Am J Transl Res 2021;13(7):8150-8157
www.ajtr.org /ISSN:1943-8141/AJTR0132237

Original Article

Serum cortisol levels and adrenal gland size in patients with chronic obstructive pulmonary disease

Peng Wei[1], Yu Li[4], Lijuan Wu[2], Junhong Wu[3], Wenbin Wu[1], Shuping Chen[1], Shujuan Qin[1], Jiemei Feng[1]

Departments of [1]Pulmonary and Critical Care Medicine, [2]Ultrasound, [3]Radiology, Guigang City People's Hospital, Guigang, Guangxi Zhuang Autonomous Region, China; [4]Department of Pulmonary and Critical Care Medicine, The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China

Received February 21, 2021; Accepted April 7, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Objective: To determine the clinical significance of serum Cortisol (Cor) levels and adrenal gland size in patients with chronic obstructive pulmonary disease (COPD). Methods: We assigned 80 patients with COPD admitted to our hospital to an observation group, and 80 healthy individuals to a control group. Serum Cor, C-reactive protein (CRP) level, and adrenal gland size were measured. Patients with COPD were divided into several subgroups according to BODE (BMI, Obstruction, Dyspnea, Exercise capacity) indexes and forced expiratory volume in the first second (FEV1), and Cor levels and adrenal gland size were compared between subgroups. The Pearson Correlation was used to analyze correlations of adrenal gland size and Cor levels with partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), FEV1, forced vital capacity (FVC), and FEV1/FVC. After 30 days' follow-up, the patients were allocated into good-prognosis group and poor-prognosis group. The clinical value of Cor levels in predicting prognosis was estimated by the receiver operating characteristic (ROC) curve. Results: Increased serum CRP levels were found in the observation group, while Cor levels and adrenal gland diameter were decreased ($P<0.05$ for each comparison). In the observation group, an increase in BODE index or decrease in FEV1 led to decreased Cor levels and adrenal gland diameter, as well as increased CRP levels ($P<0.05$, each comparison). Correlation analysis showed that adrenal gland diameter and Cor levels were positively correlated with PaO_2, FEV1, FVC, and FEV1/FVC, but negatively correlated with $PaCO_2$. The ROC curve indicated that Cor levels were valuable in predicting the prognosis (AUC>0.7, $P<0.05$). Conclusion: Cor levels and adrenal gland size are closely associated with the severity of COPD, and Cor levels are predictive of prognosis.

Keywords: Chronic obstructive pulmonary disease, cortisol, adrenal gland, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease that manifests mainly as persistent airflow limitation [1]. COPD is highly destructive, and can give rise to irreversible damage to the lungs, with a long course, resulting in a high mortality rate [2, 3]. The pathogenesis of COPD has not been fully understood, except that it presents with recurrent attacks and progressive progression. Some patients may experience acute exacerbation once or twice a year, which in turn increases the risk of death. Therefore, it is of great clinical significance to explore specific biologic indicators for prognosis evaluation [4-6].

There is evidence that COPD patients may suffer from endocrine disorders and adrenal cortex dysfunction [7, 8]. As one of the hormonal indicators in the hypothalamic-pituitary-adrenocortical (HPA) axis in vivo, Cortisol (Cor) is closely related to the development of COPD, but studies on serum Cor levels in patients with COPD remain controversial [9]. An early study has suggested that serum Cor levels increase significantly in cases with COPD [9]. However, in recent years, as measurement techniques have advanced, serum Cor levels have been found to decrease in cases with stable or exacerbated COPD [10]. The present study explores the changes in serum Cor levels and adrenal gland size in cases with COPD, with the goal of providing evidence for clinical diagnosis and treatment of COPD and prediction of prognosis.

Materials and methods

General data

Clinical data collected from 80 patients with COPD admitted to our hospital (observation group) and 80 healthy individuals (control group) were retrospectively analyzed. This study was approved by the hospital ethics committee.

Inclusion and exclusion criteria

Inclusion criteria for the observation group: (1) Patients who met diagnostic criteria of *the Guidelines for Diagnosis and Treatment of COPD* [11]; (2) Patients aged ≥18 years old; (3) Patients without other comorbid diseases; (4) Patients who had not taken drugs that might disrupt our experimental results within the last 3 months; (5) FEV1/FVC<70%.

