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Risk factors associated with acute exacerbation of chronic obstructive pulmonary disease: A retrospective analysis in 4624 patients.

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Abstract

Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) has high death rate and its hospitalization costs are more than AIDS or tuberculosis. The factors causing exacerbation are largely unknown. This study is aimed to make sense of the fatality risk factors associated with AECOPD and find the measures to take early intervention to reduce the mortality; the present study was to make a retrospective analysis of clinical data of in patients with AECOPD. Totally 4624 cases were collected, who were admitted into the 2nd hospital of Hebei medical university for AECOPD from January 2005 to December 2014. Among them, 314 cases (6.8%, death group) died during hospitalization *vs.* 4310 cases (93.2%, survival group) survived finally. To identify the fatality risk factors, T test, chi-square test, Logistic regressions were used by SPSS19.0 software. Different factors were assessed by Odd Ratio (OR) value and the results were displayed in a descending order as follow: elevated $PaCO_2$, complication, mechanical ventilation, supportive care, the damage of lung function, PaO_2, pulmonary infection, the frequency of acute attack, the length of illness course, Body Mass Index (BMI), age. The death of AECOPD is up to the synergistic effect of the fatality risk factors presented above and as a result, systematic care and multiple organ supportive therapy seem especially important in the prognosis effect of AECOPD patients.

Keywords: AECOPD, Death, Fatality risk factor, Logistic regressions.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD), is a devastating lung disease, which is characterized by reversible airflow limitation. This airflow limitation is progressive and could be exacerbated by inhalable particles and noxious gas in our daily life [1-5]. COPD is a common and frequently-occurring disease, and its morbidity could be as high as 10% around the world. The patients with COPD always experience a long illness course, high disability and mortality rate, which impose a substantial burden to our society. Recently, as the environmental degradation and atmospheric haze goes down, it is predictable that the morbidity of COPD of our country will experience a dramatic raise year by year [5-8]. It is a global health issue, with cigarette smoking being an important risk factor universally; other factors, such as exposure to indoor and outdoor air pollution, occupational hazards, and infections, are also important. As the global population ages, the burden of COPD will increase in years to come. It is worth mentioning that recent epidemiologic study had confirmed above prophesy and this trend may not be changed in the next 10 years, and in the meantime, the mortality of COPD may also experience a significant raise too [8-10]. The average COPD patient experiences two to four exacerbations per year. The more severe the COPD, the more frequent the exacerbations, hospitalizations and bacterial infections.

The challenge we will all face in the next few years will be implementation of cost-effective prevention and management strategies to stem the tide of this disease and its cost. COPD remains an important disease globally. Our greater understanding of disease pathogenesis, prognosis, and treatment should result in better outcomes for many of our patients. Against this background, recognizing fatality risk factors and figure out effective measurement to decrease the mortality of COPD would be particularly important. The objectives of this study were to assess the risk factors that may be associated with exacerbations and find the measures to take early intervention to reduce the mortality.

Materials and Methods

General data

A total of 4624 patients were admitted into our hospital for Acute Exacerbation of Chronic Obstructive Pulmonary Disease

(AECOPD) from January 2005 to December 2014. Among these patients, 314 cases died during hospitalization, which account for 6.8% of the total and were named death group. The rest 4310 cases were survived to the end, which accounted for 93.2% of the population and were named survival group. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hebei Medical University. Written informed consent was obtained from all participants.

Inclusion criteria

1. Accorded with the COPD diagnostic criteria that mentioned in the guidelines for diagnosis and management of chronic obstructive pulmonary disease which was put forward by Respiratory Society of Chinese Medical Association [11]; 2. Accorded with the diagnosis criteria of AECOPD: contained two of the following three clinical manifestations: aggravated cough, dyspnoea and purulent sputum.

Exclusion criteria

Patients with one of the following situations would be excluded: 1. Patients who were admitted into hospital for other reasons but not AECOPD; 2. Died for other reasons but not COPD; 3. Patients that did not follow medical advice; 4. Patients discharged from hospital without doctor's permission.

