Original Article

Exploring Biomarkers Beyond Exercise Testing: The Impact of Smoking on Cardiovascular and Pulmonary Health among CKD Patients

Alireza Kashefizadeh[1], Hossein Mehravaran[2], Shiva Samavat[3], Mohsen Nafar[3], Hossein Amini[4], Nooshin Dalili[3*]

[1]Department of Pulmonology, Shahid Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Pulmonary and Critical Care Division, Department of Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[3]Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: Chronic Kidney Disease (CKD) patients often face complex health challenges, including cardiovascular and pulmonary issues. Smoking is a recognized risk factor for these conditions, but its specific impact on CKD patients remains less understood.

Materials and Methods: In this cross-sectional study, we investigated the relationship between smoking habits and cardiopulmonary health among CKD patients. We examined baseline characteristics, including demographics, medical history, and biochemical markers, in a cohort of CKD patients. Cardiopulmonary parameters were assessed during exercise testing, including oxygen consumption, ventilation rates, ventilation-perfusion matching markers, and oxygen saturation levels.

Results: Our findings revealed no statistically significant differences in cardiopulmonary parameters between smokers and non-smokers within the CKD patient population. This suggests that the relationship between smoking and exercise capacity in CKD patients is complex and influenced by multiple factors. Our analysis of demographics, comorbidities, and medication history provided critical context for interpreting these results.

Conclusion: This study contributes to our understanding of the intricate relationship between smoking habits and cardiopulmonary health in CKD patients. While smoking is recognized as a risk factor, its specific impact on exercise capacity within this population may be influenced by individual variables. Further research is needed to explore these relationships in larger and more diverse cohorts. These findings underscore the importance of considering multiple variables when assessing the impact of smoking on the health of CKD patients.

Keywords: Renal insufficiency, Smoking, Cardiovascular risk, Cardiopulmonary health

***Corresponding Author:** Nooshin Dalili, MD, Nephrologist. Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Postal Address: Shahid Labbafinejad Hospital, 9th Boostan St, Tehran, Iran. Postal code: 1666663111; Tel: (+98) 912-2404331. Email: nooshindalili4@gmail.comOrcid ID: 0000-0002-1618-0937

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Introduction

Tobacco smoking stands as a formidable global public health challenge, significantly affecting cardiovascular health and contributing to a spectrum of adverse outcomes, including heart attacks, strokes, and premature deaths[1,2]. While its deleterious effects on the general population are well-established, the impact of smoking is particularly ominous for individuals grappling with chronic kidney disease (CKD) and undergoing dialysis[3]. This article delves into the intricate relationship between smoking and cardiovascular health, with a specific emphasis on CKD patients, a population facing heightened health risks[4].

CKD patients, constituting a substantial demographic in public health, demand our unwavering attention due to the silent and relentless nature of their condition, affecting millions globally [5]. The progression of CKD, if left unmanaged, leads to kidney failure, necessitating life-saving interventions such as dialysis or transplantation[6]. Moreover, CKD patients grapple not only with the physical burden of the disease but also with an elevated mortality rate, often attributed to cardiovascular complications exacerbated by smoking[7]. Despite the gravity of this issue, the existing body of research addressing the intersection of smoking, cardiovascular health, and CKD patients remains surprisingly limited[8].

Recognizing this research gap is crucial, as it leaves healthcare providers and policymakers in a precarious position, lacking comprehensive insights needed for effective interventions. In light of this, our study aims to fill this void by exploring the impact of smoking on cardiovascular and pulmonary health among CKD patients. Importantly, we seek to elucidate the rationale behind incorporating exercise testing in this context, particularly focusing on smokers with CKD. By doing so, we strive to contribute valuable knowledge that can inform targeted interventions and enhance healthcare strategies for this vulnerable population.

Methods

Study Design: This observational cohort study aims to investigate the impact of smoking on the cardiovascular and pulmonary health of chronic kidney disease (CKD) patients. Specifically, it seeks to explore how smoking habits affect cardiovascular and pulmonary outcomes in this vulnerable population. The study is conducted at Labbafinejad Hospital and includes adult patients aged 18 years and above who have been diagnosed with CKD.

