which was defined as eGFR <15 mL/min/1.73 m² or accepting renal replacement treatment and/or eGFR decreased >50% compared with the time of renal biopsy.

Statistical analysis

All the statistical analyses were carried out by using IBM SPSS Statistic software. Categorical data were analyzed using Chi-square tests and presented as frequencies (percentages). Continuous variables were expressed as mean \pm SD and analyzed with ANOVA, Kruskal-Wallis H test, Student's t-test or nonparametric Mann-Whitney U test. K-M survival analysis and Cox regression model were performed. Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Considering the demographic and clinicopathological characteristics of non-smoker group and smoker group were unbalanced. Propensity-score-matching (PSM): smokers were matched to non-smokers with 1:3 nearest neighbor matching without replacement (the caliper width was set as 0.2) in order to make the results more convincing⁹. Statistical significance was considered if $p < 0.05$.

Results

Demographic and clinicopathological characteristics

Finally, 1239 patients met the inclusion criteria (Table 1). The mean follow-up time was 60.8 ± 28.7 months. The mean age (at the time of renal biopsy) of smoker-cases compared with nonsmoker-cases was 38.6 ± 11.5 vs 33.2 ± 10.8 years. The proportion of male patients was much higher among smokers. Hypertension was reported in 37.8% of smoker subjects. The renal function was much worse in smoker group than in non-smoker group. To control the significant differences in demographic and clinicopathological characteristics between smokers and non-smokers, we performed PSM. As shown, after matching to smokers, there were 497 matched pairs left with well-balanced characteristics.

Effect of cigarette smoking on renal outcome

K-M survival analysis of data with or without PSM revealed that cigarette smoking could affect the renal survival of IgAN patients. Much more patients in smoker group (19%, 40 out of 209) than in nonsmoker group (11%, 110 out of 1030) reached endpoint ($p < 0.001$, Fig.1-A). After PSM, it was found that 13% (40 out of 318) and 20% (35 out of 179) patients reached endpoint in non-smoker and smoker group ($p = 0.042$, Fig.1-B). The univariate cox regression analysis results revealed that cigarette smoking, hypertension, female gender, serum creatinine, 24h-proteinuria, mesangial hypercellularity, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis were significantly associated with the renal outcome. After adjusted for all the important factors, multivariable cox regression showed that cigarette smoking, female gender, hypertension, serum creatinine and the pathologic changes of segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis were independent risk factors of the

progression of IgAN. After PSM, cigarette smoking was also recognized as a significant predictor of renal survival of IgAN (Table 2).

Table 2

Cox proportional hazard model for the renal outcome in 1239 IgAN patients and 497 patients matched by propensity score.

Parameter	Before PSM		After PSM	
	Univariate	Multivariate	Univariate	Multivariate
	HR(95%CI)	HR(95%CI)	HR(95%CI)	HR(95%CI)
Smoker	1.97(1.37-2.83)**	1.58(1.02-2.46)*	1.60(1.01-2.53)*	1.63(1.02-2.62)*
Female	0.64(0.47-0.89)**	2.00(1.29-3.10)**	0.78(0.25-2.47)	2.03(0.61-6.68)
Hypertension	3.22(2.32-4.45)**	1.50(1.04-2.16)*	2.31(1.45-3.66)**	1.18(0.67-1.88)
SBP	1.03(1.02-1.03)**		1.03(1.01-1.04)**	
DBP	1.04(1.03-1.05)**		1.03(1.02-1.05)**	
Serum creatinine	1.02(1.01-1.02)**	1.01(1.09-1.01)**	1.01(1.01-1.02)**	1.01(1.01-1.02)**
eGFR	0.96(0.96-0.97)**		0.96(0.95-0.97)**	
Urine protein	1.10(1.06-1.15)**	1.04(0.97-1.10)	1.12(1.06-1.19)**	1.06(0.98-1.14)
Oxford Classification				
M1	2.38(1.41-4.01)**	1.61(0.95-2.73)	4.81(1.75-13.21)**	3.29(1.18-9.13)*
E1	1.22(0.62-2.40)	0.63(0.31-1.31)	1.14(0.41-3.17)	0.54(0.18-1.62)
S1	2.97(2.03-4.37)**	1.59(1.06-2.39)*	2.65(1.55-4.53)**	1.49(0.85-2.61)
T1/T2	7.65(5.51-10.60)**	3.13(2.09-4.67)**	7.43(4.50-12.24)**	2.78(1.52-5.10)**
C1/C2	1.30(0.92-1.84)	1.07(0.74-1.55)	1.70(1.05-2.76)*	1.33(0.79-2.23)
Note: * stands for p < 0.05, ** stands for p ≤ 0.01.				
Abbreviations: HR, hazard ratio; 95 % CI, 95 % confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; M, mesangial proliferation; E, endocapillary proliferation; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; C, crescents.				

