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Association between serum creatinine levels and pulmonary function of Korean adults: the 2016-2019 Korea National Health and Nutrition Examination Survey

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[Purpose] Research on the interaction between renal and lung functions has been conducted; however, studies on the general adult population are limited. This study aimed to investigate the association between serum creatinine levels and pulmonary function in Korean adults.

[Methods] From the 2016–2019 Korean National Health and Nutrition Examination Survey, we recruited 11,380 participants who were 40 years or older for this study. Serum creatinine levels were divided into three groups: low, normal, and high. Pulmonary function was divided into three groups: normal, restrictive, and obstructive. The odds ratios for abnormal pulmonary function patterns were calculated using weighted multinomial logistic regression analysis.

[Results] The odds ratios were 0.97 for low vs. normal (0.40–2.33) and 2.00 for high vs. normal (1.18–3.38) for the restrictive pattern, and 0.12 for low vs. normal (0.02–0.49) and 1.74 for high vs. normal (0.90–3.35) for the obstructive pattern after being adjusted for age, sex, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, cardiovascular disease, total energy, and total proteins.

[Conclusion] High serum creatinine levels were associated with an increased odds ratio for restrictive and obstructive pulmonary function patterns. The odds ratio of the restrictive pattern was higher than that of the obstructive pattern. Screening for abnormal pulmonary function in individuals with high serum creatinine levels may be useful to ensure that there is no abnormal pulmonary function before the onset of potential pulmonary problems. Thus, this study highlights the relationship between renal and pulmonary function using serum creatine levels, which can be easily tested in the primary medical environment of the general population.

[Keywords] creatinine, renal function, pulmonary function, smoking status, alcohol consumption, regular exercise

INTRODUCTION

Even after recovering from COVID-19, concerns regarding potential long-term pulmonary sequelae and related dysfunction, one of the post-COVID syndromes, have been reported. According to a study by the Office for National Statistics, the proportion of patients with symptoms that persisted for five weeks after contracting COVID-19 was 21.0%; fatigue was the most common symptom, followed by coughing[1]. In addition, 20–30% of patients with mild to moderate disease and 60% of patients with severe disease showed decreased lung function due to a reduction in lung diffusing capacity[2].

Impaired lung function can also affect kidney function. In a study comprising 25 patients with stable chronic obstructive pulmonary disease with edema, it was reported that although there was no abnormality in cardiac function, the increased partial pressure of carbon dioxide caused renal vasoconstriction, resulting in decreased glomerular filtration rate and fluid retention[3]. Decreased kidney function can also affect lung function. Excess fluid is commonly observed in patients with acute renal failure, which leads to cardiac or noncardiac pulmonary edema[4]. The kidneys and lungs are physiologically linked to acid-base control, maintenance of blood pressure and fluid homeostasis, and the renin-angiotensin system[5]; however, their relationship has not been extensively studied.

In a previous study on the relationship between renal and lung function, the National Heart, Lung, and Blood Institute cohort study reported that albuminuria was associated with lung function decline in patients with chronic obstructive pulmonary disease[6]. Similarly, the National Health and Nutrition Examination Survey study of participants with chronic kidney disease showed that albuminuria was independently associated with obstructive and restrictive pulmonary function[7]. Furthermore, a study of 326 patients with type 2 diabetes mellitus revealed that renal dysfunction was associated not only with restrictive pulmonary function, but also with pulmonary diffusion function[8]. However, limited studies have confirmed the relationship between kidney and lung functions in the general population.

The glomerular filtration rate (GFR) provides the best estimation of global renal function[9]. Because GFR measurement is complex and expensive, routine evaluation of renal function is performed using endogenous biomarkers[10], of which creatinine is the most commonly used[11]. Creatinine is the final product of creatine metabolism, is present in the muscle and blood, and is mostly excreted through the kidneys. Serum creatinine levels are measured to evaluate kidney function and monitor the treatment of kidney disease[12].

In the current study, we aimed to investigate the association between serum creatinine levels and lung function in Korean adults using data from the Korea National Health and Nutrition Examination Survey (KNHANES).

