Clinical characteristics and risk factors for mortality in patients with COVID-19 and chronic obstructive pulmonary disease in Wuhan, China

Hao Zeng
Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Weiwei Huang
Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Yujie Liu
Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Lan Dong
Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, China

Qifan Zhang
Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, China

Shengmin Zhao
Department of Respiratory and Critical Care Medicine, Lung Cancer Treatment Center, West China Hospital, Sichuan University, Chengdu, China

Luowen Xin
Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Zhixin Huang
Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, China

Yalun Li (✉ 59968642@qq.com)
Department of Respiratory and Critical Care Medicine, Lung Cancer Treatment Center, West China Hospital, Sichuan University, Chengdu, China

Panwen Tian (✉ mrascend@163.com)
Department of Respiratory and Critical Care Medicine, Lung Cancer Treatment Center, West China Hospital, Sichuan University, Chengdu, China

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Research Article

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Abstract

Patients with COVID-19 and COPD are at high risks. However, the risk factors for mortality in COPD patients infected COVID-19 are limited. In this retrospective study, consecutive COPD cases infected COVID-19 in East District of People's Hospital of Wuhan University from Jan 11th 2020 to Mar 28th 2020 were included. Different outcomes were compared between dead and discharged patients. Cox regression analysis was performed to explore the risk factors for death. Totally, 52 cases were included (aged 64.0-79.0 years, 39 [75.0%] males). Common symptoms on admission were cough (43, 82.6%), fever (41, 78.8%) and expectoration (21, 40.3%). Thirty-eight (73.1%) patients were discharged, and 14 (26.9%) cases were dead which mainly caused by multiple organ failure (7, 50.0%) and respiratory failure (6, 42.9%). Multivariate analysis indicated that age > 70 years (HR, 7.859, 95% CI: 1.376, 44.875; P = 0.020) and count of lymphocyte ≤ 0.8×10^9/L (HR, 27.429, 95% CI: 3.336, 225.530; P = 0.002) were risk factors for death. The study showed that close monitoring of the risk indexes is important for early supportive care during the management of patients with COVID-19 and COPD.

Introduction

Coronavirus Disease 2019(COVID-19) is a respiratory disease caused by the 2019 novel coronavirus (2019-nCoV), has infected over 12.7 million people around the world and caused more than 560,000 deaths until 11 July, 2020[1]. It was confirmed that 2019-nCoV used angiotensin converting enzyme II (ACE-2) as the cell entry receptor[2]. While the population is generally susceptible to the 2019-nCoV, patients with any comorbidity yielded poorer clinical outcomes than those without, such as chronic obstructive pulmonary disease (COPD), diabetes, hypertension and malignancy[3].

More than 250 million people around the world live with COPD and millions remain undiagnosed[4]. Published studies showed that there were 1.5% patients with COVID-19 and COPD in the studied populations, and the mortality was 50% among patients with COVID-19 and chronic pulmonary diseases[5, 6]. COPD up-regulated ACE-2 expression in lower airways, which in part may explain the increased risk of severe COVID-19 or mortality in patients with COVID-19 and COPD[7]. Previously studies showed a worse outcomes in patients with COVID-19 and COPD compared with those without COPD, while did not descript the risk factors for mortality in these population[8, 9]. Additionally, a proportion of COPD infected COVID-19 will treat their illness at home probably under the pandemic of COVID-19[10]. So, in future scenarios of resource limited settings, it is important to stratified this population for determining who were at the higher risk and need supportive care in the hospital. In our study, we aimed to investigate the clinical characteristics of COPD infected COVID-19 patients and the risk factors for mortality, aiming to optimize the management of this population.

Results

General characteristics and clinical presentations

The study population included 38 discharged and 14 dead COPD patients infected COVID-19 from Jan 11th 2020 to Mar 28th 2020. Table 1 shows characteristics of the 52 patients included in analyses; The median age was 69.0 years (64.0-79.0) and among them 39 (75.0%) were males. Notably, three fourths patients had at least one co-morbidity, hypertension was the most frequent type of co-morbidities (21, 40.3%), followed by brain disease (10, 19.2%). The most common symptoms and signs on admission were similar to COVID-19 patients without COPD, large proportion patients presented as cough, fever and expectoration.

