Original Article
Renal impairment in patients with chronic obstructive pulmonary disease: a retrospective observational study

Shihong Li[1], Liming Zhang[1], Yajuan Zhang[2], Ye Gu[2,3], Baosen Pang[1], Yingmin Ma[1]

[1]Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing Institute of Respiratory Diseases, Beijing 100020, China; [2]Department of Respiratory Medicine, General Hospital of Chinese People's Armed Police Forces, Beijing 10039, China; [3]Department of Emergence, Beijing ChuiYangLiu Hospital Affiliated to Tsinghua University, Beijing 100022, China

Abstract: We evaluated the impact of renal impairment on lung function, frequency of acute exacerbations, and quality of life of patients with chronic obstructive pulmonary disease (COPD). This retrospective observational study was conducted at the Beijing Chaoyang Hospital, China, from Jan. 2012 to Dec. 2015. A total of 182 COPD patients were stratified into four groups based on disease severity and followed for up to one year. Indicators of renal injury (proteinuria and estimated glomerular filtration rate [eGFR]) were measured. Questionnaire surveys (COPD assessment test [CAT], quality of life assessment [British Medical Research Council, mMRC]), lung function, and 6-min walking distance (6WMD) were conducted every three months. The prevalence of renal impairment increased with COPD severity class (X^2 = 10.823, P = 0.013). COPD patients with renal impairment had significantly worse lung functions, CAT and mMRC scores, 6WMD, and increased frequency of exacerbations compared with patients without renal injury. In summary, impaired renal function is a common aggravating factor in patients with COPD which negatively affects lung function, increases frequency of exacerbations, and impairs the quality of life of patients with COPD.

Keywords: Chronic obstructive pulmonary disease, exacerbation, renal disease, risk factor

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disorder characterized by irreversible airway obstruction. According to WHO estimates, COPD is poised to become the third leading cause of death, and the fifth leading contributor to overall morbidity burden by the year 2020 [1]. Extrapulmonary comorbid conditions are aggravating factors in these patients [2, 3]. The screening and treatment of associated comorbidity is an important aspect of management of patients with COPD.

Renal impairment is often seen in COPD patients, and may largely be attributable to smoking and older age [4-6]. However, the correlation and mutual effect of renal impairment and COPD is not well-characterized. A recent study showed a higher prevalence of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR), in patients with COPD, as compared to those that did not suffer from COPD [7]. The prevalence of renal impairment differed in different regions, and by sex and study populations [4]. It is noteworthy that eGFR determined by creatinine was shown to underestimate the prevalence of CKD in COPD patients [7]. In a recent study, acute kidney injury (AKI) was shown to predict in-hospital mortality in older adult men with multiple comorbid conditions who were hospitalized because of acute exacerbation of COPD [8]. Similar results were also reported by Barakat *et al.* [9]. However, the association between renal impairment and severity of COPD is not well-characterized.

In this prospective observational study, we sought to evaluate the impact of renal impairment on lung function, quality of life and frequency of acute exacerbations of COPD patients based on different severity categories in Chinese population.

Materials and methods

Patients

A total of 182 patients with COPD who were treated as out-patient or in-patient at the authors' institution between Jan. 2012 to Dec. 2015 were enrolled in this retrospective observational study. Patients with the following conditions were excluded: 1) Acute or chronic nephritis-associated primary kidney injury; 2) Secondary renal impairment due to hypertension, diabetes, systemic lupus erythematosus nephritis, or multiple myeloma; 3) Multiple organ dysfunction; 4) Age > 80 years; 5) Myocardial infarction or congenital heart disease.

All patients were categorized according to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [10]. The diagnosis of acute exacerbation of COPD (AECOPD) was based on GOLD 2011 guidelines [10]. All patients had an acute alteration in baseline status of dyspnea, cough, or sputum which was beyond the normal variability, and which was sufficient to warrant a change in therapy.

The study was approved by the authors' Institutional Review Board. Informed consent was obtained from all patients or guardians prior to enrollment.

Measurements

Lung function tests: Lung function tests were performed for each patient every three months. The test was repeated at least three times. The maximal volume of air exhaled in the first second of a forced expiration (FEV1) was recorded. Vital capacity (VC) and forced expiratory volume (FEV) were measured by body plethysmography. Predicted normal values for FEV1 percent (FEV1%) and FEV/FVC percent (FEV/FVC%) were calculated based on age, height, weight and reference equations.

