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Association Between Decreased Renal Function and Pulmonary Function Decline in Community-dwelling Adults

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Abstract. *Background/Aim: Emerging evidence suggests that there is a close relationship between the human lung and kidney. This study evaluated whether decreased renal function was associated with accelerated pulmonary function decline in a large-scale community-based cohort. Patients and Methods: A total of 10,028 subjects of the prospective Ansung-Ansan cohort were eligible for the longitudinal analysis of changes in pulmonary function associated with decreased renal function (glomerular filtration rate <60 ml/min/1.73 m^2). Logistic regression analysis was performed to evaluate factors associated with decreased baseline renal function, and a linear mixed model compared changes in pulmonary function in participants with and without decreased renal function after propensity score matching (PSM). Results: At baseline, subjects with and without decreased renal function showed distinct characteristics, and the factors associated with decreased renal function were age, baseline forced vital capacity, hypertension, and white blood cell (WBC) count. A 1:4 PSM of age, sex, body mass index, and smoking status showed that the proportion of those with hypertension and the WBC count differed between the patients with decreased and normal renal function. In the PSM population, those with decreased renal function had a greater decline in forced expiratory volume in the first second (FEV1) than those without (p=0.0402); however, these differences were not found to be evident when hypertension and WBC count were further matched (p=0.0807). Conclusion: The results of our study demonstrated that decreased renal function was not directly associated with the rapid decline in pulmonary function in a community-based general population setting.*

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Key Words: Chronic kidney disease, pulmonary function test, decline, association.

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Pulmonary function is an objective index to measure the capacity of the human lung that can be evaluated using a number of assessments, including spirometry, total lung volume, and diffusing capacity for carbon monoxide (1). The investigation of the pattern of abnormalities present in the lung and further investigations are conducted using forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and the ratio of FEV1 to FVC (FEV1/FVC) (2). Traditionally acknowledged factors influencing pulmonary function include age, sex, weight, height, and ethnicity; however, other factors could also affect the spirometry results (3). For instance, chronic inflammation is linked to decreased lung function, and it is determined by increased levels of acute inflammatory mediators, such as C-reactive protein and interleukin-6 (4, 5).

Chronic kidney disease (CKD) is a medical condition that could have various aetiologies that are characterised by decreased renal function or renal damage (6). CKD is defined by the presence of laboratory markers of kidney injury or a decrease in glomerular filtration rate (GFR) to <60 ml/min/1.73 m^2 for 3 months; a GFR cut-off value of 60 is used to classify patients into CKD stage three and above (7, 8). The most common causes of CKD are hypertension (HTN) and diabetes mellitus (DM); however, glomerular diseases or other causes may also lead to renal function impairment (9). In general, CKD is regarded as a hyperinflammatory state associated with sustained low-grade inflammation (10). Increased levels of pro-inflammatory cytokines, chemokines, and cell adhesion molecules are observed in patients with CKD, and it was shown that

targeting these molecules could be clinically beneficial, thus emphasising that chronic inflammation plays an important role in CKD (11).

In individuals with chronic kidney disease (CKD), a prevalent issue is the decline in lung function, and research suggests a strong connection with chronic fluid overload (12). When the glomerular filtration rate (GFR) decreases, pulmonary oedema and respiratory muscle dysfunction are more common, due to fluid retention and metabolic, endocrine and cardiovascular changes (12, 13). In addition, chronic systemic inflammation is associated with decline of both pulmonary and renal functions, and growing insights suggest their association (14), the decrease in pulmonary function could be also aggravated in patients with impaired renal function; however, such an association has not been described. Thus, we aimed to evaluate the relationship between decreased GFR (defined as <60 ml/min/1.73 m^2) and pulmonary function decline by using a large-scale community-based database.