Study Population: The study cohort comprises individuals with CKD, encompassing stages 3 to 5, who are not currently undergoing dialysis treatment. Inclusion criteria stipulate that participant must possess a glomerular filtration rate (GFR) below 60 cc per minute, as calculated based on their body surface area. Additionally, individuals included in the study must be 18 years of age or older and have provided informed consent for participation.

GFR assessments are performed for all patients employing the CKD-EPI method, thereby classifying them into their respective CKD stages. Exclusion criteria encompass individuals who meet any of the following conditions:

- Those unable to walk independently or deemed unsuitable for cardiopulmonary exercise testing.
- Individuals with hemoglobin levels below 9 mg/dL.
- Patients with uncontrolled high blood pressure.
- Those currently experiencing active, untreated coronary disease.
- Individuals with any history of pulmonary diseases
- Individuals with a history of coronary heart disease, as the study aims to assess cardiopulmonary exercise performance in CKD patients before the onset of coronary artery disease.

In terms of the Recruitment Process, potential participants were identified from outpatient clinics and inpatient wards at Labbafinejad Hospital, with eligibility criteria based on age, CKD diagnosis, and absence of dialysis treatment. Recruitment efforts included informational sessions, distribution of study materials, and direct engagement with eligible individuals by trained research staff. Emphasis was placed on obtaining informed consent and ensuring that participants understood the nature and purpose of the study, as well as their rights and responsibilities. This approach aimed to facilitate a transparent and ethical recruitment process while maximizing

participation and minimizing selection bias.

Data Collection: The study entails the administration of comprehensive cardiopulmonary exercise tests to evaluate the impact of smoking on cardiovascular and pulmonary health among CKD patients. Patients are advised to abstain from vigorous exercise and caffeine consumption within the 24 hours preceding the test.

In conjunction with cardiopulmonary exercise testing, the following patient data and laboratory measurements are meticulously collected:

- Patient demographics, including age, gender, and medical history.
- Details regarding CKD management, including any ongoing dialysis treatment, its duration, and frequency.
- Laboratory measurements encompassing serum creatinine, GFR, and serum albumin.
- Patient-reported symptoms and exercise tolerance.

Cardiopulmonary Exercise Testing Protocol: For the Cardiopulmonary Exercise Testing Protocol, patients underwent a standardized exercise regimen designed to evaluate their cardiovascular and pulmonary function. This involved utilizing calibrated equipment to measure parameters such as oxygen consumption, ventilation, and carbon dioxide production during graded exercise. The protocol adhered to established guidelines for cardiopulmonary exercise testing, ensuring consistency and reliability across all assessments. Safety measures were implemented throughout the testing process to minimize risks to participants and ensure their well-being.

Statistical Analysis: Statistical analysis is performed utilizing appropriate software, such as SPSS, to assess the impact of smoking on cardiovascular and pulmonary health outcomes in CKD patients. Descriptive statistics are employed to summarize patient characteristics and baseline measurements.

Comparative analyses, including t-tests or ANOVA, are conducted to evaluate differences in cardiovascular and pulmonary health outcomes between smoking and non-smoking CKD patients. Multivariable regression models are applied to account for potential confounding factors and identify independent associations between smoking and cardiovascular and pulmonary health in this patient population.

Ethical Considerations: This study has received ethical clearance from the ethics committee at Shahid Beheshti University of Medical Sciences, with an assigned ethics code (IR.SBMU.MSP.REC.1398.766). The research meticulously adheres to ethical standards throughout its duration to safeguard the rights and welfare of all study participants, ensuring their privacy and informed consent are upheld at all times.

Table 1. Baseline characteristic of the study participants**.**

		Mean/Number*	Standard Deviation/percent**
Gender	Male	80	61.5 %
	Female	50	38.5%
Age	Male	43	11
	Female	43	11
	Total	42	11
Height		171	7
Weight		73	10
BMI		24.87	3.39
Current smoker		18	22.5%
Past medial history	Diabetes mellitus	23	28.7%
	Hypertension	32	40.0%
	Dyslipidemia	8	10.0%
Drug history	ACE inhibitors	14	17.5%
	ARB	33	41.3%
	Beta blockers	36	45.0%
	Diuretic	53	66.3%
	Nitrate	9	11.3%
	Statin	37	46.3%
	Antiplatelet	30	37.5%
Serum albumin		3.3	0.3
Serum calcium		8.4	0.5
Serum phosphorus		6.1	1.5
Serum vitamin D3		30	6
Serum Creatinine		4.2	1.2
GFR		14.27	6.73
CKD stage	3	2	2.5%
	4	23	28.7%
	5	55	68.8%

*Values are shown as mean for continuous variables and number for categorical variables, **Values are shown as standard deviation for continuous variables and percent for categorical variables.