Treatment and clinical outcome

In our cohort, the median time from onset of symptom to admission was 12.0 days (8.0-19.0). Almost all the patients received oxygen therapy, and only one patient requiring tracheal intubation and extracorporeal membrane oxygenation (ECMO) because of progressive hypoxia (Table 2). The most common anti-virus agents were arbidol (35,67.3%), oseltamivir (13,25.0%), ribavirin (10,19.2%). Thirty-eight patients (73.1%) were prescribed at least one antibacterial agent. During the time of management, we found that multiple organ failure was the most frequent type of complications (7,13.4%) and causes of death. At the end of study, 38 patients (73.1%) were cured with a median hospital stay of 19.5 days (12.8-36.0) and 14 patients (26.9%) died, with a median time 6.0 days (2.0-8.3) from onset of symptom to death, the cause of death included multiple organ failure (7,50.0%), follow by respiratory failure (6,42.9%) and severe complications (1,7.1%).

Compared characteristics of dead and discharged patients

Demographic and clinical features of dead and discharged patients are shown in table 3. As of Mar 28, 2020, fourteen (26.9%) of the patients developed clinical death events. The median age with dead patients was 80.0 years (73.5-89.3) and the median age with discharged patients was 68.5 years (63.0-70.5), the difference is statistically significant ($p<0.001$). Nine dead patients (64.3%) and 9 discharged patients (23.7%) had chest distress symptoms on admission ($p=0.016$). Hypertension (9, 64.3% vs 12, 31.6%), coronary heart disease (6, 42.9% vs 2,5.3%) and brain disease (6, 42.9% vs 4,10.5%) were more common in dead patients ($p<0.05$).

Compared laboratory characteristics, treatment and complications of dead and discharged patients

Data from laboratory tests showed that CD3, CD4, CD8, CD19, CD16+56, lymphocyte count and platelet count of dead patients on admission were lower than that of discharged patients ($p<0.05$), while neutrophil count, D-Dimer, procalcitonin, AST, urea and creatinine of dead patients on admission were higher than that of discharged patients ($p<0.05$) (Table 4). But not statistically in treatment and complications of two groups excluded antibacterial treatment and non-invasive ventilator which may be caused by the severe illness of the dead group (Table 4).

Prognostic factors of the dead COPD patients infected COVID-19

The association of clinical factors with death events is summarized in Table 5 by multivariate-adjusted Cox proportional hazards model. Compared with patients over 70 years old, patients aged 70 and under had a lower risk of developing death events with borderline statistical significance, patients over 70 years old had an increased risk of developing death events (HR=7.859, 95%CI 1.376-44.875, p=0.020). Furthermore, patients with lymphocyte count 0.8*10^9/L and below had a statistically significant higher risk for developing death events (HR=27.429, 95%CI 3.336-225.530, p=0.002). The adjusted survival curve of death events showed that patients who over 70 years old or lymphocyte count 0.8*10^9/L and below had significantly higher death events (Figure 1a and 1b).

Discussion

From the findings of our survey, our study described the clinical characteristics and risk factors for mortality of COPD infected COVID-19 patients. And we found the high case fatality rate was 14 (26.9%) which mostly caused by multiple organ failure and respiratory failure. Logically, we roundly compared the characteristics, such as clinical characteristic, laboratory characteristics and complications, of COVID-19 infected dead patients and discharged patients in the next step. Additionally, we further analyzed the risk factors for death based on multivariate analysis in COPD infected COVID-19 patients and found that age>70 years and decreased lymphocyte were risk factors for death.

Coexisting illnesses would increase the risk for severity of COVID-19 and number of studies have proved that COPD contributes to the worse outcome of Covid-19[5, 7, 11-13]. To the best of our knowledge, the data of COPD infected COVID-19 patients was still limited. In the present study, we showed that the most common symptoms and signs at admission were fever, cough, expectoration and chest tightness. Because the first two clinical manifestations were consistent with those of COVID-19 patients reported in several researches of epidemiological investigations, it is challenged to make differential diagnosis of COVID-19, resulting in delayed diagnosis and management.[4] But probably, expectoration and chest tightness might remind clinical doctors to consider the occurrences of co-morbidities[14-16]. In addition, the median age of the COPD infected COVID-19 patients was older than that of the whole population, which has been shown to be a risk factor for the progression of COVID-19[14, 17, 18]. It is also worth noting that the majority of COPD infected COVID-19 patients had at least one co-morbidity. Although almost the whole patients administrated with oxygen therapy and even the ECMO, nearly one third of the patients were died because of multiple organ failure and respiratory failure, and the mortality rate resembled that of a previous study of older patients[19]. This is partly because of a larger proportion of severely or critically patients admitted to East District of People's Hospital of Wuhan University, a designated hospital for severe COVID-19. But notably, rapid deterioration of lung function was found in the dead with a median time of 6 days from onset of symptom to death. Because of the physically frail and higher rate of co-morbidities in the elderly individuals, COPD infected COVID-19 patients have a high risk for poor outcomes[18, 19]. How to diagnose the COPD infected COVID-19 patients early and improve individual management are problems that need to be considered further under the background of COVID-19 pandemic.