Collection of clinic data

The clinical data we collected involved demographic data, laboratory data and medical information while in hospital. Specific indicator included: gender, age, occupation, height, weight, smoking history, disease duration, exacerbation frequency per year, length of hospital stay, White Blood Cell (WBC), NE%, the PH/PaO_2/$PaCO_2$/SaO_2 in arterial blood gas analysis, forced vital capacity, Forced Expiratory Volume in one second (FEV1), FEV1/Forced Vital Capacity (FVC), blood potassium, blood sodium, blood glucose, Alanine Transaminase (ALT), Aspartic Transaminase (AST), carbamide, creatinine, the results of sputum culture or imageological diagnosis, and complications.

Statistical analysis

Epidata 3.1 was used to establish this database and all process was executed by SPSS19.0 software. Measurement data were presented as means ± standard deviation and were analysed with student's T test; enumeration data were present as n% and were analysed with chi-square test; single factor analysis methods was used to analyse gender, age, smoking history, disease duration, Body Mass Index (BMI), exacerbation frequency, pulmonary function, PaO_2, $PaCO_2$, sputum culture, supportive care, mechanical ventilation, complications and any other indicators. Logistic regression was executed to future analyse the indicators that had been screened out in the process of single factor analysis.

Results

Single factor analysis

Before making logistic regression analysis, T test or Chi-square test were executed to figure out the simple effect of the indicators above respectively. The results showed that elderly patients, long disease duration, low BMI value, terrible lung function, low PaO_2, high $PaCO_2$, positive culture result of bacteria or fungus, receiving supportive care or mechanical ventilation, the more complications and exacerbation frequency per year have a close relationship with death rate. Both of these relationships have statistical significance (Table 1).

Table 1. *Single factor analysis.*

Risk factors	Death groups (n=314)	Survival groups (n=4310)	P
Gender			0.194
Male	234	3064	
Female	80	1246	
Age			<0.001
<40	0 (0)	16 (3.7)	
40-49	2 (0.6)	110 (2.6)	
50-59	18 (5.7)	504 (11.7)	
60-69	88 (28.0)	1394 (32.3)	
70-79	112 (35.7)	1646 (38.2)	
≥ 80	94 (29.9)	640 (14.8)	
Disease duration			<0.001
≤ 5 years	8 (2.6)	1016 (24.4)	
6-9 years	24 (7.9)	390 (9.3)	
10-14 years	54 (17.8)	1706 (40.9)	
15-19 years	92 (30.3)	106 (2.5)	
≥ 20 years	126 (41.4)	954 (22.9)	
Smoking			0.263
Yes	172 (54.8)	2500 (58.0)	
No	142 (45.2)	1810 (42.0)	
BMI (kg/m^2)			<0.001
<21	172 (54.8)	1220 (28.3)	
21 ≤ BMI<24	72 (22.9)	1040 (24.1)	
24 ≤ BMI<28	50 (15.9)	1106 (25.7)	
≥ 28	20 (6.4)	944 (21.9)	
Acute attack			0.002
≥ 2 times	294 (93.6)	3648 (84.6)	
<2 times	20 (6.4)	662 (15.4)	

Pulmonary function			<0.001
I	17 (8.1)	636 (22.5)	
II	23 (11.0)	937 (33.1)	
III	95 (45.5)	1090 (38.5)	
IV	74 (35.4)	168 (5.9)	
PaO_2			<0.001
<60	174 (58.8)	916 (26.7)	
≥ 60	122 (41.2)	2450 (73.3)	
$PaCO_2$			<0.001
≤ 50	58 (19.7)	1982 (58.4)	
>50	238 (80.3)	1414 (41.6)	
Bacteria culture			<0.001
Positive	154 (49.0)	1066 (24.7)	
Negative	160 (51.0)	3244 (75.3)	
Fungus culture			<0.001
Positive	92 (29.3)	892 (20.7)	
Negative	222 (70.7)	3418 (79.3)	
Supportive care			<0.001
Yes	228 (72.6)	1616 (37.5)	
No	86 (27.4)	2694 (62.5)	
Mechanical ventilation			<0.001
Yes	214 (68.2)	1410 (30.6)	
No	100 (31.8)	2900 (69.4)	
Complication			<0.001
Yes	304 (96.8)	3690 (85.6)	
No	10 (3.2)	620 (14.4)	