METHODS

Participants

This study used pooled data from the 2016-2019 KNHANE by the Korea Disease Control and Prevention Agency (KDCA). Among 18,767 individuals aged 40 or older who underwent pulmonary function test (PFT), we excluded individuals with asthma and/or pulmonary tuberculosis, with missing creatinine and PFT data, and whose PFT could not be interpreted (Figure 1). Finally, 11,380 individuals were included in the study analysis.

Outcomes

Serum creatinine levels

Based on the serum creatinine levels, the participants were classified into a normal group when the blood concentration was 0.50 to 1.4 mg/dL, a low group when it was less than 0.50 mg/dL, and a high group when it exceeded 1.4 mg/dL[13]. The serum creatinine levels were measured using a Cobas C702 analyzer (Roche, Basel, Switzerland).

PFT

For PFT, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were assessed using the Vyntus Spiro PC spirometer (Vyaire Medical, Chicago, USA). Restrictive pattern was defined as FEV1/FVC $\geq$ 0.7 and FEV1 $<$ 80% (predicted), and obstructive pattern was defined as FEV1/FVC $<$ 0.7[14].

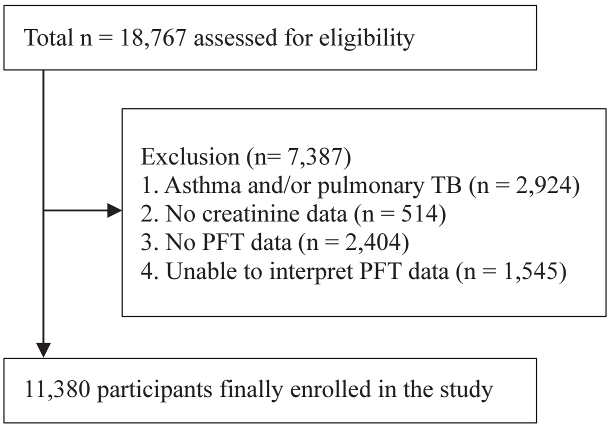

Figure 1. The selection process of study participants.

Demographic and lifestyle characteristics

The analyzed demographic and lifestyle variables were age, sex, smoking status, alcohol consumption, regular exercise, body mass index (BMI), diabetes mellitus, hypertension, cardiovascular disease, and total energy and protein levels. The demographic and lifestyle characteristics were assessed using a questionnaire. The prevalence of diabetes mellitus, hypertension, and cardiovascular disease was defined as cases diagnosed by a doctor in the health morbidity section.

Statistical analysis

Because the KNHANE is a sampling survey that uses a multi-stage stratified cluster sampling extraction method, data analysis was conducted using a complex-sample analysis that applied sample weights, strata, and clusters. To identify differences in the characteristics of participants based on serum creatinine levels, the chi-square test was used for categorical variables, and one-way ANOVA was used for continuous variables. Complex-sample logistic regression analysis was performed to confirm the association between serum creatinine levels and pulmonary function. The model was constructed in three steps. Model 1 comprised an unadjusted analysis and Model 2 was analyzed after adjusting for age, sex, smoking status, alcohol consumption, regular exercise, and BMI. Model 3 was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, BMI, diabetes mellitus, hypertension, cardiovascular disease, total energy, and total protein levels. Statistical analyses were performed using SPSS ver. 26.0 software (IBM Co., Armonk, NY, USA), and statistical significance was set at $p < 0.05$.

Ethical consideration

KNHANE was conducted with the approval of the Institutional Review Board of KDCA (2018-01-03-P-A). The KDCA exclusively offers de-identified data in accordance with the Personal Information Protection Act, so that people cannot be inferred from the survey data. KNHANES data can be downloaded from the KNHANES website[15]. Thus, no information in this study can be used to verify participants' identities.

RESULTS

Characteristics of participants according to the serum creatinine levels

Of the 11,380 participants, 4,938 (49.1%) were men and 6,442 (50.9%) were women. Their mean age was 55.8 ± 0.16 years. There were 2,720 (23.9%) individuals with abnormal lung function, 1,502 (13.2%) with restrictive patterns, and 1,219 (10.7%) with obstructive patterns.

The participants' characteristics according to their serum creatinine levels are shown in Table 1. There was a statis-

Table 1. Characteristics of the study participants.