Results

The baseline characteristics of the study participants are comprehensively summarized in Table 1, encompassing demographics, clinical history, and biochemical attributes.

The cohort consisted of 80 males and 50 females, indicating a male predominance, constituting 61.5% and 38.5% of their respective gender categories. The average age of the participants was 42 years, with a standard deviation of 11. This average remained consistent across gender subgroups, with both males and females having an average age of 43 years, each with a standard deviation of 11. Anthropometric data revealed an average height of 171 cm and an average weight of 73 kg, resulting in a calculated Body Mass Index (BMI) of 24.87, with a standard deviation of 3.39, indicating that participants, on average, fell within the normal BMI range.

Table 1 also provides insights into participants' smoking habits, medical histories (including conditions such as diabetes mellitus, hypertension, and dyslipidemia), and medication histories (involving drugs like ACE inhibitors, ARBs, beta-blockers, diuretics, nitrates, statins, and antiplatelet agents). The data sheds light on the prevalence of these conditions and the utilization of specific medications within the study population. Additionally, the table presents key laboratory parameters, including serum albumin, serum calcium, serum phosphorus, and serum vitamin D3 levels, offering baseline values and standard deviations for these biochemical markers. Notably, among smokers, the distribution across age categories varies. In the 20-30 age group, two individuals smoke, representing 16.7% of that cohort. This proportion increases in older age brackets: 21.4% of individuals aged 30-40 smoke, 22.7% of those aged 40-50 smoke, and 30.8% of individuals aged 50-60 smoke. Finally, in the 60-70 age range, 25% smoke.

Of particular significance, serum creatinine levels exhibited an average of 4.2, with a standard deviation of 1.2, a crucial marker in assessing renal health, where elevated levels often indicate impaired kidney function. Furthermore, the Glomerular Filtration Rate (GFR) was carefully assessed, demonstrating an average value of 14.27, accompanied by a standard deviation of 6.73. Additionally, participants were categorized into distinct stages of chronic kidney disease (CKD), revealing that Stage 3 CKD was identified in 2.5% of participants. In comparison, Stage 4 was prevalent in 28.7%, and Stage 5 was prominent in 68.8% of the study population.

Table 2. Results of cardiopulmonary function and oxygen utilization**.**

Parameters	Mean / Number*	Standard Deviation / percent**
VO2 ml/kg/min	18.8	3.0
VE l/min	62	6
PET CO2 mmHg	30	3
Peak VO2 ml/kg/min	63	56
VE/VCO2 l/min	36.4	2.4
O2 Saturation	96	3

*Values are shown as mean for continuous variables and number for categorical variables, **Values are shown as standard deviation for continuous variables and percent for categorical variables.

In Table 2, our study delves into the physiological aspects of oxygen utilization during cardiopulmonary testing. The average oxygen consumption per kilogram of body weight (VO2) was recorded at 18.8 ml/kg/min, with a standard deviation of 3.0 ml/kg/min, representing the quantity of oxygen consumed during physical activity. Participants displayed a ventilation rate (VE) of 62 liters per minute, with a deviation of 6 liters per minute, signifying the volume of air exchanged during exercise. The ventilation-perfusion matching marker (PET CO2) was measured at 30 mmHg, with a deviation of 3 mmHg.

Peak VO2, characterizing the rate at which oxygen is utilized during exercise, exhibited an average value of 63 ml/kg/min, displaying considerable variability with a standard deviation of 56 ml/kg/min. The ratio between ventilation and carbon dioxide output (VE/VCO2), reflecting efficiency, had an average value of approximately 36.4 liters per minute, with a deviation of 2.4 liters per minute. Lastly, the assessment of oxygen saturation in the blood (O2 Saturation) during exercise registered at 96%, with a standard deviation of approximately 3%.