In the present study, significant differences were found in characteristics and laboratory findings between the COVID-19 infected dead patients and discharged patients. As showed above, the age of dead patients was significantly higher than that in the discharged patients and further multivariate logistic regression analysis revealed age > 70 years as a strong predictor for death of COPD infected COVID-19 patients. Also, chest distress was evidently observed in the dead group which seems to be related to the deterioration of lung function and may be associated with poorer prognoses as previously reported in older patients with COVID-19[19]. Monitoring the COPD infected COVID-19 patients for the symptom was benefit for early intervention to reduce the case-fatality rates. Moreover, the proportion of patients with brain disease, hypertension or coronary heart disease was significantly higher in the dead group than in the discharged group. It has been proved that the latter two co-morbidities were predictors for mortality of COVID-19[20-22]. Brain disease may lead to adverse outcomes for COPD infected COVID-19 patients and the potential impact of brain disease on the disease outcomes requires further analysis. But our current data demonstrated that it is important to protect vital organs to increase the numbers of survivals.

Previous studies shown that viral infections mainly destroyed lymphocytes and primarily damaged the immune system, resulting in the decrease of the absolute number of lymphocytes[23]. Similarly, lymphocytopenia was observed in COVID-19 patients[24]. In the present study, we showed that lymphocyte count ≤ 0.8*10^9/L was a strong predictor for death based on multivariate analysis. Moreover, the count of CD3+, CD4+, CD8+ T cells CD19+ B cells and CD16+56+ NK cells were all significantly reduced in the dead patients. Studies also found that count of all the six indexes were decreased in dead or severe cases, and showed CD3+, CD8+ T cells ≤ 75 cell/μL were predictors for high mortality of COVID-19[11, 20, 25]. The stability of the internal immune environment is partly depending on CD4+ and CD8+ T cell. So, the level of T lymphocyte is related to the severity of disease and could be used as an indicator for dynamically monitor the progression of disease. In addition, procalcitonin (PCT), aspartate aminotransferase (AST), urea, D-Dimer and creatinine (Cr) were significantly higher in the deceased patients, while the count of platelet was significantly decreased. These indexes indicated that the dead group had a rate of bacterial infection, liver, kidney or coagulation dysfunction[19, 22]. Close monitoring of these indexes is benefit for early warning of unfavorable outcomes and determine an effective individual treatment strategy. For example, dynamically monitoring the level of PCT is benefit for initiating antibacterial agents[26-29].

Our study has several limitations. First, due to the sample size this study and does not meet the requirements of Event Per Variable (EPV), the results may not be robust enough. However, the results are interpretable and thus still displayed. The reliability of the result needs to be confirmed by further study. In addition, the mortality rate of COPD infected COVID-19 patients might be higher than that in other centers as East District of People's Hospital of Wuhan University was a designed hospital for severe COVID-19 cases.

In conclusion, this single-center retrospective study showed the characteristics of COPD infected COVID-19 patients. And we found that there were significant differences in characteristics and laboratory

findings between the COVID-19 infected dead patients and discharged patients. The results of multivariate analysis are benefit for stratifying COPD infected COVID-19 patients. Additionally, close monitoring of the risk indexes is important for early supportive care during the management of this population in the clinical work.

Material And Methods

Ethical approval

This study was conducted in accordance with the edicts of the Declaration of Helsinki and was approved by the Ethics Committee of West China Hospital of Sichuan University waived the requirement for informed consent, given the retrospective nature of the study.

Participants

This retrospective study included all confirmed cases of COPD infected COVID-19, including discharged and dead cases, from Jan 11th 2020 to Mar 28th 2020 of East District of People's Hospital of Wuhan University (Wuhan, China), a designated tertiary hospital to receive severe COVID-19 patients. Patients who did not meet the discharged criteria and not die at the end of our study were excluded to treat and observe continuously. All enrolled patients were confirmed by real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) basing on the Chinese guideline for COVID-19 management (version 5.0)[30]. COPD was defined in accordance with the criteria of the Global initiative for Chronic Obstructive Lung Disease (GOLD)[31]. Discharge standard are as follows: symptoms improved obviously, normal temperature for at least three days, inflammation in pulmonary imaging was obviously absorbed, and negative results for at least two consecutive tests of SARS-CoV-2 nucleic acid with an interval 24 hours as previously described.[11]

Data collection

Patient data including clinical characteristic (age, sex, co-morbidities, symptoms, signs, etc.), laboratory findings, treatment and complications were obtained. Co-morbidities including diabetes, hypertension, asthma, coronary heart disease, brain disease, kidney disease and malignancy are based on patient's self-report on admission. The data was check by two study investigators (P. Tian and Z. Huang) independently to verify data accuracy.