Patients and Methods

Study population. Data from the Ansan-Ansung cohort included in the Korean Genome and Epidemiology Study (KoGES), a series of large community-based epidemiological surveys investigating chronic diseases in Koreans, were analysed. In this cohort, 10,030 individuals aged 39-70 years were enrolled in 2001-2002 and were prospectively observed during the 12-year investigation period, with assessments performed every two years. Detailed information on the study design and relevant protocols has been previously published (14). In the present study, two patients who did not have data on kidney function were excluded, and 10,028 subjects were analysed. The Korea Centre for Disease Control and Prevention obtained written informed consent from all participants regarding the collection of their data, and the Institutional Review Board of Korea Ansan Hospital (IRB No. 2019AS0102) approved the study. All methods were performed in accordance with relevant national guidelines and regulations.

Lung function assessment by spirometry. Pulmonary function tests were performed by a skilled technician using a portable spirometer (Vmax-2130, Sensor Medics, Yorba Linda, CA, USA) according to standardised protocols set by the 1994 recommendations of the American Thoracic Society (ATS) (15). The participants underwent a pre-bronchodilator test on completing at least three repeated measurements; the participants showing absolute differences within 0.15 litre (l) between the largest and the next largest FVC and FEV_1 values were included. Calibration and quality control of spirometry tests assessing measures of lung function, including FEV1 (in l), FVC (in l), and FEV1/FVC, were regularly performed based on the ATS guidelines.

Covariates and definition of decreased renal function. The assessed covariates were age; sex; height; weight; body mass index (BMI); smoking and alcohol status (categorised into current, ex-, and never); and comorbid diseases, including HTN, DM, and dyslipidaemia, based on a comprehensive health assessment and prescribed medications. The evaluated laboratory values included white blood cell (WBC) count and levels of C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase, alanine aminotransferase, and sodium (Na). Decreased renal function was defined as a GFR of <60 ml/min/1.73 m^2, which was calculated according to the Modification of Diet in Renal Disease Study equation (16).

Statistical analysis. Among the descriptive characteristics, categorical variables are reported as numbers and percentages, whereas continuous variables are expressed as mean±standard deviation. Independent *t*-tests and chi-square tests were performed for continuous and categorical variables, respectively, as indicated. Multivariate analyses using a logistic regression model were performed to evaluate predictors of decreased renal function at baseline and are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). In addition, given that there was a substantial difference in the baseline characteristics between patients with GFR <60 ml/min/1.73 m^2 and those with GFR ≥60 ml/min/1.73 m^2, a 1:4 propensity score matching (PSM) according to baseline covariates including age, sex, body mass index, smoking history, and smoking status (pack-years) was applied to adjust for the differences, using the nearest neighbour method within a calliper of 0.25 of the propensity score. In an additional analysis to further adjust for differences in HTN and WBC count, 1:2 PSM was performed. Finally, linear mixed-model analyses were used to determine the best fit for the decrease in spirometric measures over time. Statistical analyses were performed using Stata statistical software version 14.2 (StataCorp LP, College Station, TX, USA), and *p*-values <0.05 were considered statistically significant.

Results

Characteristics of patients with and without decreased renal function. A comparison of baseline characteristics between subjects with GFR ≥60 ml/min/1.73 m^2 and those with GFR <60 ml/min/1.73 m^2 indicated that those with decreased renal function were older, were less frequently of the female sex, and had higher BMIs. In addition, the proportion of current smokers and drinkers was higher among those with decreased renal function. With regard to pulmonary function and comorbid diseases, baseline FEV1, FVC, and FEV1/FVC were also lower in the decreased renal function group, whereas HTN and DM were more common. In addition, the results of blood tests revealed that the group with decreased renal function had a higher WBC count and higher levels of CRP, BUN, Cr, and Na (Table I).