Table 3 provides a comprehensive comparison of several variables between smokers and non-smokers. Despite a thorough analysis, no statistically significant differences were observed across these variables between the two groups. This outcome suggests that,

Table 3. Comparison of characteristics between smokers and non-smokers**.**

		Non-smoker		Smoker		P value
		M/N*	SD/P**	M/N	SD/P	***
Age		41	11	44	11	0.30
BMI		25.11	3.50	24.05	2.89	0.24
Sex	Male	38	76.0%	12	24.0%	0.67
	Female	24	80.0%	6	20.0%	
Diabetes mellitus	No	44	77.2%	13	22.8%	0.91
	Yes	18	78.3%	5	21.7%	
Hypertension	No	38	79.2%	10	20.8%	0.66
	Yes	24	75.0%	8	25.0%	
Dyslipidemia	No	57	79.2%	15	20.8%	0.28
	Yes	5	62.5%	3	37.5%	
Systolic blood pressure		123.82	12.87	122.22	12.15	0.64
Diastolic blood pressure		81.90	9.71	80.61	7.19	0.60
Heart rate		203.52	951.72	85.22	19.07	0.60
Creatinine		4.2	1.1	4.0	1.2	0.45
Ejection Fraction		50.1	5.0	51.4	4.5	0.34
Serum albumin		3.3	0.3	3.1	0.4	0.06
Serum calcium		8.4	0.5	8.3	0.5	0.53
Serum phosphorus		6.2	1.4	5.7	1.5	0.20
Serum vitamin D3		30	6	32	6	0.19

M/N (Mean/Number), SD/P (Standard Deviation/percent), *Values are shown as mean for continuous variables and number for categorical variables, **Values are shown as standard deviation for continuous variables and percent for categorical variables, ***P value represents the differences between two group in case of interest variable.

within the scope of this study, smoking did not appear to exert a substantial impact on various parameters, including age, BMI, sex, diabetes mellitus, hypertension, dyslipidemia, systolic and diastolic blood pressure, heart rate, creatinine levels, ejection fraction, serum albumin, serum calcium, serum phosphorus, and serum vitamin D3. These findings contribute to a more nuanced understanding of the relationship between smoking and these specific characteristics within the study cohort, emphasizing the need for further exploration of potential factors influencing cardiopulmonary outcomes in CKD patients.

Table 4 presents a comprehensive comparison of cardiopulmonary test results between smokers and non-smokers, detailing key parameters such as oxygen consumption (VO2 ml/kg/min), ventilation rate (VE l/min), ventilation-perfusion matching marker (PET CO2 mmHg), peak oxygen consumption (Peak VO2 ml/kg/min), ventilation efficiency represented by VE/VCO2 (l/min), oxygen saturation (O2 Saturation), and the ratio of ventilation to oxygen consumption (VE/VO2). The table provides means and standard deviations for each parameter, offering insights into the central tendencies and variations within the groups. Additionally, p-values are included to indicate the significance of differences observed between smokers and non-smokers for each variable.

Notably, the p-values underscore that no statistically significant differences were detected in these cardiopulmonary parameters between the two groups. This finding highlights the similarity in cardiopulmonary test results, irrespective of the participants' smoking status. Despite the scholarly presentation through tabular data, it is crucial to emphasize the noteworthy result that smoking did not lead to significant variations in the examined cardiopulmonary parameters. This reinforces the need for a nuanced interpretation of the data, suggesting that other factors may play a role in influencing these outcomes within the study population. Further exploration and discussion of potential contributing factors may enhance the comprehensive understanding of the interplay between smoking and cardiopulmonary health among CKD patients.

Table 4. Comparison of the results of cardiopulmonary test between smokers and non-smokers**.**

Parameters	Non-smoker		Smoker		P value
	M/N*	SD/P **	M/N	SD/P	***
VO2 ml/kg/min	18.9	3.0	18.7	3.0	0.8
VE l/min	61	5	63	8	0.3
PET CO2 mmHg	30	3	30	2	0.8
Peak VO2 ml/kg/min	64	64	60	8	0.7
VE/VCO2 l/min	36.3	2.4	37.0	2.3	0.2
O2 Saturation	96	3	96	2	0.5
VE/VO2	3.33	0.54	3.42	0.59	0.5

M/N (Mean/Number), SD/P (Standard Deviation/percent), *Values are shown as mean for continuous variables and number for categorical variables, **Values are shown as standard deviation for continuous variables and percent for categorical variables, ***P value represents the differences between two group in case of interest variable.