COPD assessment test: COPD assessment test (CAT) was performed to measure health-related quality of life every three months. The test contained 8 questions covering the impact of disease-related symptoms such as cough, phlegm, feeling of tightness in the chest and breathlessness on an uphill walk. Each question was scored on a scale of 0 to 5. Total score was independently calculated by two investigators.

Modified British Medical Research Council questionnaire: The modified British Medical Research Council questionnaire (mMRC) scale was used to quantitate the severity of dyspnea on a 5-point (0-4) scale. The assessment was performed every three months.

Six-minute walking distance (6MWD): 6MWD was carried out according to the American Thoracic Society (ATS) guidelines every three months [11]. A 50 m segment of straight, unimpeded hallway was marked. Distance walked by the patient in six minutes was measured. The test was repeated three times at ten-minute intervals and the average value was used for analysis.

Definition of renal impairment: Routine urine examination and serum creatinine were measured using an automated biochemistry analyzer every three months. GFR was then calculated using MDRD formula. A decline of eGFR was defined as two consecutive values below 60 mL/min/1.73 m^2. Renal impairment was defined by presence of proteinuria and decline in eGFR.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (GraphPad, San Diego, CA, USA). Quantitative variables were described as the mean ± standard deviation. Categorical variables were expressed as median and quartiles. The Mann-Whitney's U test was used for non-parametric data. Chi-squared test was used to examine differences with categorical variables. Student's *t* test was used for analysis of continuous variables. A *P* value < 0.05 was considered as statistically significant.

Results

Patient characteristics

A total of 182 (115 men and 67 women; mean age [SD]: 68.34 [± 8.12] years) patients were included in the analysis. Mean (± SD) body mass index (BMI) was 22.64 ± 3.83 kg/m^2.

Smoking history

Out of 182 patients, 126 had a history of smoking, of which 95% were men. 48 patients had quit smoking prior to their enrollment in the study, while 78 patients were current smokers. The median duration of time elapsed since

Table 1. Clinical characteristics of COPD patients in different groups

Characteristics	Group A (n = 16)	Group B (n = 54)	Group C (n = 27)	Group D (n = 86)
Age (yrs)	68.16 ± 8.92	63.64 ± 9.51	72.26 ± 7.59	69.28 ± 9.25
BMI (kg/m^2)	22.15 ± 3.45	23.68 ± 4.16	24.56 ± 2.96	24.68 ± 4.86
Lung function				
FEV1/FVC (%)	65.59 ± 8.52	62.61 ± 6.36	60.58 ± 5.26	51.26 ± 9.56
FEV1 (V/L)	2.86 ± 0.78	1.56 ± 0.68[*]	1.21 ± 0.49[*]	1.12 ± 0.53[*,#]
FEV1%Pred	77.82 ± 16.28	62.68 ± 15.46	54.42 ± 9.55[*]	46.27 ± 15.91[*,#]
FVC (V/L)	3.27 ± 0.63	2.28 ± 0.54[*]	1.86 ± 0.53[*]	1.73 ± 0.66[*,#]
FVC1%Pred	116.01 ± 18.11	89.78 ± 15.46[*]	67.56 ± 8.73[*]	68.83 ± 18.25[*]
CAT score	6.85 ± 3.88	13.08 ± 5.85[*]	11.65 ± 3.22[*]	24.82 ± 8.54[*,※]
mMRC scale	1.11 ± 0.85	1.78 ± 0.58[*]	1.63 ± 0.66[*]	2.81 ± 0.98[*,#,※]
6MWD (m)	363.36 ± 67.29	263.58 ± 86.32[*]	317.43 ± 72.59[#]	218.01 ± 76.53[*,#,※]
AECOPD	0	0.92 ± 0.38[*]	1.32 ± 0.54[*]	4.14 ± 0.67[*,#,※]
EF (%)	66.82 ± 8.84	59.06 ± 10.82	62.63 ± 9.22	58.82 ± 11.54
Laboratory results				
CRP (mg/L)	28.46 ± 11.25	69.29 ± 12.34[*]	77.82 ± 13.42[*]	84.29 ± 19.27[*,#]
ALT (U/L)	26.15 ± 3.45	30.28 ± 6.16	33.51 ± 5.92	30.28 ± 6.86
AST (U/L)	28.85 ± 0.78	34.51 ± 7.24	32.58 ± 6.15	35.46 ± 8.25
TB (μmol/L)	16.82 ± 3.28	18.68 ± 5.46	19.42 ± 6.55	23.27 ± 8.91
BNP (pg/mL)	175.01 ± 18.16	216.56 ± 20.18	208.96 ± 18.75	260.15 ± 25.36
Associated comorbidity (n, %)				
Ischemic heart disease	1 (6.25)	5 (9.26)	3 (11)	11 (12.9)
Hypertension	2 (12.5)	10 (18.5)	4 (14.81)	16 (18.82)
Cerebrovascular disease	1 (6.25)	2 (3.7)	1 (3.7)	5 (5.88)
Diabetes mellitus	1 (6.25)	5 (9.26)	3 (11.11)	9 (11.76)
Lung cancer	0 (0)	1 (1.85)	1 (3.7)	3 (3.5)
Osteoporosis	0 (0)	2 (3.7)	2 (7.4)	7 (8.24)
Digestive organ disease	2 (12.5)	9 (16.67)	5 (18.51)	17 (20)
Anemia	0 (0)	2 (3.7)	1 (3.7)	5 (5.88)