Hypertension and renal vasculopathy were associated with cigarette smoking and progression of IgAN

Association between cigarette smoking and hypertension or renal vasculopathy was analyzed. The results indicated that compared with non-smokers, smoker subjects were associated with higher risk of hypertension (OR1.876;95%CI:1.371-2.567;p<0.001) and renal vasculopathy (OR1.569;95%CI:1.163-2.118;p=0.003). Further analysis indicated that non-smoker subjects without hypertension or renal vasculopathy have remarkable favorable outcome than other patients. However, smoker with hypertension and renal vasculopathy had the worst renal outcome, which indicated that cigarette smoking, hypertension and renal vasculopathy could accelerate the progression of IgAN (Fig.2). In subgroup analyses by gender, the association between cigarette smoking and renal outcomes appeared to be much stronger among female patients than male patients, although there was no significant difference in the rate of renal survival between female smoker patients and male smoker patients (Fig.3). Further analysis found that the patients with severer renal dysfunction were more vulnerable to cigarette smoking (Fig.4).

Discussion

IgAN is the primary glomerulonephritis with the highest incidence in the world, accounting for 15–32% of glomerular diseases in China¹⁰. About 20% of patients will progress to ESRD within 20 years after diagnosis¹. Cigarette smoking is one of the most important risk factors for premature death, especially the increased morbidity and mortality¹¹. In China, cigarette smoking has been a common phenomenon. The mortality burden of individuals from smoking has increased in recent decades¹². The deleterious effect of smoking has been investigated in CKD patients. It was found that current smoking was an independent risk factor for progression of microalbuminuria, macroalbuminuria and ESRD among diabetic nephropathy patients. As for ex-smokers and nonsmokers, there was no significant difference for their progression of this disease¹³. A retrospective study of IgAN showed that cigarette smoking was an important predictor for the progression of IgAN⁵. However, another observational study found that cigarette smoking does not have a direct connection with IgAN⁶. It was noticed that these studies did not include renal pathological changes and did not perform a propensity-score-matching to balance the difference between smoking and non-smoking subjects to reduce the influence of confounding factors. Therefore, whether the cigarette smoking is related to the prognosis of IgAN is still controversial.

In the current study, it was demonstrated that cigarette smoking was significantly associated with renal survival of IgAN patients. We found that comparing with non-smokers, the risk of ESRD or eGFR decreased > 50% was significantly higher in smokers among IgAN patients, 19% (40 out of 209) vs 11% (110 out of 1030), Moreover, the patients with severer renal dysfunction, were more vulnerable to cigarette smoking. Based on these results, special attention should be paid to the cigarette smoking patients who were in CKD stage 3 or 4. It was also noticed that IgAN patients who were smokers were more likely to have hypertension and renal vasculopathy changes, and a worst renal outcome compared with other

patients who without hypertension or cigarette smoking. In order to decrease the obvious unbalanced influence of data, we performed propensity-score matching to make our results more convictive. From the analyses based on the matched pairs, we concluded that cigarette smoking is an independent risk factor for the progression of IgAN patients. Moreover, the relationships between cigarette smoking and hypertension, renal vasculopathy changes in biopsy were verified by the analyses of matched pairs.