Table 5. Comparison of the results of cardiopulmonary test between different stages of CKD**.**

	Stage III		Stage IV		Stage V		P value
	M/N*	SD/P**	M/N	SD/P	M/N	SD/P	***
VO2 ml/kg/min	16.5	0.7	19.1	3.0	18.8	3.0	0.5
VE l/min	60	1	63	7	61	5	0.4
PET CO2 mmHg	34	1	30	3	29	3	0.06
Peak VO2 ml/kg/min	53	4	79	105	57	6	0.2
VE/VCO2 l/min	34.8	1.1	36.6	1.8	36.4	2.7	0.6
O2 Saturation	97	1	96	2	96	3	0.7
VE/VO2	3.61	0.11	3.37	0.60	3.33	0.54	0.7

M/N (Mean/Number), SD/P (Standard Deviation/percent), *Values are shown as mean for continuous variables and number for categorical variables, **Values are shown as standard deviation for continuous variables and percent for categorical variables, ***P value represents the differences between two group in case of interest variable.

Table 5 presents a comparison of cardiopulmonary test results across various stages of chronic kidney disease (CKD). It outlines mean values and standard deviations for parameters including VO2 ml/kg/min, VE l/min, PET CO2 mmHg, Peak VO2 ml/kg/min, VE/VCO2 l/min, O2 Saturation, and VE/VO2. The stages compared are III, IV, and V, with the respective mean values and standard deviations displayed for each stage. The p-values indicate the significance of differences between the stages for each variable, with Stage V often exhibiting higher mean values compared to the other stages, though not always statistically significant.

Discussion

The presented data provide a comprehensive insight into the characteristics and cardiopulmonary test results within our study population, primarily consisting of chronic kidney disease (CKD) patients. The demographic and clinical profiles showcased a preponderance of males and a relatively homogeneous age distribution. Moreover, the prevalence of medical conditions and medication use among the participants was highlighted, which is crucial for contextualizing our study's focus on exercise intolerance. The examination of kidney function, as reflected by serum

creatinine levels and Glomerular Filtration Rate (GFR), offers important insights into renal health. Additionally, the distribution of CKD stages underscores the predominance of advanced CKD stages, underscoring the significance of our investigation.

The physiological aspects of oxygen utilization during cardiopulmonary testing, as demonstrated in the data, revealed noteworthy parameters such as oxygen consumption, ventilation rates, ventilation-perfusion matching markers, and oxygen saturation levels during exercise. Notably, the variability in Peak VO2 suggests diversity in exercise capacity among participants.

Further analysis, examining the comparison of characteristics between different subgroups within the study population, revealed no statistically significant differences across various variables. These variables encompassed age, BMI, comorbidities, medication history, and various biochemical parameters. This finding underscores the complex interplay between smoking habits and these specific characteristics in CKD patients.

Lastly, the detailed examination of cardiopulmonary parameters about smoking habits revealed no statistically significant differences, indicating that smoking did not exert a substantial impact on the cardiopulmonary test results within our study population. These cumulative findings provide valuable insights into the intricate relationship between smoking, cardiopulmonary health, and the unique characteristics of CKD patients.

CKD is a complex and heterogeneous condition. CKD patients exhibit varying degrees of renal impairment, comorbidities, and individual responses to smoking [9]. This heterogeneity within the CKD population can lead to substantial variability in cardiopulmonary parameters. As a result, the differences between smokers and non-smokers may be obscured or diluted, making it challenging to detect significant associations[10].

Cardiopulmonary health is influenced by a multitude of factors, including renal function, cardiovascular comorbidities, respiratory health, and physical fitness[11]. Smoking is just one of these factors[12]. Other elements, such as the severity of CKD, medication use, and concurrent health conditions, may have a more pronounced impact on cardiopulmonary parameters. The complex interplay of these variables can mask the specific effects of smoking[13]. Moreover, the sample size of the study may have been insufficient to detect subtle differences in cardiopulmonary parameters between smokers and non-smokers within the CKD population. With a limited sample, the study may lack the statistical power to identify significant associations, particularly if the effect of smoking is relatively small.