Inclusion criteria for the control group: (1) Patients aged ≥18 years old; (2) Patients without other comorbid diseases; (3) Patients who had not taken drugs that might disrupt our experimental results within the last 3 months.

Exclusion criteria: (1) Patients complicated by other severe diseases; (2) Patients who were participating in other studies simultaneously; (3) Patients with organic lesions in the lungs; (4) Lactating or pregnant women; (5) Patients suffering from mental illness or those with poor compliance.

Measurement of lung function

All study subjects were tested for lung function, including forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and FEV1/FVC, using the Anke FGC-A + spirometer (AnkeBio, Anhui, China) on the next day of enrollment. A blood gas analyzer (Kangli Medicines, Guangdong, China) was used to quantify the levels of partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$).

Lung function in the observation group was graded by FEV1%: grade I, ≥80%; grade II, 50%-79%; grade III, 30%-49%; and grade IV, <30% [11].

Quantification of Cor and CRP

Venous blood (5 mL) was sampled in the next morning and centrifuged at 3000 r/5 min for 5 minutes. Serum Cor levels were measured by electrochemiluminescence (ECL; Elecss-2010 ECL immunoassay analyzer, Roche, Switzerland), and C-reactive protein (CRP) levels were measured by immunoturbidimetry (AU400 automatic analyzer, Olympus, Japan). The kits were purchased from Beyotime Biotech, Shanghai, China.

Detection of adrenal glands

Adrenal gland size was measured by Brilliance16-slice spiral CT scanner (Philips, Netherlands) the next day.

Evaluation of BODE index

In the observation group, BODE (BMI, Obstruction, Dyspnea, Exercise capacity) assessment was performed on the next day of enrollment [12]: (1) body mass index (BMI) >21 kg/m^2 was scored 0; BMI≤21 kg/m^2 was scored 1. (2) FEV1/FVC ≤35% was scored 3; FEV1/FVC of 36%-49% was scored 2; FEV1/FVC of 50%-64% was scored 1, FEV1/FVC >65% was scored 0. (3) Except during strenuous exercise, no significant dyspnea or shortness of breath when walking up a gentle slope or walking quickly was scored 0; needing to stop and breathe when walking on the flat ground was scored 1; needing to stop and breathe when walking on the flat ground for several minutes or 100 meters was scored 2; shortness of breath or difficulty in breathing when dressing/undressing and being unable to get out of the house was scored 3. (4) 3 points for 6-minute walking distance <149 meters, 2 for walking 150-249 meters, 1 for walking 250-349 meters, and 0 for walking >350 meters. The total scores of 0-2 were classified as Grade 1, 3-4 as Grade 2, 5-6 as Grade 3, and >7 as Grade 4.

Follow-up

After 30 days of follow-up, the patients were allocated into a good-prognosis group and a poor-prognosis group. Good prognosis: dyspnea, cough and other symptoms disappeared after treatment, with $PaCO_2$ ranging from 35 mmHg to 45 mmHg. Poor prognosis: patients' symptoms were not relieved at all or were even aggravated after treatment.

Outcome measures

Main outcome measures: Cor and CRP levels and adrenal gland size were compared bet-

Table 1. Comparison of general information between the two groups

Item	Observation group (n=80)	Control group (n=80)	χ^2/t	P
Gender (n)			0.456	0.499
Male	52	56		
Female	28	24		
Age (years)	57.1±6.6	56.8±6.9	0.281	0.779
Smoking history (n)			0.421	0.516
Yes	51	47		
No	29	33		
FEV1 (%)	61.2±4.4	92.1±4.8	42.444	<0.001
FVC (%)	80.3±6.4	97.8±5.3	18.837	<0.001
FEV1/FVC	60.7±4.9	94.5±5.6	44.982	<0.001
PCO_2 (mmHg)	43.71±6.54	39.05±5.78	4.775	<0.001
PO_2 (mmHg)	61.89±6.63	94.21±7.54	28.792	<0.001

Note: PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV1/FVC: forced expiratory volume in the first second/forced vital capacity.

ween the observation group and control group. (2) COPD patients were divided into several subgroups according to BODE index and FEV1, and Cor levels and adrenal gland size were compared between subgroups.