Variable	Creatinine			
	Low	Normal	High	p value
Participants, n	117	11145	115	
Age, years	56.6 ± 1.17	55.4 ± 0.16	66.3 ± 1.15	< 0.001
Sex				< 0.001
Men	4.6	49.2	80.2	
Women	95.4	50.8	19.8	
Smoking status, %				< 0.001
Current	9.4	19.5	23.8	
Past	5.6	25.8	46.1	
No	85.0	54.7	30.1	
Alcohol consumption, %				0.060
< 1 / month	47.3	37.8	47.4	
1-4 / month	36.8	34.4	25.0	
≥ 2 / week	15.9	27.8	27.7	
Regular exercise, %				0.263
Yes	44.5	43.0	34.3	
No	55.5	57.0	65.7	
Body mass index, kg/m^2	24.3 ± 0.39	24.2 ± 0.03	25.5 ± 0.36	0.003
Diabetes mellitus, %				< 0.001
Yes	17.7	9.8	40.8	
No	82.3	90.2	59.2	
Hypertension, %				< 0.001
Yes	30.4	25.9	79.4	
No	69.6	74.1	20.6	
Cardiovascular disease, %				< 0.001
Yes	0.0	2.3	12.4	
No	100.0	97.7	87.6	
Total energy	1606.9 ± 72.28	1961.4 ± 11.98	1742.1 ± 74.93	< 0.001
Total proteins	56.5 ± 3.20	69.4 ± 0.52	63.0 ± 3.34	< 0.001
Pulmonary function*, %				< 0.001
Normal pattern	86.3	76.4	41.5	
Restrictive pattern	11.8	13.0	33.9	
Obstructive pattern	2.0	10.6	24.6	

* Restrictive pattern = FEV_1/FVC ≥ 0.7 and FEV_1 < 80% (predicted), Obstructive pattern = FEV_1/FVC < 0.7.

tically significant difference in abnormal lung function according to serum creatinine levels ($p < 0.001$), with 13.8% participants in the low group (restrictive pattern, 11.8%; obstructive pattern, 2.0%), 23.6% in the normal group (restrictive pattern, 13.0%; obstructive pattern, 10.6%), and 58.5% in the high group (restrictive pattern, 33.9%; obstructive pattern, 24.6%). Age ($p < 0.001$), sex ($p < 0.001$), smoking status ($p < 0.001$), BMI ($p = 0.003$), diabetes mellitus ($p < 0.001$), hypertension ($p < 0.001$), cardiovascular disease ($p < 0.001$), total energy ($p < 0.001$), and total proteins ($p < 0.001$) significantly differed according to the serum creatinine levels. However, no significant differences were observed in terms of alcohol consumption or regular exercise.

Distribution of FEV_1 and FVC by serum creatinine levels

Figure 2 shows the 25th, 50th (median), and 75th percentiles of the distributions of FEV_1 and FVC according to the serum creatinine levels. Overall, the normal serum creatinine group had higher FEV1 and FVC values than the low and high serum creatinine groups.

The means and standard deviations of FEV1 were 2.73

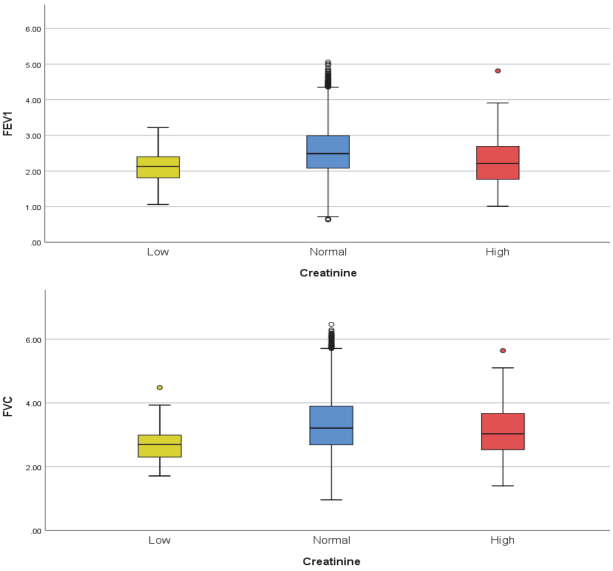

Figure 2. Distribution of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) by serum creatinine levelss.