Among men, those with decreased renal function had higher ages and BMIs, and there was a higher percentage of current smokers and drinkers. However, a comparison of pulmonary function and comorbidities revealed that only FEV1 and FVC differed, and HTN was more common in the decreased renal function group. A comparison of laboratory results revealed a significantly higher WBC count and higher CRP, BUN, and Cr levels among those with decreased renal function. Contrastingly, in women, those with decreased

Table I. *Baseline characteristics of patients based on the cut-off of GFR 60 ml/min/1.73 m^2.*

Demographics	Total			Male			Female		
	GFR ≥60 ml/min/ 1.73 m^2 group (N=9,805)	GFR <60 ml/min/ 1.73 m^2 group (N=223)	*p*-Value	GFR ≥60 ml/min/ 1.73 m^2 group (N=4,668)	GFR <60 ml/min/ 1.73 m^2 group (N=88)	*p*-Value	GFR ≥60 ml/min/ 1.73 m^2 group (N=5,137)	GFR <60 ml/min/ 1.73 m2 group (N=135)	*p*-Value
Age	52.077±8.847	61.399±7.799	<0.0001	51.728±8.760	58.227±8.414	<0.0001	52.394±8.914	63.467±6.624	<0.0001
Female sex	4668 (47.61%)	88 (39.46%)	0.0160			n/a			n/a
Height, cm	160.042±8.639	157.276±8.979	<0.0001	166.868±5.845	166.366±4.876	0.3427	153.839±5.530	151.350±5.337	<0.0001
Weight, kg	63.014±10.089	62.750±10.706	0.7012	67.462±9.774	69.945±8.971	0.0188	58.974±8.556	58.114±9.062	0.2496
BMI, kg/m^2	24.560±3.147	25.268±3.074	0.0009	24.179±2.925	25.202±2.747	0.0012	24.907±3.299	25.309±3.277	0.1613
Smoking status			0.0090			0.0370			0.2230
Current smoker	5,664 (58.55%)	144 (65.45%)		893 (19.23%)	20 (23.26%)		4,771 (94.85%)	124 (92.54%)	
Ex-smoker	1,499 (15.50%)	39 (17.73%)		1,434 (30.88%)	35 (40.70%)		65 (1.29%)	4 (2.99%)	
Never smoker	2,511 (25.96%)	37 (16.82%)		2,317 (49.89%)	31 (36.05%)		194 (3.86%)	6 (4.48%)	
Alcohol drinking status			<0.0001			<0.0001			0.0160
Current drinker	4,467 (45.97%)	129 (58.64%)		854 (18.39%)	24 (27.59%)		3,613 (71.21%)	105 (78.95%)	
Ex-drinker	628 (6.46%)	24 (10.91%)		474 (10.21%)	17 (19.54%)		154 (3.04%)	7 (5.26%)	
Never drinker	4,622 (47.57%)	67 (30.45%)		3,315 (71.40%)	46 (52.87%)		1,307 (25.76%)	21 (15.79%)	
Pulmonary function									
Baseline FEV1, l	2.899±0.700	2.428±0.693	<0.0001	3.334±0.645	3.007±0.642	<0.0001	2.499±0.473	2.038±0.387	<0.0001
Baseline FVC, l	3.647±0.895	3.128±0.886	<0.0001	4.279±0.706	3.962±0.706	<0.0001	3.066±0.614	2.565±0.437	<0.0001
Baseline FEV1/FVC, %	79.868±7.788	78.137±9.180	0.0071	77.895±8.386	76.094±10.403	0.1162	81.683±6.699	79.516±8.006	0.0031
Comorbid disease									
Hypertension	1,447 (14.76%)	106 (47.53%)	<0.0001	605 (12.97%)	44 (50.00%)	<0.0001	842 (16.40%)	62 (45.93%)	<0.0001
Diabetes mellitus	646 (6.59%)	29 (13.00%)	<0.0001	348 (7.46%)	11 (12.50%)	0.0760	298 (5.80%)	18 (13.33%)	<0.0001
Dyslipidemia	242 (2.47%)	2 (0.90%)	0.1320	143 (3.06%)	1 (1.14%)	0.5240	99 (1.93%)	1 (0.74%)	0.5210
Laboratory data									
Blood tests									
WBC count, 10^3/μl	6.552±1.818	7.147±2.075	<0.0001	6.805±1.863	7.261±1.984	0.0231	6.322±1.746	7.073±2.137	<0.0001
C-reactive protein, mg/dL	0.237±0.538	0.330±0.527	0.0109	0.252±0.548	0.404±0.707	0.0480	0.224±0.529	0.282±0.360	0.0705
BUN, mg/dl	14.248±3.565	19.761±7.964	<0.0001	14.951±3.595	20.974±7.337	<0.0001	13.609±3.414	18.970±8.279	<0.0001
Creatinine, mg/dl	0.831±0.166	1.366±0.942	<0.0001	0.939±0.159	1.627±1.289	<0.0001	0.733±0.097	1.196±0.563	<0.0001
AST, IU/l	29.834±18.676	29.700±11.924	0.8697	32.765±22.796	31.739±15.043	0.5325	27.171±13.369	28.370±9.173	0.1415
ALT, IU/l	28.163±26.744	26.789±16.244	0.2216	33.407±33.533	32.716±21.599	0.7697	23.394±17.192	22.926±9.805	0.5943
Na, mmol/l	142.537±2.198	143.045±2.149	0.0006	142.794±2.189	142.648±2.123	0.5341	142.303±2.179	143.304±2.135	<0.0001