Several studies reported that the adverse effects of cigarette smoking on progression of renal disease have been related to blood pressure elevation and renal hemodynamics^{13,14}. Several potential mechanisms may explain the relationship between cigarette smoking and the progression of IgAN. First of all, smoking induces oxidative stress by depleting antioxidants. On the other hand, IgAN is characterized by the deposition of IgA immune complexes, which leading to complement activation, increasing oxidative stress and promoting inflammatory cascade¹⁵. That may be a plausible explanation why in our study those patients with severe impaired kidney function were more vulnerable to cigarette smoking. Second, smoking may theoretically cause renal injury through the pathogenic effect of nicotine^{16,17}. The direct harmful effects on vasculature promoting renal atherosclerosis are possibly a major mechanism¹⁴. It has also been suggested that nicotine could promote the proliferation of mesangial cell and effect endothelial function. It is known that the pathological feature of IgAN is diffuse mesangial cell proliferation and mesangial matrix increase^{16,17}. And our analyses did show that cigarette smoking patients with more hypertension and the renal vasculopathy changes in biopsy, accelerating the process of IgAN and leading to bad renal outcomes.

Sex differences have been reported in several studies of cigarette and CKD. Some demonstrated that smoking increases the risk of kidney failure in both men and women¹⁴. In contrast, other studies showed that male smokers were associated with a higher risk of renal dysfunction¹⁸. However, our study found that women patients were more susceptible to cigarette smoking in patients with IgAN. Results of some studies were consistent with ours; risk associated with smoking with low exposure dose in women and men were 1.0 and 0.8, for high exposure dose, they were 1.45 and 1.24¹⁹, and a cohort study reported that female sex was an independent risk factor after adjusting for other relevant factors²⁰. Because the rising rates of smoking in female individuals were observed in recent years. More attentions should be paid to these patients in clinical practice. Considering that the vast majority of smoking subjects in our study were men, larger studies were needed to clarify whether female IgAN patients are more vulnerable to cigarette smoking.

However, our study still has some limitations. First, this is a retrospective study just in a hospital center and the smoking status of all the subjects during the follow-up period were unclear. Second, we did not investigate the effect of therapeutic drugs on this smoking situation. Besides, the mean follow-up time of 61.5 months was relatively short, especially for IgAN, such a slow progressing disease.

Conclusion

Cigarette smoking is a significant risk factor on progression of IgAN patients. We need pay more attention to those smoking-IgAN patients who have severe renal function and been women.

Declarations

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Contributions:

Research idea and study design: Wei Qin, Yi Tang; Data acquisition: Wei Qin, Siqing Wang, Zheng Jiang, Lingqiu Dong; Data analysis/interpretation: Siqing Wang;

Statistical analysis: Siqing Wang; Supervision: Wei Qin.

Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Siqing Wang take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Disclosure Statement

The authors declare they have no conflicts of interest regarding this paper.

Informed consent

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article. As for patients who with age less than 18 years, we got informed consent from a parent and/or legal guardian.