Data presented as mean ± SD or median (four percentile). BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD assessment test; mMRC, modified British medical research council; 6MWD, 6-min walking distance; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; EF, ejection fraction; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; BNP, B-type natriuretic peptide. [*]P < 0.05 vs. Group A; [#]P < 0.05 vs. Group B; [※]P < 0.05 vs. Group C.

cessation of smoking was 4.0 years (range, 2.0-11.25). The average cigarette consumption in current smokers and in those that had quit smoking was 51.32 ± 18.28 and 43.64 ± 28.43 packs per year, respectively. The mean CAT scores for the above two groups was 19.82 ± 9.86 and 19.93 ± 8.17, respectively.

Clinical characteristics

The clinical characteristics of COPD patients are shown in **Table 1**. The number of patients in the four COPD severity groups (Group A, B, C and D) was 16 (8.79%), 54 (29.67%), 27 (14.84%) and 86 (47.25%), respectively. The mMRC scale score in group D was significantly greater than that in groups A, B and C (P < 0.05 for all). Patients in group B, C and D had significantly decreased FEV1, FEV1% predicted, FVC, and FVC% predicted as compared to that in group A, while patients in group D had the worst results (P < 0.05 for all). The 6MWD in group A was significantly longer than that in groups B and D (P < 0.05). The number of AECOPD in group D was significantly more than that in groups A, B and C (P < 0.05).

There was no significant difference in the prevalence of associated co-morbid conditions in the four groups.

Table 2. Renal function parameters in different groups of COPD patients

Characteristics	Group A	Group B	Group C	Group D	X^2	P value
n	16	54	27	85		
Proteinuria, n (%)	0	5 (9.25)*	3 (11.11)*	18 (21.18)*,#	13.213	0.004
Decline in eGFR, n (%)	1 (6.25)	4 (7.41)	3 (11.11)	17 (20.00)*,#	9.797	0.020
Renal impairment, n (%)	1 (6.25)	6 (11.11)*	4 (14.81)*	26 (30.59)*,#,※	18.128	0.000

*$P < 0.05$ vs. Group A; #$P < 0.05$ vs. Group B; ※$P < 0.05$ vs. Group C.

Table 3. The influence of renal dysfunction on COPD patients

Indicators	Without renal impairment (n = 145)	With renal impairment (n = 37)	t	P value
FEV1%Pre	61.45 ± 15.13	43.89 ± 14.42	4.257	0.019
FEV1/FVC%	60.59 ± 10.38	50.28 ± 13.52	1.254	0.682
CAT score	15.82 ± 4.85	26.56 ± 6.68	16.253	0.015
mMRC scale	1.89 ± 0.79	2.98 ± 0.81	8.286	0.020
6MWD	310.38 ± 52.62	226.52 ± 61.68	11.658	< 0.001
AECOPD	1.80 ± 0.52	3.8 ± 0.83	9.328	< 0.001

Data are presented as mean ± standard deviation. FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD assessment test; mMRC, modified British medical research council; 6MWD, 6-min walking distance; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Renal impairment

A significant difference in renal impairment was observed between the four different groups ($P < 0.0001$). Patients in the Group A had the lowest degree of renal impairment among the four groups ($P < 0.05$). However, renal impairment mostly occurred in group D ($P < 0.05$). Patients with severe COPD were more likely to have impaired renal function (**Table 2**).