GFR: Glomerular filtration rate; BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; WBC: white blood cell; BUN: blood urea nitrogen; AST, aspartate aminotransferase; ALT: alanine aminotransferase; Na: sodium.

Table II. *Factors associated with decreased renal function at baseline.*

	Univariate model		Multivariate model	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Demographics				
Age	1.139 (1.118-1.161)	<0.0001	1.124 (1.097-1.151)	<0.0001
Female sex	1.338 (1.018-1.759)	0.037		
BMI	1.074 (1.031-1.119)	0.0007		
Smoking status				
Current smoker	Ref			
Ex-smoker	1.061 (0.741-1.521)	0.7464		
Never smoker	0.599 (0.416-0.864)	0.006		
Alcohol drinking status				
Current drinker	Ref			
Ex-drinker	1.354 (0.868-2.112)	0.1811		
Never drinker	0.500 (0.370-0.677)	<0.0001		
Pulmonary function test				
Baseline FEV1	0.464 (0.387-0.556)	<0.0001		
Baseline FVC	0.337 (0.269-0.422)	<0.0001	0.081 (0.654-0.991)	0.0410
Baseline FEV1/FVC	0.974 (0.959-0.990)	0.0012		
Comorbid disease				
Hypertension	5.159 (3.931-6.770)	<0.0001	2.925 (2.105-4.064)	<0.0001
Diabetes mellitus	2.171 (1.457-3.235)	0.0001		
Dyslipidemia	0.374 (0.093-1.515)	0.1683		
Laboratory data				
Blood tests				
WBC count	1.163 (1.093-1.238)	<0.0001	1.160 (1.075-1.251)	0.0001
C-reactive protein	1.156 (1.023-1.307)	0.0197		
AST	1.000 (0.993-1.007)	0.9886		
ALT	0.998 (0.990-1.005)	0.5212		
Na	1.113 (1.043-1.188)	0.0013		

GFR: Glomerular filtration rate; OR: odds ratio; CI: confidence interval; BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; WBC: white blood cell; AST, aspartate aminotransferase; ALT: alanine aminotransferase; Na: sodium; Ref: reference.

renal function were older and were less often current drinkers. In line with the results of the total population, women with decreased renal function had significantly lower FEV1, FVC, and FEV1/FVC ratios, as well as higher rates of HTN and DM. Regarding laboratory data, in the decreased renal function group, a higher WBC count and higher BUN, Cr, and Na levels were observed (Table I).

Predictors of decreased renal function at baseline and propensity-score matching. The results of the multivariate logistic regression analysis were as follows: age (OR=1.124, 95% CI=1.097-1.151, $p<0.0001$), baseline FVC (OR=0.081, 95% CI=0.654-0.991, $p=0.0410$), HTN (OR=2.925, 95% CI=2.105-4.064, $p<0.0001$), and WBC count (OR=1.160, 95% CI=1.075-1.251, $p=0.0001$) (Table II).