Secondary outcome measures: The Pearson's Correlation was adopted to analyze possible correlations of adrenal gland size and Cor levels with PaO_2, $PaCO_2$, FEV1, FVC, and FEV1/FVC in the observation group. After 30 days of follow-up, the patients were allocated into a good-prognosis group and a poor-prognosis group. The clinical value of Cor levels in predicting the prognosis of patients was estimated by the receiver operating characteristic (ROC) curve.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. Categorical data were expressed as number/percentage and analyzed by χ^2 test. Continuous data were expressed by ($\bar{x}$ ± sd), with multiple-group comparisons conducted with analysis of variance, and inter-group comparisons with SNK test. The Pearson Correlation was adopted to determine correlations of adrenal gland size and Cor levels with PaO_2, $PaCO_2$, FEV1, FVC and FEV1/FVC. The clinical value of Cor levels in predicting the prognosis of patients was assessed by ROC curves. $P<0.05$ was considered significant.

Figure drawing

ROC curves were drawn with GraphPad prism 8.

Results

Comparison of general data

The observation group and control group were comparable for sex, age, and smoking history ($P>0.05$ for each comparison). Compared with the control group, the observation group showed lower FEV1, FVC, FEV1/FVC and PO_2 and higher PCO_2 ($P<0.001$, **Table 1**).

Comparison of Cor, CRP level, and adrenal gland size between two groups

Decreased Cor levels and adrenal gland diameter were observed in the observation group, but serum CRP levels increased ($P<0.001$, **Table 2**). An image of adrenal gland is shown in **Figure 1**.

Cor, CRP level, and adrenal gland size in patients with different lung function grades

Compared with patients at grade I (lung function classification), those at grade II-IV presented with lower Cor levels, smaller adrenal gland diameter, and higher CRP levels ($P<0.05$). Moreover, patients at grade IV had lower Cor levels, smaller adrenal gland diameter, and higher CRP levels than those at grade II or III ($P<0.05$); and patients at grade III had lower Cor levels and higher CRP levels compared to those at grade III ($P<0.05$, **Table 3**).

Cor, CRP level, and adrenal gland size in patients with different grades of BODE index

Cor levels were lower, adrenal gland diameter was smaller, and CRP levels were higher in

Table 2. Comparison of Cor, CRP, and adrenal gland size between the two groups

Item	Observation group (n=80)	Control group (n=80)	t	P
Cor (mmol/L)	84.61±23.46	342.65±109.55	20.601	<0.001
CRP (mg/L)	12.78±8.57	1.34±0.65	11.905	<0.001
Adrenal gland size (cm)				
Right body part	3.03±0.64	3.87±0.45	9.603	<0.001
Right outer limb	3.11±0.69	3.65±0.31	6.385	<0.001
Right inner limb	3.06±0.56	3.73±0.48	8.731	<0.001
Left body part	3.05±0.42	3.82±0.47	10.926	<0.001
Left external limb	3.07±0.46	3.61±0.33	8.531	<0.001
Left internal limb	3.09±0.41	3.74±0.50	8.991	<0.001

Note: Cor: cortisol; CRP: C-reactive protein.