Multivariate logistic regression analysis

We incorporated the indexes that have proven to have statistics significance into multivariate logistic regression model. The results shows that age, disease duration, BMI value, exacerbation frequency per year, lung function, PaO_2, $PaCO_2$, the results of bacteria and fungus, supportive care, mechanical ventilation and complications are risk factors that are associated with death rate. For COPD patients, every increased age group, decreased BMI scale, worse lung function grade and increased disease duration, the mortality risk increased 1.109/1.653/4.063/1.807 times respectively. The patients with more than 2 times acute exacerbation per year, positive results of bacteria or fungus culture, complications, the need of supportive care and mechanical ventilation, low PaO_2 and increased $PaCO_2$ experience 2.396, 2.929, 1.615, 5.108, 4.387, 4.401, 3.584, 5.752 times increase in death rate compared with patients without these risk factors respectively. All of these results have statistical significance with $P<0.05$ (Table 2).

Table 2. *Logistics regression analysis.*

Variate	Regression coefficient (B)	Significance (P)	Odds ratio (OR)	95% CI of OR value	
				Lower bound	Upper bound
Age	2.896	0.033	1.109	1.005	1.214
BMI	0.502	0.016	1.653	1.13	2.667
Lung function	3.181	<0.001	4.063	3.123	4.864
Disease duration	2.214	0.019	1.807	1.643	1.932
Frequency of acute attack	5.431	0.028	2.396	1.559	3.682
Bacteria culture (+)	0.657	0.031	2.929	2.323	3.693
Fungus culture (-)	0.943	0.016	1.615	1.253	2.082
Complications	16.525	0.008	5.108	2.705	9.645
Supportive care	4.206	0.017	4.387	3.397	5.664
Mechanical ventilation	5.027	0.018	4.401	3.442	5.628
PO_2	1.234	0.034	3.584	2.809	4.566
PCO_2	3.715	0.025	5.752	4.282	7.725

Discussion

It has been documented that there were about 40 million patients who suffered from COPD, and most of them were older than 40 years old with smoking history. Foreign study has reported that the death rate of COPD inpatients range from 2.5%-30% [12-14]. Gudmundsson et al. [15] have reported that age, the frequency of acute attack, FEV1, over-breathing, pulmonary hypertension, LTOT and mechanical ventilation have close relationship with death of hospitalized patients with

COPD. Postma et al.'s [16] research have proved that all of smoking, age, pneumonia, pulmonary hypertension, lung function status were risk factors that leaded to the death of COPD patients. The domestic studies have reported that the risk factors to COPD included age, smoking, acute attack frequency, lung function status, combined with pulmonary hypertension, PaO_2, $PaCO_2$, usage of corticosteroids, pseudomonas pyocyanceinfection, complicated with diabetes and chronic renal failure. Ingrids' groups research proved that age, pulmonary function status, VC, DLco, and MVV had close relationship with the death of COPD, while BMI, PaO_2, $PaCO_2$, TLC, RC, quality of life had no relationship with it. In this study, through retrospective analysis, we found that fatality risk factors associated with AECOPD include impaired PaO_2, increased $PaCO_2$, complications, mechanical ventilation, received supportive care, exacerbation of lung function status, pulmonary infection, increased times of acute attack, long disease duration, lower BMI, old age; and our result was in accordance with most paper [17].