Impact of renal impairment on lung function, CAT, mMRC, 6MWD, and number of AECOPD

A total of 37 (20.33%) patients in the study population exhibited renal impairment. Patients with kidney injury had significantly worse FEV-1% predicted, CAT scores, mMRC scale scores, 6MWD, and AECOPD as compared to patients who had no renal impairment (**Table 3**).

Discussion

COPD is one of the leading causes of morbidity and mortality worldwide; the prevalence and mortality rates have shown a rising trend. Uncovering the characteristics of associated comorbidity in COPD patients may help further risk-stratification and treatment. In the present study we observed that the incidence of renal impairment increased with the increase in COPD severity. Secondly, COPD patients with renal impairment had a significantly deteriorated quality of life and a higher incidence of exacerbation as compared to that in patients who had normal kidney function.

Renal impairment in patients in the most severe group accounted for an astounding 30.59%, while patients in A, B and C groups had less than 15% of renal dysfunction. The prevalence of renal impairment in patients with COPD and its association with severity of COPD is not well-characterized. However, a large population-based analysis of comorbidity in COPD did show an elevation in the prevalence in four different types of renal disease, namely acute renal failure, chronic kidney disease, unspecified chronic kidney disease, and unspecified kidney failure [12]. In another study, chronic renal failure was diagnosed in 6.3% of COPD patients, in which men outnumbered women [13]. The overall prevalence of renal impairment seemed higher in our study as compared to that reported by an earlier study. The broader definition of renal impairment may partly explain such a difference.

Hypoxemia and hypercapnia usually occur simultaneously in patients with COPD. These conditions are associated with sodium retention, renal tubular and interstitial damage, along with reduced glomerular filtration caused by arterial stiffness [14-16]. These factors contribute to renal impairment in patients with COPD. Endothelins are common mediators in the pathophysiological bases of COPD and renal dysfunction. Sofia *et al.* in their study observed that changes in endothelins were

associated with changes in $PaCO_2$ and PaO_2. COPD patients had a significantly higher 24 h urinary excretion of endothelin as compared to controls, and the corrected renal clearance of endothelin showed a strong correlation with GFR values during acute exacerbations of COPD [17].

Based on a GOLD classification, the assessment of COPD severity is based on lung function, risk of acute exacerbation, mMRC dyspnea score, and CAT scores to reflect health-related quality of life. Since group C and D are known to have a higher risk of mortality, patients with kidney dysfunction in this group are more likely to have worse outcomes as compared to their counterparts in groups A and B. However, controversies exist concerning the predictability of renal injury in COPD patients. While renal failure doubled the risk of short-term mortality in a large sample analysis, it was not considered as a prognostic factor for long-term mortality [18]. Another prospective study also demonstrated that the number and duration of hospital admissions depended primarily on the severity of lung disease and not on renal failure [19]. Population heterogeneity may partly explain these discrepancies between the results of different studies.

Our findings confirmed that COPD patients with renal impairment have significantly worse lung function and clinical symptoms compared with those without kidney involvement. The lung function indicators included FEV1% predicted and FEV1/FVC%. However, we were unable to perform further classification of renal function because some patients with severe renal dysfunction were transferred to the Division of Nephrology and their data could not be obtained.

Some additional limitations in the current study are as follows: This was a single-center observational with a relatively small sample size. Secondly, renal impairment was defined by the presence of proteinuria and eGFR determined based on creatinine. Thus GFR may have been underestimated. Lastly, we did not evaluate the prognostic effect of renal impairment in COPD patients. Renal injury is a common accompaniment of COPD and negatively affects lung function, quality of life, and frequency of acute exacerbations of COPD.

Disclosure of conflict of interest

None.

Address correspondence to: Yingmin Ma, Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing Institute of Respiratory Diseases, Beijing 100020, China. Tel: +8610-51718030; Fax: +8610-51718030; E-mail: ma.yingmin@163.com

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