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# Risk Factors for Depression in Patients with Chronic Obstructive Pulmonary Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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**Background:** Depression is a major comorbidity in patients with chronic obstructive pulmonary disease (COPD). The aim of this prospective study was to investigate socio-demographic and clinical factors and serum markers of inflammation, including cytokines that, may be a cause or an association with COPD-related depression.

**Material/Methods:** This study enrolled 53 patients who were hospitalized in the Department of Respiratory Medicine of Hefei First People's Hospital, China between October 2015 and October 2016. Patients were consecutively recruited who were diagnosed with COPD and without lower respiratory tract disease, psychiatric disorders, or a family history of cognitive disorders. All patients were investigated for symptoms of depression. Lung function testing included forced expiratory volume in 1 second ($FEV_1$). Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were measured.

**Results:** Of the 53 patients with COPD, 40 (75.47%) patients had symptoms of depression. Univariate analysis showed that gender, smoking, a high level of education, duration of a cough, $FEV_1$, and serum CRP level were associated with depression. A multivariate logistic regression model identified two risk factors for depression in patients with COPD: serum CRP level and $FEV_1$.

**Conclusions:** The findings of this study showed that the risk factors for COPD-related depression included male gender, heavy smoking, higher academic qualifications, and duration of cough, but the two strongest risk factors were a high serum CRP level and low $FEV_1$.

**MeSH Keywords:** C-Reactive Protein • Depression • Pulmonary Disease, Chronic Obstructive • Respiratory Physiological Phenomena • Risk Factors

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## Background

Chronic obstructive pulmonary disease (COPD) is a common clinical condition that is associated with a high morbidity, comorbidities and has a high mortality rate [1]. By 2020, COPD is projected to be the world's third leading cause of death, after ischemic heart disease (IHD) and cerebrovascular disease (stroke) [2]. In China, 8.2% of the population above 40 years-of-age have COPD [3].

Even with the current medical progress in the diagnosis and management of COPD, the prevalence, the number of hospital admissions, and mortality rate have not declined. In 2015, a global survey was published of cause-specific mortality between 1990–2013, which showed that COPD is a global health problem that is still associated with significant mortality [4]. In the clinical management of COPD, there is a recognized requirement to improve the quality of life for the patient, as well as treatment of the symptoms, but clinicians may not be aware that COPD is often complicated by depression [5], which reduces the quality of life of patients [6], adversely impacts on adherence to medications [7], increases the number of hospital admissions [8], is associated with poor clinical prognosis [9] and increases the rate of suicide [10].

The characteristics of depression in patients with COPD have been extensively studied and have been reported to include younger patient age, female gender, smoking, lower $FEV_1$, duration of cough, an increase in the 50-item St. George's Respiratory Questionnaire (SGRQ) score, and a history of cardiovascular disease [5,11]. Other factors associated with COPD-related depression have been reported to include the level of education, and degree of dyspnea [12,13].

Depression is a mental illness that is caused by many factors [14]. There are differences in demographic and clinical characteristics between male and female patients with depression in China that are different from those in Western countries [15]. The factors associated with COPD-related depression may be different in Chinese patients. As a chronic airway inflammatory disease, COPD is associated with the presence of serums inflammatory mediators [16]. Immune factors have been shown to have a role in depression, and levels of inflammatory mediators can affect mood [17]. Therefore, a study of the relationship between COPD, depression, and serum cytokines and other inflammatory mediators may be useful for understanding the link between depression and COPD.

The aim of this prospective study was to investigate socio-demographic and clinical factors in patients with COPD and symptoms of depression and to measure serum markers of inflammation, including cytokines, which may be a cause or an association with COPD-related depression.

## Material and Methods

### Patients

This prospective study included consecutive patients with COPD hospitalized in the Respiratory Medicine Department of Hefei First People's Hospital, China between October 2015 and October 2016. The patients were diagnosed with COPD based on the guidelines established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [18]. All participants were more than 18-years-of-age and had no recent history of COPD exacerbations. Patients with prolonged intellectual cognitive impairment, mental illness other than depression, asthma, bronchiectasis, a family history of mental illness, and lower respiratory tract diseases, or those who could not complete serum cytokine tests were excluded.

This study was approved by the Ethics Committee of the First People's Hospital of Hefei. All the participants signed informed consent forms.

### Data collection

We recorded the socio-demographic and clinical information for the patient participants, including gender, age, height, weight, education, smoking history, history of asthma, and duration of cough for all participants. Two months after discharge from hospital, each patient had blood taken for serum analysis of cytokines and inflammatory mediators. Pulmonary function measurements were undertaken for the patients who did not have an acute exacerbation of COPD within the past two months, according to the GOLD criteria [18]. There were 53 patients with COPD who completed the pulmonary function and serology tests.