Ashitani et al. and Gabay et al. [18,19] has reported that the onset of COPD has close relationship with age. With increasing age, the body's immune function and the function of organs experience significant degradation, and lung is no exception. As a result, occurrence of lung infection is very common, and this may be the reasons of age to be independent risk factors of COPD. In the present study, we found that the older the patients are, the more chance the patients die. Every one increase in age grades, the death risk increases 1.109 times, and the result is in accordance with relevant documents. Hyoxemia could stimulate the increase of RBC in blood. As a result, the blood viscosity will increase and the blood is more likely to clot. Accordingly, the patients are more likely to thrombose, and result to pulmonary hypertension. Hypercapnia could induce the right shift of oxyhemoglobin dissociation curve; increase the blood supply of brain; increase the intracranialpressure and finally lead to disturbance of consciousness. In the other hand, CO_2 could impair the vascular endothelium and alveolar epithelium, aggravate pulmonary oedema, increase the chance of infection and finally lead to the further exacerbation of COPD [18]. In this study, hypoxia and hypercapnia were proven to be important risk factor that lead to the death of COPD suffers once again. Blood gas analysis could reflect disturbance of the internal environment homeostasis. As a result of hypoxia and hypercapnia, acid-base imbalance, electrolyte disturbance and infectious toxic encephalopathy is the direct cause of COPD patients.

For COPD patients, pulmonary function experiences a progressive decrease; and the worse basal lung function is, the faster the impair progress [18-20]. In this study, we make an analysis of the lung function status of every patient that incorporated into this research and found that in death group the patients with pulmonary function at III or IV grade account for 80.9% and its proportion is higher than survival group. Every one grade increase in lung function, the death risk increase 4.063 times [21-23]. Makoto et al. has reported that spirometry plays a significant role in the diagnosis, disease evaluation and clinical effect evaluation. Masashi et al. has reported that BMI is an independent risk factor for COPD, and this point has been conformed once again. In the clinical work, BMI was used to assess nutritional status. The decrease of BMI indicated bad nutritional status and weakened function of immune system. As a result, the risk of infection and complication are increase. In the same times, low BMI patients always exist respiratory muscle weakness, which leads to lower PaO_2, $PaCO_2$, and exacerbation of respiratory failure and which make it to be a death related risk factor. Mechanical ventilation is a common tool in the treatment of COPD, and it could dramatically prolong the life span of patients. In the other hand, Gianfranco et al. [13], has reported that mechanical ventilation is a death related factor for COPD. The reasons may attribute to the patients' basal health condition. The patients, who need mechanical ventilation, always complicated with hypercapnia, electrolyte disturbance and MODS, which indicated the patients' worse condition [24-27]. In addition, mechanical ventilation increases the risk of lower respiratory infection, which increases the death risk too. The patients need mechanical ventilation always has a hypermetabolic and hypercatabolic state, and with a high body proteolysis rate, which lead to hypoproteinemia and as a result, decrease the patients' survival rate. Finally, mechanical ventilation always make a heavy load to patients' family; which isn't afford to most of Chinese family and limited the clinic effect of mechanical ventilation. As a consequence, MOF or death is inevitable. So, in the process of mechanical ventilation, beside airway management, nutritional support, maintaining the balance of electrolyte and acid-base equilibrium avoid infection and complications are assignable. Complications are also death risk factor for COPD, because they can accelerate the process of disease, and complicated the medical treatment. So attaching importance to complication is assignable too.

In conclusion, COPD is a chronic progressive disease; many risk factors interact each other, and finally lead to the death of patients, which cannot be interpreted by single factor analysis. In Ingrid team's opinion, PaO_2 and $PaCO_2$ are associated with death risk, only in the condition that the patient has a severe impaired lung function. On account of regional difference and different family economy condition, the direct factor that leads to death is different from each other. COPD is an airway disease with systemic influence, which is often complicated with other disease. So in the process of treatment, we must attach importance to the protection of systemic and organ protection in order to lower the death rate of AECOPD.

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Conflict of Interest

All authors have no conflict of interest regarding this paper.

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