In the PSM population, the baseline characteristics of patients with decreased renal function differed in terms of the comorbidity of HTN, WBC count, BUN, and Cr levels. On the other hand, in this population, men with decreased renal function had HTN more frequently as well as higher BUN and Cr levels, and women with decreased renal function had lower baseline FEV1 and FVC, a higher frequency of HTN, and higher laboratory levels of WBC count, BUN, and Cr (Table III).

Pulmonary function changes in patients with decreased renal function and without. Figure 1A-C shows the changes in absolute values of FVC and FEV1 during the follow-up period. Patients with decreased renal function showed a significantly higher decline in FEV1 than those with normal renal function ($p=0.0402$), whereas the changes in FVC and FEV1/FVC were comparable ($p=0.7582$ and $p=0.1911$, respectively). However, when additional matching with HTN and WBC count was performed, the slope plot demonstrated that the differences in FEV1, FVC, and FEV1/FVC were not evident in the longitudinal analysis (Figure 1D-F).

Discussion

Although studies have demonstrated that decreased pulmonary function is associated with an early decline in kidney function, to the best of our knowledge, the association between

Table III. *Characteristics of patients after 1:4 propensity-score matching.*

Demographics	Total			Male			Female		
	GFR ≥60 ml/min/ 1.73 m^2 group (N=875)	GFR <60 ml/min/ 1.73 m^2 group (N=219)	*p*-Value	GFR ≥60 ml/min/ 1.73 m^2 group (N=343)	GFR <60 ml/min/ 1.73 m^2 group (N=86)	*p*-Value	GFR ≥60 ml/min/ 1.73 m^2 group (N=532)	GFR <60 ml/min/ 1.73 m^2 group (N=133)	*p*-Value
Age	61.449±7.998	61.406±7.801	0.9433	58.367±8.884	58.314±8.451	0.9599	63.436±6.661	63.406±6.653	0.9629
Female sex	343 (39.20%)	86 (39.27%)	0.9850			n/a			n/a
Height	156.594±9.081	157.303±9.015	0.3014	165.377±5.746	166.488±4.794	0.0671	150.932±5.702	151.363±5.376	0.4307
Weight	61.711±10.696	62.661±10.744	0.2405	69.020±9.353	69.898±9.012	0.4337	56.999±8.672	57.982±9.065	0.2471
BMI	25.070±3.144	25.222±3.066	0.5190	25.186±2.749	25.185±2.759	0.9979	24.994±3.375	25.246±3.260	0.4393