± 0.00 in the normal group, 2.25 ± 0.04 in the low group, and 2.45 ± 0.07 in the high group, indicating a statistically significant difference (p < 0.001). The means and standard deviations of FVC were 3.52 ± 0.01 in the normal group, 2.82 ± 0.05 in the low group, and 3.29 ± 0.08 in the high group, presenting a significant difference (p < 0.001).

Association between serum creatinine levels and pulmonary function

The association between serum creatinine levels and pulmonary functions is presented in Table 2. In Model 1, the odds ratio (OR) of the restrictive pattern (OR, 4.78; 95% CI, 2.98–7.67) and obstructive pattern (OR, 4.26; 95% CI, 2.47–7.33) increased in the high group compared to that in the normal group. In Model 2, in the high group, the OR of the restrictive pattern was 2.17 (95% CI, 1.29–3.65) and the OR of the obstructive pattern was 1.49 (95% CI, 0.79–2.83). In Model 3, the ORs for the restrictive pattern and the obstructive pattern significantly increased to 2.00 (95% CI, 1.18–3.38) and 1.74 (95% CI, 0.90–3.35), respectively.

OR of abnormal patterns according to serum creatinine status by age

Sub-analysis was performed by dividing the subjects into two groups: < 60 years and ≥ 60 years (Table 3). In the <60 years group, after all the confounding variables were adjusted, the OR of the restrictive pattern (OR, 2.94; 95% CI, 1.80–4.79) and obstructive pattern (OR, 2.38; 95% CI, 0.63–8.97) was significantly increased in the high group (p < 0.001). In the ≥ 60 years, after all the confounding variables were adjusted, the ORs of restrictive and obstructive patterns increased in the high group, but it was not statistically significant.

Table 2. Odds ratio and 95% confidence intervals for abnormal patterns according to serum creatinine status.

Model	Creatinine			
	Low	Normal	High	p value
Model 1				
Normal pattern		Reference		< 0.001
Restrictive pattern	0.80 (0.40-1.57)	1	4.78 (2.98-7.67)	
Obstructive pattern	0.16 (0.05-0.53)	1	4.26 (2.47-7.33)	
Model 2				
Normal pattern		Reference		0.001
Restrictive pattern	1.12 (0.51-2.44)	1	2.17 (1.29-3.65)	
Obstructive pattern	0.15 (0.02-0.42)	1	1.49 (0.79-2.83)	
Model 3				0.004
Normal pattern		Reference		
Restrictive pattern	0.97 (0.40-2.33)	1	2.00 (1.18-3.38)	
Obstructive pattern	0.12 (0.02-0.49)	1	1.74 (0.90-3.35)	

Values are presented as odds ratio (95% confidence interval).

Table 3. Odds ratio of abnormal patterns according to serum creatinine status by age.

Model	Creatinine			
	Low	Normal	High	p value
Age < 60				
Unadjusted				< 0.001
Normal pattern		Reference		
Restrictive pattern	0.78 (0.25-2.35)	1	3.40 (1.27-9.06)	
Obstructive pattern	0.69 (0.61-0.78)	1	3.62 (0.78-16.94)	
Adjusted*				< 0.001
Normal pattern		Reference		
Restrictive pattern	1.12 (0.32-3.88)	1	2.94 (1.80-4.79)	
Obstructive pattern	1.47 (0.60-3.58)	1	2.38 (0.63-8.97)	
Age ≥ 60				
Unadjusted				< 0.001
Normal pattern		Reference		
Restrictive pattern	0.70 (0.30-1.64)	1	3.64 (2.03-6.56)	
Obstructive pattern	0.19 (0.05-0.65)	1	2.39 (1.31-4.36)	
Adjusted*				0.057
Normal pattern		Reference		
Restrictive pattern	0.85 (0.26-2.73)	1	2.41 (1.16-4.97)	
Obstructive pattern	0.18 (0.03-0.85)	1	1.63 (0.77-3.46)	

* Adjusted for age, sex, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, cardiovascular disease, total energy, and total protein.

