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The Course of Renal Functions in COPD. Two Statition: Exacerbation and Stable Period

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Abstract:

OBJECTIVE: Comorbidities in chronic obstructive pulmonary disease (COPD) are important factors that determine the prognosis of the disease. However, there are few studies about renal dysfunction. We aimed to compare the renal functions in COPD patients with stable and exacerbation periods and to determine the frequency of acute renal failure (ARF) during exacerbation.

MATERIALS AND METHODS: The files of 320 patients with COPD (forced expiratory volume in 1 s/forced vital capacity <70% in pulmonary function test) who were admitted to our hospital between 2015 and 2016 were evaluated retrospectively. After exclusion criteria, 113 patients were included in the study. Data were analyzed by appropriate statistical method.

RESULTS: Ninety (80.4%) of the patients were male and 23 (19.6%) were female. In the exacerbation period, blood urea nitrogen ($P < 0.001$), creatinine ($P < 0.001$), white blood cell ($P < 0.001$), C-reactive protein ($P < 0.001$), and sedimentation ($P < 0.001$) were higher than that in the stable period. Furthermore, hemoglobin ($P = 0.021$) and estimated glomerular filtration rate (eGFR) ($P < 0.001$) were significantly lower. The number of emergency department admission in patients with eGFR <60 ml/min during the exacerbation more than the patients with eGFR ≥60 ml/min. Twenty (17.7%) patients have developed ARF during exacerbation (eGFR <60 ml/min).

CONCLUSION: In COPD exacerbation period, kidney function is affected negatively in most patients (even if it does not reach the ABY border) and tends to improve in the stable period. In patients with COPD, it is thought that the causes of respiratory failure negatively affect renal function.

Keywords:

Acute renal failure, chronic obstructive pulmonary disease, renal function

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Introduction

Chronic obstructive pulmonary disease (COPD) affects 9%–10% of the population who are greater than 40 years and its frequency increases with aging.[1,2] It is expected that COPD will be the third leading cause of death worldwide by 2030. Global burden of disease study showed that COPD was the eighth disease in order of disability-adjusted life years in 2005 and fifth disease in 2013. Besides comorbidities, smoking is the leading cause of increase in frequency and mortality rate of the disease. COPD is a disease which has many negative systemic effects and comorbidities.[3] Renal function impairment in COPD patients was not yet investigated sufficiently.

Renal function tests are followed up closely in many diseases to decide the severity of the disease and choice of medical treatment. Furthermore, they are one part of severity scoring systems in pneumonia.[4] Dehydration secondary to high fever, acute inflammatory reaction, decrease in oral intake, or hypoxemia may cause impairment in renal functions in some diseases.[5] The aim of this study was to compare the renal functions between stable COPD patients and

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patients who were in the exacerbation period and also to investigate the frequency of acute renal failure (ARF) in COPD exacerbation.

Materials and Methods

Data collection and patient selection

COPD patients who were hospitalized due to exacerbation between 2015 and 2016 were detected retrospectively by means of medical records. Three hundred and twenty patients were enrolled into the study. Local ethics committee approval was taken.

Patients who were >40 ages, who were previously diagnosed as COPD by spirometry (forced expiratory volume in 1 s [FEV1]/forced vital capacity [FVC] <%70) and hospitalized at least once due to COPD exacerbation, who had medical record that was taken in stable phase of the disease, and who had at least 3 months between exacerbation period and stable phase were enrolled into the study. COPD patients who were admitted to the intensive care unit from the emergency department, who did not have spirometry proving COPD, and who were taking chemotherapy at the beginning of the study were excluded. Patients who did not take chemotherapy at least 3 months and who had stable or cured malignancy were enrolled into the study. One hundred and thirteen patients who met these criteria were finally included in the study [Figure 1].