Smoking status			0.7780			0.8530			0.7800
Current smoker	562 (64.23%)	144 (65.75%)	76 (22.16%)	20 (23.26%)		486 (91.35%)	124 (93.23%)		
Ex-smoker	147 (16.80%)	38 (17.35%)	132 (38.48%)	35 (40.70%)		15 (2.82%)	3 (2.26%)		
Never smoker	166 (18.97%)	37 (16.89%)	135 (39.36%)	31 (36.05%)		31 (5.83%)	6 (4.51%)		
Drinking status			0.3970			0.2180			0.6290
Current drinker	517 (59.29%)	128 (58.72%)	75 (22.06%)	23 (26.74%)		442 (83.08%)	105 (79.55%)		
Ex-drinker	68 (7.80%)	23 (10.55%)	49 (14.41%)	17 (19.77%)		19 (3.57%)	6 (4.55%)		
Never drinker	287 (32.91%)	67 (30.73%)	216 (63.53%)	46 (53.49%)		71 (13.35%)	21 (15.91%)		
Pulmonary function									
Baseline FEV1	2.504±0.669	2.428±0.696	0.1416	106.205±17.370	103.824±18.487	0.2656	2.155±0.421	2.031±0.385	0.0028
Baseline FVC	3.206±0.859	3.131±0.890	0.2624	101.488±15.270	99.518±16.229	0.2947	2.698±0.503	2.560±0.439	0.0054
Baseline FEV1/FVC	78.614±8.078	78.053±9.157	0.4175	76.265±8.129	76.094±10.403	0.8882	80.143±7.674	79.395±7.963	0.3335
Comorbid disease									
Hypertension	249 (28.49%)	104 (47.49%)	<0.0001	81 (23.68%)	43 (50.00%)	<0.0001	168 (31.58%)	61 (45.86%)	0.0020
Diabetes mellitus	96 (10.98%)	29 (13.24%)	0.3480	43 (12.57%)	11 (12.79%)	0.9570	53 (9.96%)	18 (13.53%)	0.2330
Dyslipidemia	28 (3.20%)	2 (0.91%)	0.0640	14 (4.09%)	1 (1.16%)	0.3230	14 (2.63%)	1 (0.75%)	0.3260
Laboratory data									
Blood tests									
WBC count, 10^3/μl	6.599±1.790	7.143±2.086	0.0005	6.945±1.736	7.265±2.005	0.1394	6.376±1.790	7.064±2.141	0.0008
C-reactive protein, mg/dl	0.266±0.538	0.319±0.485	0.1844	0.314±0.770	0.371±0.628	0.4685	0.235±0.304	0.285±0.362	0.1456
BUN, mg/dl	14.805±3.428	19.611±7.589	<0.0001	15.464±3.468	20.627±6.193	<0.0001	14.380±3.337	18.953±8.326	<0.0001
Creatinine, mg/dl	0.819±0.159	1.315±0.528	<0.0001	0.945±0.157	1.498±0.402	<0.0001	0.738±0.094	1.196±0.566	<0.0001
AST, IU/l	29.097±11.658	29.785±12.012	0.4376	31.096±12.391	31.930±15.165	0.6378	27.808±10.981	28.398±9.234	0.5270
ALT, IU/l	26.866±17.132	26.849±16.381	0.9895	31.656±20.510	32.942±21.794	0.6080	23.778±13.703	22.910±9.871	0.4053
Na, mmol/l	142.790±2.148	143.046±2.150	0.1151	142.522±2.251	142.686±2.127	0.5413	142.962±2.062	143.278±2.140	0.1174