Depression was evaluated using the Chinese version of the 24-scale Hamilton Depression Rating Scale (HDRS) or HAM-$D_{24}$ [19]. A score of >24 on the HDRS was considered to indicate severe depression; 17–24 was considered as moderate depression; 7–17 was considered as mild depression; and <7 was considered as normal [20].

Body mass index (BMI) was calculated by measuring weight and height. Heavy smoking was defined as the number of smoking years × the number of cigarettes smoked per day >400; seldom smoking was defined as the number of smoking years × the number of cigarettes smoked per day <400, and no smoking meant never smoked.

Lung function was assessed to diagnose COPD and determine its severity based on the standardized method recommended by the American Thoracic Society (ATS) [21] using the MasterScreen Pulmonary Function Testing System (CareFusion.





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Germany). The parameters evaluated were forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FVC), as per the guidelines from the ATS and European Respiratory Society (ERS) on standardization of lung function testing [21].

Venous blood samples were taken from each patient at 07.00 hrs and anticoagulated with ethylene diamine tetraacetic acid (EDTA). Two ml of blood was centrifuged to obtain serum, which was immediately stored at –80°C for further analysis of C-reactive protein (CRP), interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-α by the enzyme-linked immunosorbent assay (ELISA) using the human CRP, IL-6, IL-8 and TNF-α ELISA kits (Wuhan Huamei Biological Engineering Co., Ltd., Hubei, China).

### Statistical analysis

The Shapiro-Wilk test was used to verify the normal distribution of continuous variables. The normal distribution data (BMI, $FEV_1$, FVC) was denoted by $\bar{\chi}\pm s$, and the non-normal segment data (age, duration of cough, presence of asthma, $HAM\text{-}D_{24}$, IL-6, IL-8, TNF-α, CRP) was represented by p50 (p25, p75). Normally distributed data (BMI, $FEV_1$, and FVC) were compared using a t-test. Other distribution data (age, duration of cough, presence of asthma, IL-6, IL-8, TNF-α and CRP) were compared using the Mann-Whitney U test. The two sample composition ratios were compared using the chi-square test (gender, smoking, and degree of respiratory failure) and Fisher's exact test. Univariate and multivariate logistic regression analysis was used to assess the risk factors associated with depression. Co-linear analysis was used to perform corrections for multiple comparisons. The analysis was performed using the IBM SPSS Statistic 19.0 (International Business Machines (IBM), Corporation), and $p<0.05$ indicated statistical significance.

## Results

### Descriptive results

In this prospective study, 91 COPD patients without prolonged intellectual cognitive impairment, family history of mental illness, asthma, bronchiectasis and other sub-respiratory tract diseases were initially recruited, of which 53 patients completed the serum cytokine tests.

Of the 53 patients, 37 were men and 86% of them had depression; 16 patients were women and 50% of them had depression. The median age of the patients with and without depression was 77 yrs (range, 52–82 yrs) and 80 yrs (range, 65–83 yrs), respectively. The incidence of depression was greater for heavy smokers (87.5% *vs.* 57.1%) (p=0.012) and for middle school or higher level educated patients with COPD (95% *vs.* 73.7% *vs.* 50%, p=0.009).

The C-reactive protein (CRP) levels (normal level, 3.0 mg/dL) were significantly increased in COPD patients with depression compared with those without depression: mean 20 mg/dL (range, 13–30 mg/dL) *vs.* mean 13 mg/dL (range, 9–20 mg/dL) (p=0.043). Duration of cough was greater in COPD patients with depression (p=0.005). The $FEV_1$ was lower in COPD patients with depression (0.78±0.26 L *vs.* 0.99±0.31 L) (p=0.043). The BMI, age, history of asthma, respiratory failure, FVC, IL-8, TNF-α and IL-6 were similar between the two patients groups with COPD (Table 1).

### Risk factors for depression

In the univariate regression analysis, gender (OR=0.156, 95% CI: 0.040–0.609) (p=0.007), level of education (OR=3.879, 95% CI: 1.486–10.127) (p=0.006), smoking history (OR=5.250, 95% CI: 1.350–20.417) (p=0.017), $FEV_1$ (OR=0.067, 95% CI: 0.006–0.773) (p=0.030), duration of cough (OR=1.094, 95% CI: 1.004–1.191) (p=0.040), and CRP (OR=1.351, 95% CI: 1.131–1.613) (p=0.001) were associated with depression (Table 2).