Pulmonary function test

Pulmonary function test (PFT) was performed by spirometry (Sensormedics Vmax Series 20C Respiratory Analyzer, Yorba Linda, CA, USA) according to the American Thoracic Society guideline.[6] Parameters of FEV1, FVC, and FEV1/FVC were measured, and patients who had FEV1/FVC <70% were diagnosed as COPD.[3]

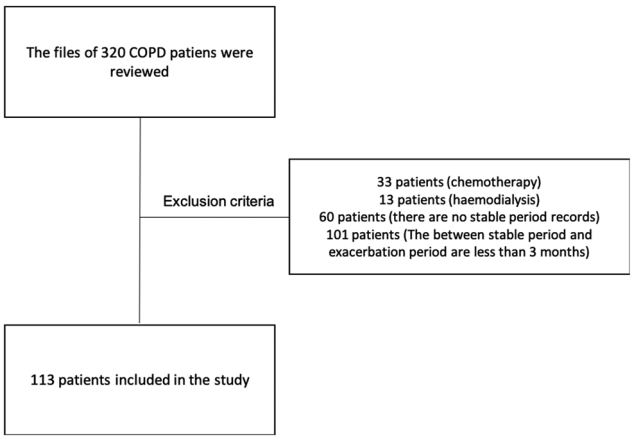

Figure 1: Determination of patients who were analyzed according to inclusion and exclusion criteria

Recorded parameters

Age, gender, height, weight, smoking history, biomass exposure, PFT parameters (FEV1%, FEV1cc, FVC%, FVCcc, and FEV1/FVC), modified Medical Research Council (mMRC) levels, stage of the disease according to combined assessment of GOLD 2011,[7] numbers of application to emergency department and numbers of hospitalization because of COPD exacerbation within last 1 year, use of long-lasting oxygen therapy, use of noninvasive mechanical ventilation Bilevel positive airway pressure (BiPAP), comorbidities, and results of arterial blood gas analysis were recorded for all patients who participated in the study.

Renal function tests (blood urea nitrogen [BUN] and creatinine) that were measured both in exacerbation period and stable phase, hemogram, C-reactive protein (CRP), and erythrocyte sedimentation rate values of the patients were recorded. Cause of exacerbation, status of hospital discharge, and mortality within 3 months after hospital discharge were recorded for all of the participants.

Estimated Glomerular Filtration Rate (eGFR) was calculated via Cockroft–Gault method using gender, age, weight, and serum creatinine levels.[8]

Grouping of the patients

Patients who had higher eGFR in the exacerbation period than in the stable phase were classified as Group 1 and patients who had lower eGFR in the exacerbation period than that in the stable phase were classified as Group 2. Patients also were evaluated on the basis of ARF. Data analysis primarily was done for whole of the participants and then between the groups.

Statistical analysis

Data were analyzed by SPSS 20 (SPSS 20.0 version IBM Corp.; Armonk, NY, USA) package program. Kolmogorov–Smirnov test was performed for normality test. Parameters that did not show normal distribution (age, number of hospitalization within 1 year, number of application to emergency department within 1 year, oxygen saturation (SO_2), oxygen partial pressure (PO_2), CRP, FEV1, and FEV1/FVC) according to the analysis were compared by Mann–Whitney U-test and other parameters and whole parameters that showed normal distribution were compared by *t*-test. Chi-square test was performed for significance of two categorical variables. Parametric variables were stated as mean ± standard deviation, categorical variables were stated as percentage, and the limit of statistical significance was accepted as $P < 0.05$.

Results

Demographic properties, parameters of PFT, and stages of COPD according to the GOLD 2011 combined assessment are shown in Table 1.

Comorbidities, causes of COPD exacerbation, and status of hospital discharge of patients are shown in Table 2. The rate of patients who did not take chemotherapy for at least 3 months, who had stable or cured lung malignancy, was 8.8% (n = 10).

Renal function tests in stable phase and exacerbation period and other laboratory parameters of patients are summarized in Table 3. Most of the patients had higher BUN and creatinine and lower eGFR level in exacerbation period, although the levels did not reach to the ARF level.