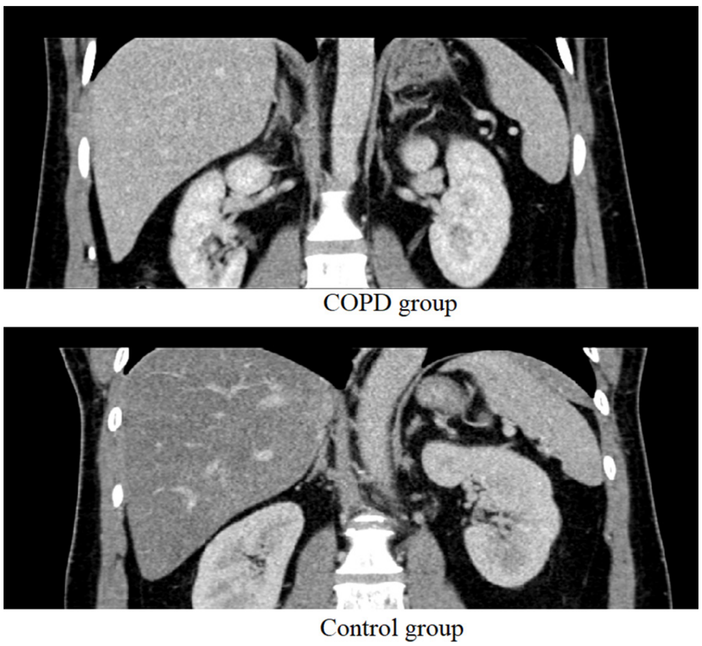

Figure 1. CT images of cortisol in each group. COPD: chronic obstructive pulmonary disease.

patients at grade 2-4 (BODE index classification) than those at grade 1 (P<0.05); compared with patients at grade 2-3, those grade 4 had lower Cor levels, smaller diameter and higher CRP levels (all P<0.05); and lower Cor levels and higher CRP levels were found in patients at grade III compared to those at grade II (all P<0.05; **Table 4**).

Correlation analysis results

The Pearson's Correlation analysis showed that Cor levels, and adrenal gland diameter (right body, right outer limb, right inner limb, left body, left outer limb, and left inner limb) in patients with COPD were positively correlated with PaO_2, FEV1, FVC and FEV1/FVC, but negatively correlated with $PaCO_2$ (P<0.05, **Table 5**).

Results of ROC curve analysis

The follow-up results showed that the prognosis of 21 patients was poor. According to results of ROC curve analysis, the AUC of Cor in predicting the prognosis of patients was 0.812 at a cut-off value of 79.985 mmol/L (P<0.05, **Table 6** and **Figure 2**).

Discussion

With persistently high prevalence and mortality rates, COPD has been regarded as one of the major diseases endangering human health; therefore, it is of great clinical importance to probe COPD-specific biologic indicators to diagnose and treat the disease and assess the prognosis [13-16].

COPD usually induces dysfunction of the HPA axis, and then gives rise to disordered hormone secretion [7]. Persistent stimulation leads to abnormalities in HPA axis and imbalances in its regulation ability. The diameter of the adrenal gland, one of the key organs of the HPA axis, is often associated with the severity of diseases [7]. In the present study, we noticed that the adrenal gland diameter decreased in patients with COPD. Those patients were further grouped according to different lung function grades and the severity of COPD, and it turned

Table 3. Comparison of Cor and CRP levels and size of adrenal glands in patients with different lung function severity

Item	Grade I (n=25)	Grade II (n=21)	Grade III (n=21)	Grade IV (n=13)	F	P
Cor (mmol/L)	102.89±5.34	83.26±8.57[a]	75.23±12.21[a,b]	54.21±5.54[a,b,c]	100.904	<0.001
CRP (mg/L)	7.98±2.24	11.34±3.45[a]	14.93±3.76[a,b]	20.23±1.09[a,b,c]	55.549	<0.001
Adrenal gland size (cm)						
Right body part	3.62±0.58	3.03±0.39[a]	2.98±0.34[a]	2.01±0.24[a,b,c]	39.973	<0.001
Right outer limb	3.64±0.51	3.01±0.4[a]	2.99±0.38[a]	2.04±0.19[a,b,c]	43.256	<0.001
Right inner limb	3.69±0.55	3.05±0.49[a]	3.01±0.43[a]	2.08±0.22[a,b,c]	34.764	<0.001
Left body part	3.78±0.51	3.11±0.45[a]	3.06±0.43[a]	2.15±0.14[a,b,c]	41.184	<0.001
Left external limb	3.57±0.34	3.03±0.29[a]	2.96±0.21[a]	2.01±0.14[a,b,c]	94.992	<0.001
Left internal limb	3.71±0.52	3.11±0.43[a]	3.05±0.34[a]	2.16±0.12[a,b,c]	41.549	<0.001

Note: Cor: cortisol; CRP: C-reactive protein. Compared with grade I patients, [a]P<0.05; compared with grade II patients, [b]P<0.05; compared with grade III patients, [c]P<0.05.