GFR: Glomerular filtration rate; BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; WBC: white blood cell; BUN: blood urea nitrogen; AST, aspartate aminotransferase; ALT: alanine aminotransferase; Na: sodium.

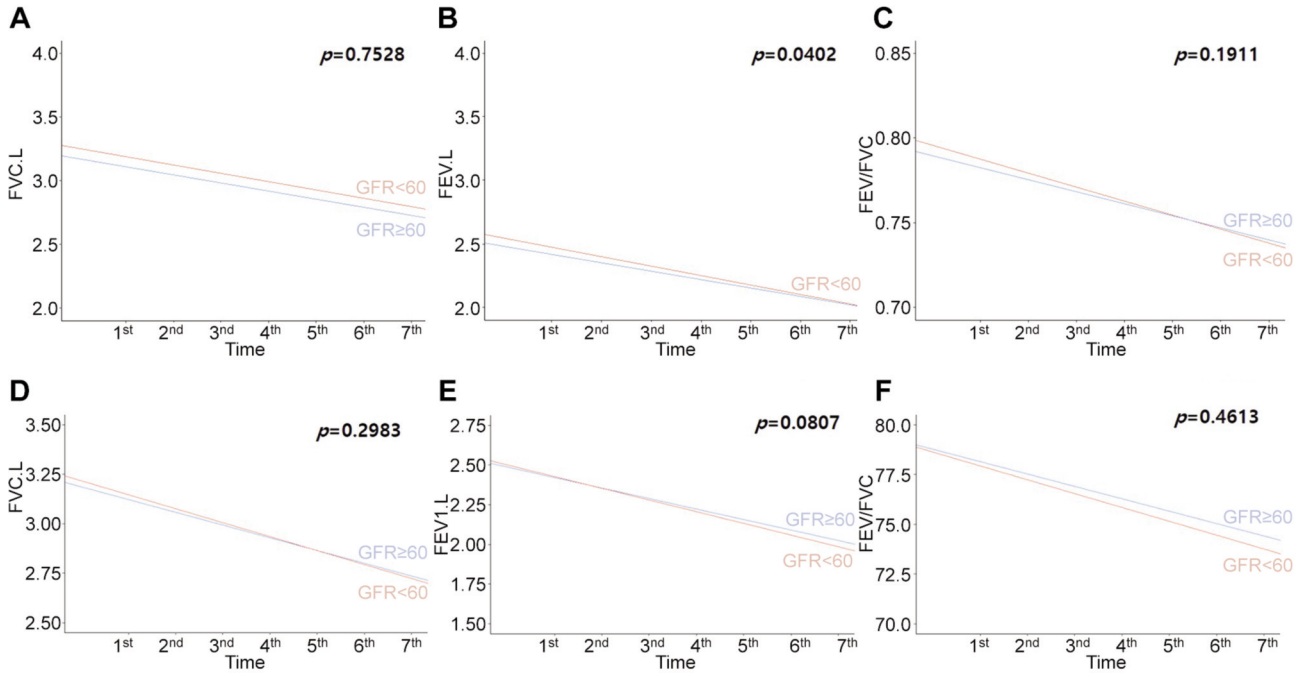

Figure 1. *Lung function decline in patients with and without decreased kidney function using linear mixed model. (A) Slope figure of the linear mixed model after 1:4 propensity matching of age, sex, BMI, and smoking status for FVC. (B) Slope figure of the linear mixed model after 1:4 propensity matching of age, sex, BMI, and smoking status for FEV1. (C) Slope figure of the linear mixed model after 1:4 propensity matching of age, sex, BMI, and smoking status for FEV1/FVC. (D) Slope figure of the linear mixed model after 1:2 propensity matching of age, sex, BMI, smoking status, hypertension, and WBC count for FVC. (E) Slope figure of the linear mixed model after 1:2 propensity matching of age, sex, BMI, smoking status, hypertension, and WBC count for FEV1. (F) Slope figure of the linear mixed model after 1:2 propensity matching of age, sex, BMI, smoking status, hypertension, and WBC count for FEV1/FVC. FEV1, Forced expiratory volume in the first second; FVC: forced vital capacity; WBC: white blood cell; BMI, body mass index.*

decreased renal function and alterations in pulmonary function measures has not been investigated. By using data from a large prospective community-based cohort, we investigated the relationship between decreased renal function and pulmonary function decline. Patients with decreased renal function had distinct clinical characteristics compared to those without decreased renal function. Furthermore, the relevant factors associated with decreased renal function at baseline were age, FVC, HTN, and WBC count. Finally, the differences in the clinical factors appeared to decrease substantially after PSM; however, the differences in WBC count and HTN existed. In the population that underwent additional matching, subjects with decreased renal function did not present an expedited reduction in pulmonary function.

On the contrary, some previous studies have suggested that chronic kidney disease (CKD) is more comorbid in individuals with low lung function and respiratory disease (17-19). These studies have proposed numerous pathophysiological mechanisms that contribute to this association. Many risk factors are common to both diseases, such as older age, smoking, higher levels of inflammatory markers (20) and systemic chronic inflammatory comorbidities, such as HTN and DM (21), which can affect the lungs and airways causing direct organ damage or inducing the development of endothelial dysfunction contributing to the strong association between Chronic obstructive pulmonary disease (COPD) and CKD (22). However, the association of reduced lung function with adverse kidney outcomes still remained statistically significant even after accounting for various potential confounders.