Table 1: Demographic properties of patients and data related to chronic obstructive pulmonary disease (pulmonary function test, stage, modified Medical Research Council, exacerbation in the last 1 year)

	n (%)
Age, mean (%)	71.91±9.59
Sex (%)	
Female	23 (19.6)
Male	90 (80.4)
Smoking (%)	
Current	1 (1.0)
Ex-smoker	90 (80.4)
Never	1 (1.0)
Biomass (%)	
Yes	92 (82.9)
No	19 (17.1)
mMRC (%)	
1	43 (38.1)
2	51 (45.1)
3	15 (13.3)
4	4 (3.5)
PFT*	
FEV1 (cc)	1226.47±827.42
FEV1 (%)	47.97±16.86
FVC (cc)	2049.20±700.04
FVC (%)	65.50±17.87
FEV1/FVC	59.98±49.20
GOLD 2011-Group (%)	
A	27 (23.9)
B	23 (20.4)
C	19 (16.8)
D	44 (38.9)
In the last 1 year**	
The number of emergency department admission	1 -10 (median=1)
The number of hospitalization	1 -5 (median=1)
LTOT (%)	
Yes	28 (24.8)
No	85 (75.2)
BPAP (%)	
Yes	15 (13.3)
No	98 (86.7)

*Median values are written, **Minimum and maximum range are specified. mMRC: Modified medical research council, PFT: Pulmonary function test, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, GOLD: Global obstructive lung disease, LTOT: Long-time oxygen therapy, BPAP: Bilevel positive airway pressure

Number of emergency department application was found higher and SO_2 level was found lower in Group 2 (n = 11, 9.7%) compared to Group 1 (n = 102, 90.3%) (P = 0.020, P = 0.045, respectively). Statistically significant difference was not detected between the groups in terms of other parameters.

The frequency of ARF (eGFR <60 ml/min) during COPD exacerbation was 17.7% (n = 20) in the study population. The mean age of patients who developed ARF was higher than who did not (80.45 ± 7.19 vs. 70.08 ± 9.06, P < 0.001). There was no statistically significant difference in terms of other parameters [Table 4].

Discussion

This study showed that eGFR of COPD patients decreased during the exacerbation period compared with stable phase of the disease, and the frequency of ARF in patients with COPD exacerbation should not be underestimated.

It was seen that BUN and creatinine levels were increased in COPD patients during exacerbation period but mostly did not exceed the upper level of reference range. Related

Table 2: Comorbidities, causes of chronic obstructive pulmonary disease exacerbation, status of hospital discharge

	n (%)
Comorbidity	
Lung cancer	
Yes	10 (8.8)
No	103 (91.2)
HT	
Yes	43 (38.1)
No	70 (61.9)
DM	
Yes	25 (22.1)
No	88 (77.9)
CAD	
Yes	28 (25.0)
No	84 (75.0)
CHF	
Yes	6 (5.3)
No	107 (94.7)
OSAS	
Yes	5 (4.4)
No	108 (95.6)
Causes of acute exacerbation	
Infection	106 (93.8)
Cor pulmonale	4 (3.5)
PTE	3 (2.7)
3-month mortality	
Yes	4 (3.6)
No	107 (96.4)
Discharged	111 (98.4)

HT: Hypertension, DM: Type 2 diabetes mellitus, CAD: Coronary artery disease, CH: Congestive heart failure, OSAS: Obstructive sleep apnea syndrome, PTE: Pulmonary tumor embolism

to these parameters, eGFR levels were found to be lower in the exacerbation period than that in the stable phase. Although this decrease was not under the limit of renal failure (60 ml/min), it was striking. Decrease in the renal blood flow is the main cause of reduction in eGFR. Hypoxemia and hypercapnia are two of many other causes of decrease in blood flow.[5] Especially, vasoconstriction related to hypoxemia reduces eGFR by affecting renal blood flow. Approximately 25% of our patients who had chronic respiratory failure and their hypoxemia were deepening during exacerbation. We associated reduction of eGFR with hypoxemia.