In the multivariate regression model, CRP (OR=1.295, 95% CI: 1.018–1.717) (p=0.037) and $FEV_1$ (OR=0.001, 95% CI: 0.000–0.524) (p=0.031) were the risk factors for depression (Table 3). The co-linearity, with variance inflation factors (VIF) of serum levels of CRP (VIF=1.940), gender (VIF=2.243), education (VIF=1.927), smoking (VIF=2.575), duration of cough (VIF=1.424) and $FEV_1$ (VIF=1.112) were not significantl (Table 4).

## Discussion

This study analyzed the relationship between depression and chronic obstructive pulmonary disease (COPD) and factors, including cytokines, socio-demography and clinical characteristics. The results showed that male patients, heavy smoking, middle school or higher education, long duration of cough, reduced forced expiratory volume in 1 second ($FEV_1$). and high serum C-reactive protein (CRP) levels were associated with an increased incidence of depression in patients with COPD. Some of these factors (smoking, cough, and low $FEV_1$) were consistent with previous studies [5,11]. However, the present study has shown that male gender was associated with depression in COPD and that a raised serum CRP level was a strong risk factor of COPD-related depression.

Previous studies have shown a link between the immune response and depression [22–24]. Patients with COPD show some degree of systemic inflammation characterized by increased levels of inflammatory mediators, including interleukin (IL)-6, IL-8, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) [25]. Changes in levels of inflammatory cytokines were also associated with depression [26,27]. In the





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**Table 1.** Characteristics of COPD patients with and without depression.

| | N | No depression | Depression | P |
|---|---|---|---|---|
| **Age** | | 80 (65.83) | 77 (75.82) | 0.926 |
| ***Gender (n,%)*** | | | | 0.08 |
| Male | 37 | 5 (13.5%) | 32 (86.5%) | |
| Female | 16 | 8 (50%) | 8 (50%) | |
| ***Education (n,%)*** | | | | 0.009 |
| No education | 14 | 7 (50.0%) | 7 (50.0%) | |
| Primary school | 19 | 5 (26.3%) | 14 (73.7) | |
| Middle school or higher | 20 | 1 (5.0%) | 19 (95.0%) | |
| ***Smoking (n,%)*** | | | | 0.012 |
| Heavy smoking | 32 | 4 (12.5%) | 28 (87.5) | |
| Seldom Smoking or no smoking | 21 | 9 (42.9%) | 12 (57.1%) | |
| **HAMD score** | | 4.38±1.60 | 11.55±4.19 | <0.001 |
| **BMI (kg/m$^2$)** | | 20.64±2.25 | 21.43±3.13 | 0.407 |
| ***Respiratory failure (n, %)*** | | | | 0.285 |
| II-respiratory failure | 18 | 6 (33.3%) | 12 (66.7%) | |
| No respiratory failure | 35 | 7 (20.0%) | 28 (80%) | |
| **Years of cough (year)** | | 13 (9.20) | 20 (13.30) | 0.034 |
| **Years of asthma (year)** | | 8 (3.10) | 10 (5.19) | 0.432 |
| **FEV$_1$ (L)** | | 0.99±0.31 | 0.78±0.26 | 0.043 |
| **FVC (L)** | | 1.70±0.48 | 1.65±0.48 | 0.775 |
| **IL-8 (pg/ml)** | | 802.8 (795.0, 806.8) | 801.8 (799.1, 806.7) | 0.951 |
| **TNF-α (pg/ml)** | | 29.4 (22.7, 33.2) | 23.3 (13.1, 47.1) | 0.358 |
| **IL-6 (pg/ml)** | | 35.8 (30.6, 57.4) | 31.4 (27.1, 41.6) | 0.123 |
| **CRP (mg/L)** | | 3.10 (1.21, 7.40) | 13.02 (3.27, 16.05) | 0.005 |

The normal distribution data (BMI, FEV$_1$ and FVC) is denoted by mean ± standard deviation and the non-normal segment data (age, time of cough, time of asthma, IL-6, IL-8, TNF-α and CRP) is represented by median (lower quartile, higher quartile).
FVC – forced vital capacity; FEV$_1$ – forced expiratory volume in the first second; BMI – body mass index; CRP – C-reactive protein; IL-6 – interleukin-6; IL-8 – interleukin-8; TNF-α – tumor necrosis factor-α; m – meters; kg/m$^2$ – kilograms per square meter; L – liter; ml – milliliter; pg – picogram.

present study, we selected four cytokines, CRP, IL-6, IL-8 and TNF-α, and analyzed the relationship between each cytokine and depression. The serum CRP levels of patients with COPD and depression were significantly increased when compared with patients without depression, indicating that CRP may be a risk factor of depression. There were no changes in serum levels of IL-6, IL-8 and TNF-α.