DISCUSSION

The current study aimed to identify the association between serum creatinine levels and pulmonary function in Korean adults aged > 40 years. Complex-sample logistic regression analysis showed that the OR for restrictive and obstructive lung function significantly increased in the group with high serum creatinine levels. This phenomenon was observed even after adjusting for confounding variables, such as age, sex, smoking status, alcohol consumption, regular exercise, BMI, diabetes mellitus, hypertension, cardiovascular disease, total energy, and total protein levels. In particular, the OR for the restrictive pulmonary function pattern was higher than that for the obstructive pattern.

Previous studies have shown a similar relationship between renal and lung function. In a study comprising 1246 men, Jung et al.[14] revealed that male smokers had lower FEV1 and FVC in cases of albuminuria. Yu et al.[16] found that in a cohort comprising 1454 Australian and 5824 Chinese individuals, an increased risk of reduced renal function was related to obstructive lung function, and that FEV1 and FVC < 3.05 L increased the risk of impaired renal function. A small Japanese study also reported that reduced GFR is associated with reduced pulmonary diffusing capacity[17]. In another retrospective longitudinal analysis, an increased risk of chronic kidney disease was associated with decreased airflow as measured by the FEV1/FVC ratio[18].

Although the mechanism of the complex interaction between the kidneys and lungs has not been clearly elucidated, systemic inflammation and oxidative stress have been shown to play important roles[19,20]. Alge et al.[21], who highlighted the interactions between the kidney and lungs in critically ill patients, reported that acute kidney injury (AKI) increased the generation of inflammatory cytokines, such as interleukin-6 (IL-6), causing increased trafficking of lymphocytes and neutrophils to the lungs, which contributed to the acute response distance syndrome. Klein et al.[22] also found that IL-6 contributes to lung injury after AKI in a study in wild-type mice. Furthermore, Ahuja et al.[23] revealed that IL-6 deletion or blockade reduced lung inflammation and injury following renal ischemia-reperfusion injury.

IL-6 is a pro-inflammatory cytokine that is elevated in the serum of patients with AKI and is associated with a higher risk of death[24]. Nakazawa et al.[25] investigated the association between severe AKI and multiorgan dysfunction and stated that neutrophil extracellular trap (NET) formation due to renal necroinflammation leads to organ dysfunction through cytokine and histone release. Neutrophils are a type of white blood cells and front-line immune cells against the invasion of pathogens in blood vessels[26]. Neutrophils traverse the bloodstream and detect and devour an invading pathogen. However, when it is no longer possible to fight the pathogen, as a last resort, they act as a NET to trap pathogens by spouting out their DNA like a net[27]. NETs are net-like structures composed of DNA-histone complexes and antibacterial peptides[28].

In another study, mice with AKI had a lower oxygen saturation and higher bacterial load than mice without AKI in a mouse model of *Pseudomonas aeruginosa* inhalation-induced AKI[29]. In addition, increased expression of genes that lead to apoptosis in the lungs has been observed in animal models of acute renal injury and acute renal failure[30]. This explains the possibility that the increase in oxidative stress in the lungs, promoted by acute renal failure and the induction of apoptosis, may have affected the deterioration of lung function.

In the sub-analysis according to age in this study, the OR of the restrictive and obstructive patterns was significantly increased in the high group compared to that in the normal group in the < 60 years of age. However, no statistically significant results were obtained in the ≥ 60 years of age. Further studies are required to determine the differences in results according to age.

The current study has some limitations. First, since this was a cross-sectional study, it was difficult to infer a causal relationship between renal and lung function. In the future, a prospective cohort study is needed to determine the causes. Second, there is a possibility that subjective judgment was involved because some variables were based on a questionnaire.

Despite these limitations, this study is meaningful in that it evaluated the relationship between renal and pulmonary function using serum creatine levels, which can be easily tested in the primary medical environment based on data with a guaranteed representation of the general population. Screening for abnormal pulmonary function in individuals with high serum creatinine levels may be useful to ensure that there is no abnormal pulmonary function before the onset of potential pulmonary problems. Understanding the link between the kidneys and lungs could potentially improve the health outcomes of patients and guide healthcare providers to better understand when and how to manage a possible decline in lung function due to kidney disease.

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