Table 3: Comparison of laboratory parameters between the period of chronic obstructive pulmonary disease exacerbation and stable phase

	Mean±SD	Minimum	Maximum	*P*
BUN (mg/dL)				
Exacerbation	23.01±10.41	3	58	<0.001
Stable	16.09±5.72	4	40	
Creatinine (mg/dL)				
Exacerbation	1.04±0.32	0.56	2.38	<0.001
Stable	0.82±0.22	0.3	1.8	
eGFR (ml/dk)				
Exacerbation	71.20±28.29	4.56	151,-.79	<0.001
Stable	89.39±31.24	38.27	187.57	
WBC (/uL)				
Exacerbation	11595±7850	4280	14900	<0.001
Stable	7514±1717	4100	10600	
Hgb (g/dL)				
Exacerbation	13.33±1.91	8.3	19.5	0.021
Stable	13.64±2.07	9.2	18.5	
CRP (mg/L)				
Exacerbation	56.24±47.56	0.1	320	<0.001
Stable	6.66±5.67	0.1	49	
Sedimentation (mm/h)				
Exacerbation	38.42±29.06	1	114	<0.001
Stable	15.65±13.50	1	79	

SD: Standard deviation, BUN: Blood urea nitrogen, eGFR: Glomerular filtration rate, WBC: White blood cell, Hgb: Hemoglobin, CRP: C-reactive protein

Barakat *et al*. founded the frequency of ARF during COPD exacerbation as 1.9% in a study that examined 36.107 COPD patients in England. Patients who were more than 35 years old and had ICD code of COPD exacerbation in the database were included in this study.[9] Because the limit of age starts from 40 years for COPD according to the GOLD guideline, it may be thought that there was a methodological mistake in this study. It was also not true to select patients who had ICD code of "COPD exacerbation." Definitive diagnosis of COPD is only possible by showing FEV1/FVC <%70 via spirometry.[3] Other studies investigating renal functions in COPD patients were focused on chronic renal failure.[10,11] In our study, the frequency of ARF during COPD exacerbation was found to be 17.7%. We thought several reasons for this high level of frequency. First, because our center is a tertiary hospital, more complicated and older patients may apply. Previous studies showed that frequency of ARF increased with aging.[9,12,13] Second, approximately 25% of the study population had indication for long-lasting oxygen therapy due to chronic respiratory failure. Hypoxemia is one of the important causes that reduce eGFR.

Table 4: Comparison of patients who had ARF and did not in terms of disease parameters

	ARF positive (n=20; 17.7%)	ARF negative (n=93; 82.3%)	*P*
Age/years (mean±SD)	80.45±7.19	70.08±9.06	<0.001
The number of hospitalization in last the 1 year*	1	1	0.441
The number of emergency department admission in the last 1 year*	1	1	0.859
SO2	82.45±5.20	82.75±10.53	0.354
pH	7.36±0.05	7.36±0.07	0.586
PO2	46.0±14.1	50.74±5.8	0.314
PCO2	50.0±10.23	49.1±16.4	0.637
FEV1 (cc)	1040±439	1266±886	0.384
FEV1 (%)	51.4±15.6	47.2±17.1	0.385
FVC (cc)	1890±573	2083±722	0.301
FVC (%)	68.4±20.0	64.87±17.4	0.582
FEV1/FVC	56.5±12.1	55.4±10.4	0.784
Sex, *n* (%)			0.761
Female	3 (13.6)	19 (86.4)	
Male	16 (17.8)	74 (82.2)	
GOLD 2014-(Group), *n* (%)			
A	4 (14.8)	23 (85.2)	0.323
B	7 (30.4)	16 (69.6)	
C	2 (10.5)	17 (89.5)	
D	7 (15.9)	37 (84.1)	