CRP is an acute phase protein that increases in inflammatory conditions, and during bacterial and viral infections [28,29]. CRP is useful in evaluating COPD exacerbations [30]. A high serum CRP level has been reported to be a risk factor for re-hospitalization in COPD [31] and poor outcome [32]. In stable COPD patients, serum CRP levels were independently associated with total COPD assessment test score [33]. The other risk factor of depression in our study was lower FEV$_1$. Respiratory symptoms can have harmful effects resulting in a reduction in





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**Table 2.** Univariate logistic regression of risk factors for COPD-related depression.

| | OR | CI (95%) | P |
|---|---|---|---|
| **Age** | 1.025 | 0.946–1.112 | 0.541 |
| ***Gender*** | 0.156 | 0.040–0.609 | 0.007 |
| ***Education*** | 3.879 | 1.486–10.127 | 0.006 |
| ***Smoking*** | 5.250 | 1.350–20.417 | 0.017 |
| ***Respiratory failure*** | 0.707 | 0.372–1.343 | 0.290 |
| **BMI (kg/m$^2$)** | 1.101 | 0.880–1.376 | 0.401 |
| **Years of cough (year)** | 1.094 | 1.004–1.191 | 0.040 |
| **Years of asthma (year)** | 1.044 | 0.953–1.144 | 0.351 |
| **$FEV_1$ (L)** | 0.067 | 0.006–0.773 | 0.030 |
| **FVC (L)** | 0.820 | 0.220–3.056 | 0.768 |
| **IL-8 (pg/ml)** | 1.029 | 0.955–1.108 | 0.454 |
| **TNF-α (pg/ml)** | 0.998 | 0.967–1.030 | 0.906 |
| **IL-6 (pg/ml)** | 0.984 | 0.962–1.007 | 0.168 |
| **CRP (mg/L)** | 1.351 | 1.131–1.613 | 0.001 |

**Table 3.** Multivariate logistic regression of risk factors for COPD-related depression.

| | OR | CI (95%) | P |
|---|---|---|---|
| Gender | 0.084 | 0.004–1.648 | 0.103 |
| Education | 5.428 | 0.725–40.620 | 0.099 |
| Smoking | 1.117 | 0.060–20.910 | 0.941 |
| Time of cough (year) | 0.926 | 0.755–1.136 | 0.459 |
| $FEV_1$ (L) | 0.001 | 0.000–0.524 | 0.031 |
| CRP (mg/L) | 1.295 | 1.018–1.717 | 0.037 |

**Table 4.** Collinear diagnosis of CRP, gender, education, smoking, time of cough and FEV1.

| | VIF |
|---|---|
| CRP | 1.940 |
| Gender | 2.243 |
| Education | 1.927 |
| Smoking | 2.575 |
| Time of cough | 1.424 |
| FEV1 | 1.112 |

the quality of life of the patient [34,35]. Depression is associated with worse health status and lower quality of life [36,37]. We hypothesized a link between a high CRP level, infection, risk of exacerbations, respiratory symptoms and depression in patients with COPD.

Two factors related to socio-demography (gender and education) are different from GOLD [38]. Many Western studies have shown that women with COPD are more likely to have depression, because they bear more family stress than men [39,40]. However, the results of our study showed that men are more likely to have depression. This could be because in China the traditional Confucian ideas are predominant, whereby men take full responsibility to support the family, while most women are expected to be housewives [39], so men bear more family pressure. In addition, depression is closely related to smoking [41]. Smoking is an important risk factor of COPD [42], and also closely related to depression [43,44]. In this study, 92% of men smoked but only 6% females did, which could also be related to the higher rate of depression in men.

In the present study, when compared with patients with no education and primary school education, more patients with middle school or higher education were found to have depression. However, previous studies had shown that when compared to





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patients with no education, elementary school, middle school and high school education, patients with a bachelor degree had fewer depressive symptoms [12,45]. The potential reasons for this difference could be firstly that highly educated patients have less depression because they can better understand their own diseases and implement self-management of diseases such as epilepsy, diabetes and COPD [46–48]. However, in this study, the majority of the 'well-educated' group only graduated from middle school, so they were not highly educated people. Also, due to the older age of these patients, many of them did not have an understanding of the disease, and could not implement self-management, leading to depression

This study had some limitations. The study had a small sample size and was conducted at a single center, and is not a comprehensive representation of COPD patients with depression and its biological subtype characteristics in China as a whole. This study was a small prospective, observational study, but the findings are of interest and should be followed up in future with larger, multi-center controlled clinical studies.

## Conclusions

The findings of this study showed that the risk factors for COPD-related depression included male gender, heavy smoking, higher academic qualifications, and duration of cough, but the two strongest risk factors were a high serum CRP level and low $FEV_1$.

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