The comparison of baseline characteristics revealed a clear disparity between subjects with GFR <60 ml/min/1.73 m^2 and those with ≥60 ml/min/1.73 m^2. Briefly, patients with decreased renal function had a higher age, included a greater proportion of men, higher BMIs, and a greater proportion of current smokers and drinkers. Intriguingly, patients with decreased renal function had poor pulmonary function, suggesting a potential link between renal and pulmonary functions. In particular, in both men and women, significantly lower values of FEV1 and FVC were observed, whereas these differences appeared to decrease in the PSM population. Moreover, comorbidities, such as HTN and DM, were more frequent in the decreased renal function group at baseline; there is abundant evidence illustrating augmented inflammation in HTN and DM (23, 24). Corroborating the available evidence,

more subjects with decreased renal function had elevated inflammatory markers of WBC and C-reactive protein compared to those without decreased renal function.

Despite adjusting for the baseline factors of age, sex, BMI, and smoking status, differences in comorbidities, such as HTN and WBC count, were continuously observed. The early decrease in FEV1 in subjects with decreased renal function compared to those with normal renal function in this prospective observational study seems to be attributable to several factors. First, heightened inflammation is now regarded as a state that can result in endothelial dysfunction, potentially affecting airway resistance (25). As a growing body of evidence suggests the presence of a higher degree of inflammation in the presence of decreased renal function (26), the pro-inflammatory setting could have resulted in a rapid decline in FEV1. Second, although the cause remains uncertain, systemic inflammation may modulate pulmonary function in an intrinsic manner (5, 27). Third, HTN could be relevant to the reduction of pulmonary function, as described by Miele *et al*. and Schnabel *et al*. (28, 29). Supporting this assumption, the baseline factors associated with decreased renal function included WBC count and HTN. Therefore, the greater decrease in FEV1 in patients with decreased renal function may not be a direct cause of kidney impairment. Indeed, in a further analysis adjusting for the differences in HTN and WBC count, the decrease in FEV1 in the total population was not apparent.

Our results suggest that although a profound interaction exists between kidney and lung function, this may be mediated by the presence of inflammation and comorbid diseases and may not have a causal relationship. Therefore, although it could be generally suggested that patients with poor renal function require regular follow-up with regard to an earlier decrease in pulmonary function, the presence of inflammation and comorbidities such as HTN should be systematically evaluated. In particular, given that pulmonary function gradually decreases as a consequence of aging and is aggravated in men and following exposure to smoking (17, 30, 31), the influence of decreased renal function in a susceptible population, which requires continuous screening and consultation, remains to be better understood. Therefore, further large-scale studies are required to evaluate whether decreased renal function affects pulmonary function, especially in older patients and those who smoke.

An advantage of the present study is that it is the first to investigate whether decreased renal function is related to accelerated pulmonary function decline. However, there are several limitations. First, although the number of subjects was large at baseline, those being followed-up decreased gradually during the follow-up period and was small at the end of the observation period. Second, due to the limitations of the study design, we could only demonstrate an association and not establish a causal relationship. Additional investigations are required to analyse the causal relationship between decreased renal function and the accelerated decline in pulmonary function. Third, the precise cause of decreased renal function could not be identified, as this information was not provided in the Ansung–Ansan cohort database.

Conclusion

Decreased renal function was not directly associated with a rapid decline in pulmonary function in a community-based general population setting, but appeared to be affected by the presence of systemic inflammation and comorbidity of HTN.

Conflicts of Interest

The Authors declare that no conflicts of interest exist.

Authors' Contributions

Conceptualization: SSA and CYK, Data curation: SSA, JY, HSL, and CYK, Formal analysis: JY and HSL, Funding acquisition: None, Investigation: SSA, JY, and CYK, Methodology: SSA, JY, HSL, and CYK, Project administration: SSA, JY, HSL, and CYK, Resources: SSA and CYK, Software: SSA, JY, HSL, and CYK, Supervision: HSL, Validation: JY and HSL, Visualization: SSA, JY, and CYK, Writing - original draft: SSA and CYK, Writing - review & editing: SSA, JY, HSL, and CYK.

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