*The median value is indicated. ARF: Acute renal failure, SO2: Oxygen saturation, PO2: Oxygen partial pressure, PCO2: Carbon dioxide partial pressure, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, GOLD: Global obstructive lung disease

The HUNT study showed that the prevalence of renal failure was 0.5%, 4%, and 18.5% in patients aged 20-49, 50-69, and ≥70 years, respectively.[13] However, patients participating in the HUNT study did not know whether they had renal failure or not. In our study, patients who previously had renal function impairment were excluded and the mean age was higher in patients who developed ARF (P = 0.001). Our study population was relatively older; the mean age of patients was 71.91 ± 9.59 years. In consistent with our study, almost all of the patients were >65 years old in the study of Incalzi *et al*. and the frequency of renal failure was 43% in their study.[11]

Frequency of renal failure was found to be 9.6% in females and 5.1% in males in another study in which patients with previous renal failure were excluded and investigating patients who had eGFR <60 ml/min (P = 0.08) were also excluded; multivariable analysis showed that female gender, cachexia, NGAL, and sTNF-R1 were the independent risk factors for development of renal failure.[12] Another study showed that female gender was protective for the development of ARF.[9] Our study was not suitable for multivariable analysis due to the low number of participants. However, univariable analysis showed that there was no difference between female and male gender (P = 0.761). The difference between studies in terms of inclusion criteria may cause contradictory results about effect of gender on the development of ARF.

The current study did not show any relation between combined assessment of COPD stages according to GOLD 2011 and development of ARF (P = 0.323). Previous studies evaluating ARF development according to the GOLD spirometric staging found similar results.[9,12] Barakat *et al*. showed that frequency of ARF gradually increased from spirometric Stage I to III but decreased in Stage IV, and as a result, spirometric staging did not have any statistically significant effect on the development of ARF.[9]

We used the formula of Cockcroft–Gault to calculate eGFR. This formula contains gender, age, serum creatinine level, and weight. Serum creatinine level changes with muscle mass and related to this with weight. The formulae that did not consider weight miscalculate eGFR and they measure low eGFR in people who had high amount of muscle mass and vice versa.[14] Besides, consideration of race in Cockcroft–Gault formula is an advantage. "Modification of Diet in Renal Disease" formula was used in the study of Incalzi *et al*. Because weight is disregarded in this formula, eGFR values may be measured higher than required so that this condition may explain the reason for the higher frequency of eGFR<60 mL/dk (43%) in the study of Incalzi *et al*. than other studies on the subject.[11]

Our study had some limitations. First, the number of patients was relatively low. This condition caused inequality between groups of patients and prevented making multivariable statistical analysis. Hence, we could only evaluate the frequency of ARF in patients with COPD exacerbation. The second limitation was the lack of our knowledge about use of medications related to comorbidities of patients and long-term oxygen therapy. Especially, nonsteroid anti-inflammatory drugs are effective on renal function impairment.[15] While hypoxemia which causes vasoconstriction increases in a patient who is not compliant to long-term oxygen therapy, eGFR will decrease.[5] The third limitation of the study was the inclusion of patients with pneumonia as the cause of COPD exacerbation. Because renal function impairment is the main cause of hospitalization and mortality in patients with pneumonia, its frequency cannot be underestimated.[4] Renal function impairment of the patients with pneumonia could affect the mean of the whole study population.

Besides these limitations, positive properties of the study were as follows: All of the patients were more than 40 years old, their diagnosis of COPD was proven by spirometry, there was at least 3 months between exacerbation period and stable phase, and exclusion of patients who previously had renal failure and were currently taking chemotherapy.

Conclusion

Renal functions tend to be impaired in patients with COPD exacerbation. This impairment becomes evident in older patients and low level of SO_2. Because comorbidities and their medications can be effective on renal functions in patients with COPD, larger prospective studies including carefully selected patients were needed.

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Conflicts of interest
There are no conflicts of interest.

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