Table 4. Comparison of Cor and CRP levels and adrenal gland size in patients with different BODE levels

Items	BODE grade I (n=24)	BODE grade II (n=21)	BODE grade III (n=20)	BODE grade IV (n=15)	F	P
Cor (mmol/L)	101.56±6.36	83.67±8.44[a]	74.37±13.45[a,b]	56.76±5.87[a,b,c]	74.249	<0.001
CRP (mg/L)	7.44±2.98	11.56±3.21[a]	14.98±3.72 [a,b]	19.46±1.17[a,b,c]	49.562	<0.001
Adrenal gland size (cm)						
Right body part	3.61±0.52	3.05±0.37[a]	3.02±0.35[a]	2.13±0.17[a,b,c]	39.312	<0.001
Right outer limb	3.61±0.53	3.04±0.39[a]	3.00±0.37[a]	2.10±0.21[a,b,c]	37.705	<0.001
Right inner limb	3.67±0.56	3.03±0.37[a]	3.01±0.48[a]	2.10±0.19[a,b,c]	35.052	<0.001
Left body part	3.74±0.54	3.13±0.42[a]	3.07±0.46[a]	2.16±0.17[a,b,c]	35.855	<0.001
Left external limb	3.55±0.36	3.03±0.31[a]	3.02±0.29[a]	2.04±0.16[a,b,c]	69.669	<0.001
Left internal limb	3.73±0.50	3.09±0.41[a]	3.04±0.39[a]	2.13±0.16[a,b,c]	43.718	<0.001

Note: Cor: cortisol; CRP: C-reactive protein. Compared with grade I patients, [a]P<0.05; compared with grade II patients, [b]P<0.05; compared with grade III patients, [c]P<0.05.

Table 5. Size of adrenal glands and Cor level in the observation group are correlated with blood oxygen partial pressure PaO_2, $PaCO_2$, FEV1, FVC, FEV1/FVC level (r (P))

Items	FEV1 (%)	FVC (%)	FEV1/FVC	PCO_2 (mmHg)	PO_2 (mmHg)
Cor (mmol/L)	0.482 (<0.001)	0.453 (<0.001)	0.442 (<0.001)	0.334 (0.004)	0.376 (<0.001)
Adrenal gland size (cm)					
Right body part	0.443 (0.024)	0.403 (<0.001)	0.417 (<0.001)	0.317 (<0.001)	0.371 (0.034)
Right outer limb	0.378 (0.017)	0.396 (0.002)	0.332 (<0.001)	0.335 (<0.001)	0.412 (<0.001)
Right inner limb	0.399 (0.003)	0.371 (<0.001)	0.396 (0.029)	0.392 (0.008)	0.417 (0.044)
Left body part	0.345 (0.012)	0.338 (<0.001)	0.342 (<0.001)	0.314 (<0.001)	0.379 (<0.001)
Left external limb	0.371 (0.043)	0.396 (0.037)	0.386 (0.040)	0.332 (0.023)	0.392 (<0.001)
Left internal limb	0.442 (0.039)	0.345 (<0.001)	0.318 (<0.001)	0.375 (<0.001)	0.404 (<0.001)

Note: Cor: cortisol; CRP: C-reactive protein; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV1/FVC: forced expiratory volume in the first second/ forced vital capacity.

out that the increase in severity of lung dysfunction or BODE index classification led to reduced adrenal gland diameter in COPD, suggesting that adrenal gland diameter might be associated with the development of COPD. Correlation analyses also revealed close corre-

Table 6. ROC curve results

Item	Cut-off value	AUC	95% CI	Sensitivity	Specificity	*P* value
Cor (mmol/L)	79.985	0.812	0.706, 0.918	0.763	0.905	<0.001

Note: ROC: receiver operating characteristic.