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Figures

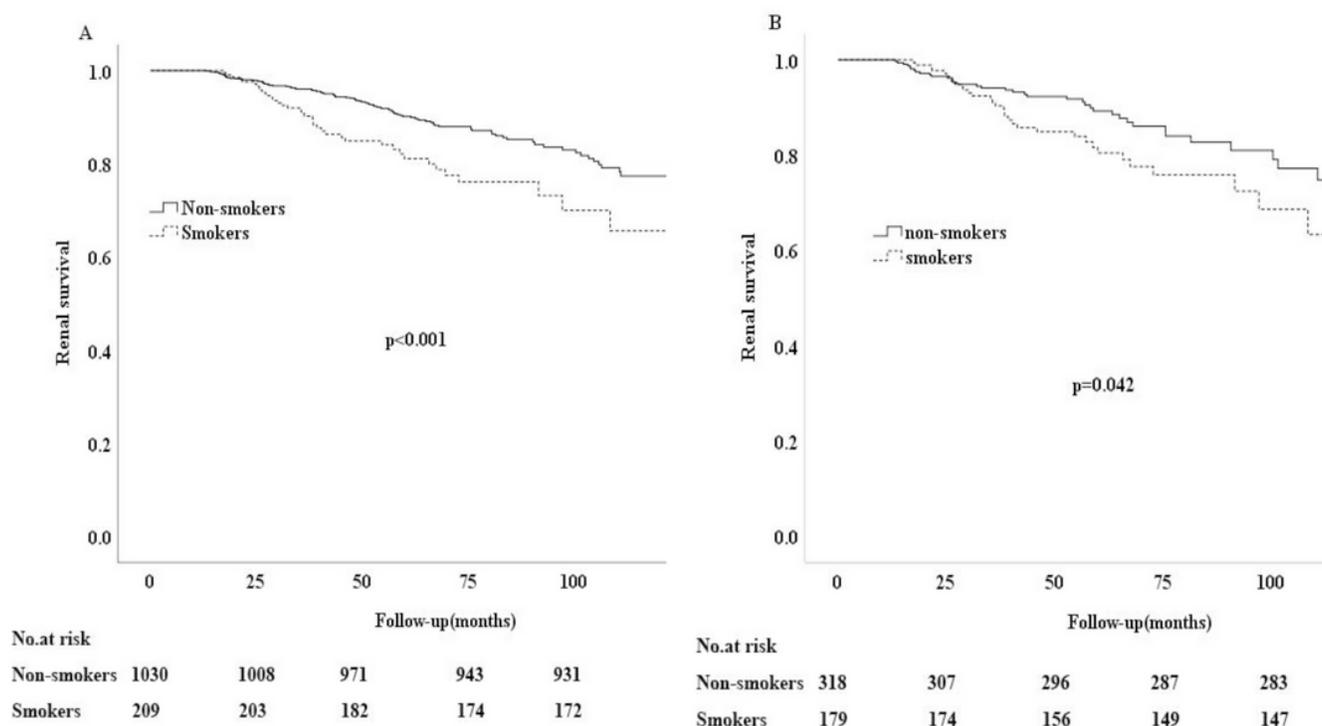


Figure 1

Kaplan-Meier analysis for the endpoint. Note: The endpoint was 50% decline in eGFR and/or ESRD. (A) Kidney survival rates in non-smoker and smoker group; (B) Kidney survival rates in non-smoker and smoker group matched by propensity score.