Statistical analysis

All statistical analyses were performed with procedures of IBM SPSS Statistics version 21 (Chicago, IL, USA). The categorical variables were presented as counts (percentages) and analyzed using chi-square test in different outcome groups. Continuous variables were presented as mean±standard or median (Q1, Q3) and analyzed using t test and Mann-Whitney U test, respectively. Risk factors of death were identified by adopting multivariate logistic regression analysis, and the way in which a univariable ($P \leq 0.05$) is

incorporated into the model is enter. Covariables were chosen a priori based on a review of literature[5, 11, 19, 22]. Statistical significance was set at a two-sided P ≤ 0.05.

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Declarations

Authors' contributions

PT, LX , ZH and LY made substantial contributions to the study concept and design. HZ, HW and YL were in charge of the manuscript draft. PT, ZH, LD, and QZ took responsibility for obtaining ethical approval and collecting samples. PT, ZH, LD, QZ and SZ made substantial contributions to data acquisition. HZ, HW, YL, SZ and LX processed statistical data. PT and YL reviewed the data. TP and YL made substantial revisions to the manuscript.

Competing interests' statement

The authors declare that they have no conflict of interest.

Abbreviations

COVID-19, coronavirus Disease 2019; COPD, chronic obstructive pulmonary disease; ACE-2, angiotensin converting enzyme II; RT-PCR, reverse transcription-polymerase chain reaction; ECMO, extracorporeal membrane oxygenation; PCT, procalcitonin; AST, aspartate aminotransferase; Cr, creatinine; EPV, Event Per Variable.

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Tables

Table 1. Characteristics of COVID-19 infected COPD patients

Characteristic	Patients (n=52), No. (%), median (IQR)
Median age (IQR), Year	69.0 (64.0,79.0)
Male sex	39 (75.0%)
Co-morbidities	
With	39 (75.0%)
Diabetes	3 (5.7%)
Hypertension	21 (40.3%)
Asthma	8 (15.3%)
Coronary heart disease	8 (15.3%)
Brain disease	10 (19.2%)
Kidney disease	2 (3.8%)
Malignancy	4 (7.6%)
Symptoms and signs at on admission	
Fever	41 (78.8%)
Cough	43 (82.6%)
Expectoration	21 (40.3%)
Chest tightness	18 (34.6%)
Chest pain	1 (1.9%)
Dyspnea or shortness of breath	13 (25.0%)
Diarrhea	4 (7.6%)
Fatigue	16 (30.7%)
Asthma	11 (21.1%)
Panting	4 (7.6%)
Chills	4 (7.6%)

IQR: interquartile range

Table2. Treatment and clinical outcome of COVID-19 infected COPD patients

Treatment	Patients (n=52), No. (%), median (IQR)
Physiotherapy	
Oxygen therapy	49 (94.2%)
High flow oxygen therapy	15 (28.8%)
Non-invasive ventilator	8 (15.3%)
Tracheal intubation	1 (1.9%)
ECMO	1 (1.9%)
Medicine therapy	
Arbidol	35 (67.3%)
Lianhua Qingwen	25 (48.0%)
Xuebijing	13 (25.0%)
Oseltamivir	13 (25.0%)
Ribavirin	10 (19.2%)
Thymosin /Thymalfasin	13 (25.0%)
Gamma globulin	17 (32.6%)
Antibacterial treatment	38 (73.1%)
Anti-fungus treatment	2 (3.8%)
Complications	
ARDS	2 (3.8%)
Pulmonary embolism	2 (3.8%)
Impaired renal function	3 (5.7%)
Impaired liver function	1 (1.9%)
Multiple organ failure	7 (13.4%)
Clinical outcomes	
Discharge	38 (73.1%)
Death	14 (26.9%)
Onset of symptom to admission	12.0 (8.0,19.0)
Hospital stay, days	19.5 (12.8,36.0)
Onset of symptom to death	6.0 (2.0,8.3)

Cause of death	
Multiple organ failure	7 (50.0%)
Respiratory failure	6 (42.9%)
Severe complications	1 (7.1%)

IQR: interquartile range; ECMO, extracorporeal membrane oxygenation; ARDS: acute respiratory distress syndrome.