Cardiopulmonary parameters are influenced by intricate physiological processes involving the heart, lungs, circulation, and oxygen utilization[14]. Smoking, while detrimental to many aspects of health, may not have a direct and immediate impact on all cardiopulmonary parameters assessed in the study. Some parameters may require more extended exposure or a greater cumulative dose of toxins from smoking to manifest significant changes[15].

Comparing our study's findings with those of another investigation reveals notable disparities in the associations between smoking and cardiopulmonary health outcomes among chronic kidney disease (CKD) patients. While our study, as detailed in Table 4, observed no statistically significant differences in various cardiopulmonary parameters between smokers and non-smokers, there are related studies that delineate significant variations in VO2max levels among different smoking groups during cardiopulmonary exercise testing (CPET)[16]. Specifically, the other study documented a significant reduction in VO2max levels in smokers compared to non-smokers, aligning with previous research indicating adverse effects of smoking on cardiorespiratory function [16]. Notably, these discrepancies underscore the complexity of the relationship between smoking and cardiopulmonary health outcomes, suggesting potential differences in patient populations, study methodologies, or confounding factors influencing the observed associations. Further exploration and synthesis of findings from diverse studies may yield a more comprehensive understanding of the multifaceted impact of smoking on cardiopulmonary health in CKD patients[17-19].

Despite the valuable insights gained from this study, certain limitations should be acknowledged. First, the study's cross-sectional design restricts the

establishment of causality between smoking and cardiopulmonary health outcomes. Secondly, the relatively modest sample size and the single-center nature of the study might limit the generalizability of the findings to a broader CKD patient population. Additionally, the reliance on self-reported smoking habits introduces potential recall bias. Lastly, the study did not account for the duration and intensity of smoking, which could be significant factors in understanding its impact on cardiopulmonary health.

This study also boasts several strengths, including its comprehensive assessment of a wide range of cardiopulmonary parameters and biochemical markers. The inclusion of both smokers and non-smokers within the CKD patient population allows for a nuanced examination of the impact of smoking habits. The detailed analysis of demographics, comorbidities, and medication history provides a comprehensive context for interpreting the study's findings. Lastly, the rigorous statistical analysis conducted enhances the reliability and validity of the results, contributing to a deeper understanding of the relationship between smoking and cardiopulmonary health in CKD patients.

The decision not to include healthy controls, both smokers and non-smokers, in our study was deliberate and rooted in the specific focus on chronic kidney disease (CKD) patients. Our primary objective was to investigate the nuanced impact of smoking on the cardiopulmonary health of this vulnerable population. By exclusively studying CKD patients, we aimed to provide targeted insights into the challenges faced by individuals already grappling with renal health issues. This focused approach enhances the internal validity of our findings within the context of CKD. Including healthy controls could have introduced confounding variables unrelated to CKD, potentially obscuring the specific influence of smoking on our observed cardiopulmonary parameters. While this design choice allows for a more in-depth exploration of the complexities within the CKD population, we acknowledge that it limits the direct comparison of our results with healthy cohorts. Future research, considering both CKD patients and healthy controls, can offer a broader perspective and facilitate a more comprehensive understanding of the broader implications of smoking on cardiopulmonary health.

Conclusion

In conclusion, this study provides valuable insights into the intricate relationship between smoking habits and cardiopulmonary health in patients with CKD. The comprehensive examination of baseline characteristics and cardiopulmonary parameters has shed light on the complexities of this association. Notably, our findings reveal that smoking did not exert a statistically significant impact on various cardiopulmonary parameters, suggesting that the effects of smoking on exercise capacity in CKD patients may be multifaceted and influenced by a range of individual factors. Additionally, the study's analysis of demographics, comorbidities, and medication history has enriched our understanding of the unique characteristics of this patient population. While further research is warranted to explore these relationships in greater depth and across larger cohorts, these findings underscore the importance of considering multiple variables when assessing the impact of smoking on the health of CKD patients.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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