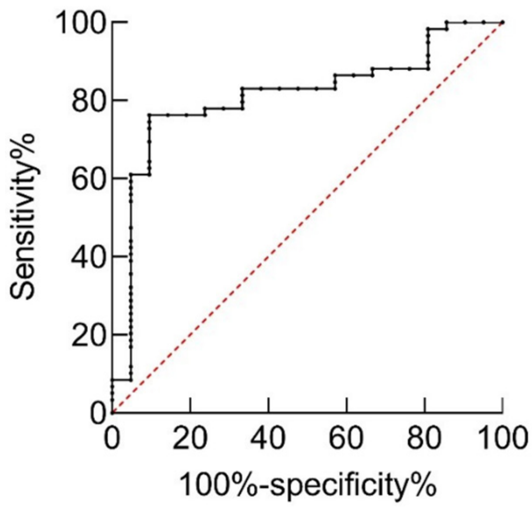

Figure 2. ROC curve results. ROC: receiver operating characteristic.

lations between adrenal gland size and lung function indicators and blood gas, which further indicated that adrenal gland size was closely related to disease severity. In addition, the present study found that there was no statistical difference in adrenal gland size between lung function grade II and grade III patients or BODE grade II and grade III patients. One possible reason for this outcome is that patients with lung function grade II and III or BODE grade II and III are in the middle stage of disease progression with stable adrenal gland size, but the specific mechanism still needs to be further explored.

Cortisol (Cor) is one of the important hormones in the HPA axis that is abnormally secreted in patients under stress [17-19]. The results of studies on Cor levels in patients with COPD are controversial [9, 10]. A previous study suggests that Cor is over-expressed in cases with COPD, and excessive Cor levels cause persistent damage and lead to a vicious cycle [9]. However, due to advanced measurement technologies and improved laboratory capabilities, there are different views. Some studies suggest that serum Cor levels decrease in patients with stable or exacerbated COPD [20-22]. In the present study, serum Cor levels in patients with COPD were lower than those of healthy controls. After further grouping them according to lung function grade and the severity of disease, we found that Cor levels decreased with the increase in severity of lung dysfunction or BODE index classification. In addition, the correlation analysis showed that Cor levels were positively correlated with PaO_2, FEV1, FVC, and FEV1/FVC, suggesting the involvement of Cor in COPD. Possible mechanisms for decreased Cor levels in COPD are as follows [21, 22]: (1) Some patients at high altitude or with hypoxemia are in a state of long-term hypoxia and ischemia, which leads to suppression of pituitary function and excessive secretion of adrenocorticotropic hormones by the hypothalamus, resulting in reduced secretion of Cor; (2) Patients with COPD require higher energy consumption than the normal population, and a long-term high metabolic state gives rise to malnutrition and deterioration of the disease, thereby affecting the adrenal function and leading to insufficient Cor secretion; (3) Systemic inflammatory reactions occurs frequently in cases with COPD, which induces an increase in inflammatory factors in patients with exacerbated COPD, weakens the ability of adrenal glands to secrete Cor and reduces the serum Cor levels. There are few clinical biologic indicators to predict the prognosis of COPD, so we assessed the clinical value of Cor in predicting prognosis by ROC curve. The AUC of Cor in predicting the prognosis of patients was 0.812 at a cut-off value of 79.985 mmol/L, indicating that Cor is clinically valuable and can be used as a biologic indicator to predict prognosis.

This study also has the following limitations: (1) We ignored the circadian rhythm of Cor and changes in Cor levels at different time periods, making it difficult to obtain dynamic data; (2) Few indicators were selected, so possible mechanisms were not explored in depth.

In summary, Cor levels and adrenal gland size are closely associated with the severity of COPD, and Cor levels are predictive of prognosis.

Acknowledgements

This work was supported by the Scientific Research and Technology Development Plan of Guigang: Key Technology and Trial Production (1803006).

Disclosure of conflict of interest

None.

Address correspondence to: Jiemei Feng, Department of Pulmonary and Critical Care Medicine, Guigang City People's Hospital, No. 1 Zhongshan Middle Road, Gangbei District, Guigang 537100, Guangxi Zhuang Autonomous Region, China. Tel: +86-18978586537; E-mail: fengjiemei163@163.com

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