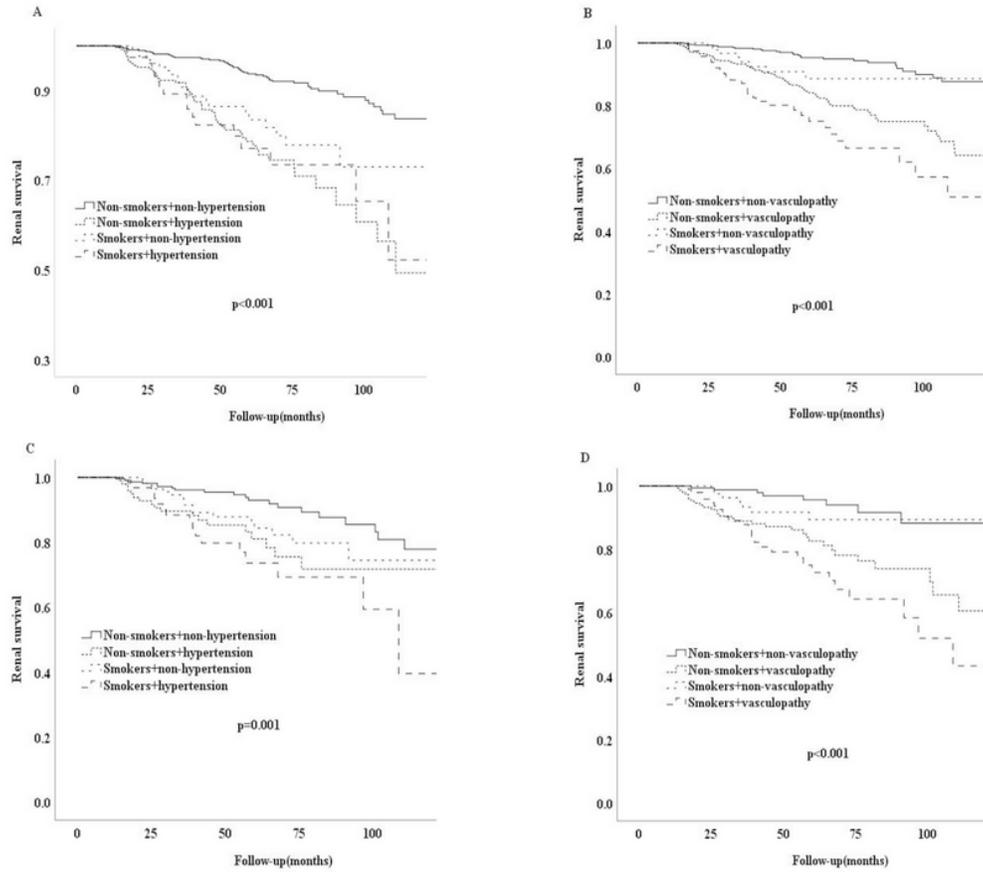


Figure 2

Kaplan-Meier analysis for the endpoint. Note: The endpoint was 50% decline in eGFR and/or ESRD. (A) Kidney survival rates in non-smoker and smoker group in patients with hypertension and without; (B) Kidney survival rates in non-smoker and smoker group in patients with renal vasculopathy and without; (C) Kidney survival rates in non-smoker and smoker group matched by propensity score in patients with hypertension and without; (D) Kidney survival rates in non-smoker and smoker group matched by propensity score in patients with renal vasculopathy and without.

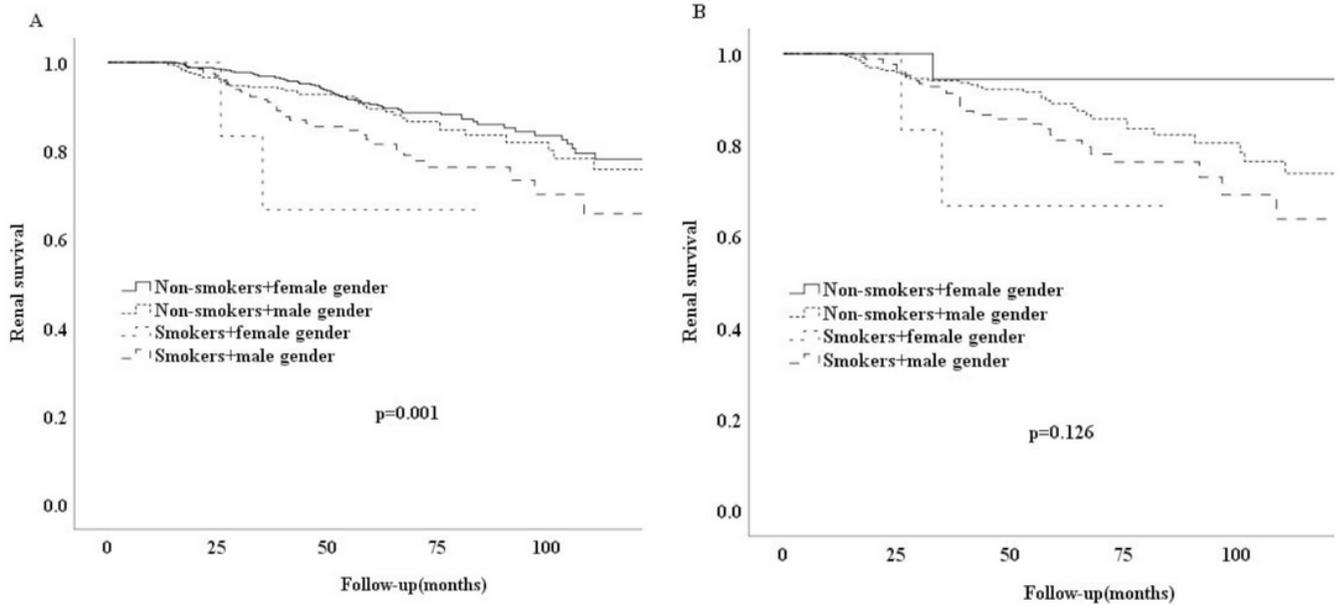


Figure 3

Kaplan-Meier analysis for the endpoint. Note: The endpoint was 50% decline in eGFR and/or ESRD. (A) Kidney survival rates in non-smoker and smoker group in female or male patients ; (B) Kidney survival rates in non-smoker and smoker group matched by propensity score in female or male patients.

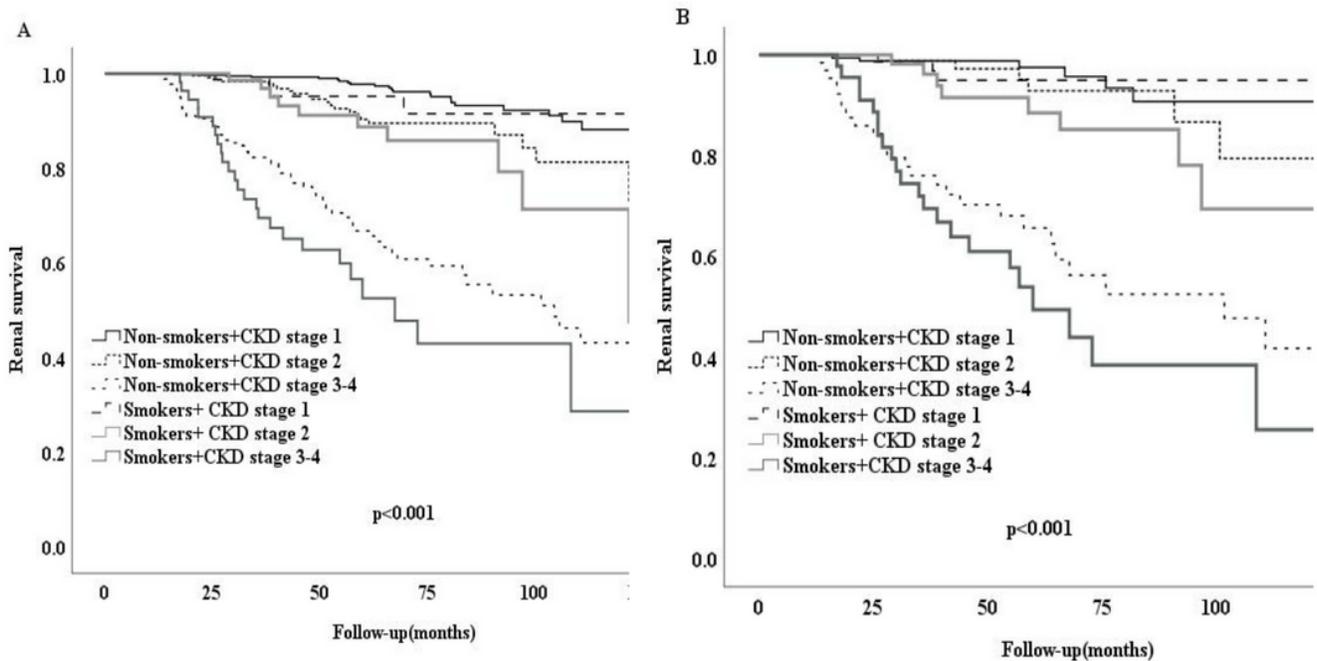


Figure 4

Kaplan-Meier analysis for the endpoint. Note: The endpoint was 50% decline in eGFR and/or ESRD. (A) Kidney survival rates in non-smoker and smoker group in patients in stage 1 or 2 or 3-4 CKD group; (B) Kidney survival rates in non-smoker and smoker group matched by propensity score in patients in stage 1 or 2 or 3-4 CKD group.