Table 3. Characteristics of COVID-19 infected dead patients and discharged patients

Characteristic	Dead (n=14)	Discharged (n=38)	*P*
Sex (male)	10 (71.4%)	29 (76.3%)	1.000
Age	80.0 (73.5,89.3)	68.5 (63.0,70.5)	<0.001
Onset of symptom to admission, median (IQR)	11.5 (4.8,17.0)	12.0 (8.0,20.0)	0.569
Former smoker or current smoker	0 (0)	6 (15.8%)	0.275
Symptoms and signs at on admission			
Fever	10 (71.4%)	31 (81.6%)	0.680
Cough	11 (78.6%)	32 (84.2%)	0.949
Expectoration	8 (57.1%)	13 (34.2%)	0.135
Chest distress	9 (64.3%)	9 (23.7%)	0.016
Pectoralgia	0 (0)	1 (2.6%)	1.000
Dyspnea or shortness of breath	2 (14.3%)	11 (28.9%)	0.470
Diarrhea	1 (7.1%)	3 (7.9%)	1.000
Fatigue	7 (50.0%)	9 (23.7%)	0.138
Asthma	3 (21.4%)	8 (21.1%)	1.000
Panting	2 (14.3%)	2 (5.3%)	0.620
Chills	1 (7.1%)	3 (7.9%)	1.000
Co-morbidities			
Diabetes	0 (0)	3 (7.9%)	0.555
hypertension	9 (64.3%)	12 (31.6%)	0.033
Asthma	2 (14.3%)	6 (15.8%)	1.000
Coronary heart disease	6 (42.9%)	2 (5.3%)	0.004
Brain disease	6 (42.9%)	4 (10.5%)	0.026
Kidney disease	1 (7.1%)	1 (2.6%)	1.000
Malignancy	1 (7.1%)	3 (7.9%)	1.000

IQR: interquartile range

Table4. Laboratory characteristics, treatment and complications of COVID-19 infected dead patients and discharged patients

	Dead (n=14)	Discharged (n=38)	*P*
Laboratory characteristics			
PaO2 mmHg	75.0 (57.0,117.0)	94.0 (73.8,132.0)	0.181
PCO2 mmHg	37.0 (36.0,43.0)	44.0 (37.0,45.0)	0.183
PH	7.4 (7.3,7.5)	7.4 (7.4,7.4)	0.685
CD3 (/uL), mean±SD	273.4±126.5	831.6±361.7	0.000
CD4 (/uL), mean±SD	157.1±61.4	500.6±242.8	0.000
CD8 (/uL), mean±SD	94.8±69.3	309.2±193.5	0.000
CD19 (/uL), median (Q1, Q3)	63.0 (53.8,95.0)	138.5 (99.0,211.8)	0.001
CD16+56 (/uL), median (Q1, Q3)	60.5 (29.3,160.0)	179.0 (106.3,256.8)	0.010
WBC count ($\times10^9$/L), median (Q1, Q3)	5.6 (4.6,13.6)	5.3 (4.3,6.5)	0.150
Neutrophil count ($\times10^9$/L), median (Q1, Q3)	5.3 (3.4,12.0)	3.4 (2.4,4.3)	0.004
Lymphocyte count ($\times10^9$/L), mean±SD	0.6±0.2	1.4±0.6	0.000
Hemoglobin (g/L), median (Q1, Q3)	121.0 (109.5,133.0)	129.0 (121.0,138.0)	0.178
Platelet count ($\times10^9$/L), median (Q1, Q3)	156.0 (111.0,210.0)	220.0 (184.0,282.0)	0.002
D-Dimer (mg/L), median (Q1, Q3)	2.3 (0.7,12.3)	0.6 (0.4,1.2)	0.004
PCT (ng/mL), median (Q1, Q3)	0.14 (0.08,1.06)	0.05 (0.04,0.10)	0.000
ALB (g/L), mean±SD	34.2±4.3	36.4±4.7	0.149
GLB (g/L), median (Q1, Q3)	24.5 (22.2,25.6)	22.4 (19.9,25.8)	0.197
ALT (U/L), median (Q1, Q3)	23.0 (15.5,29.0)	20.0 (15.0,31.8)	0.759
AST (U/L), median (Q1, Q3)	35.0 (24.0,44.5)	25.0 (18.5,34.0)	0.039
Urea (mmol/L), median (Q1, Q3)	7.9 (5.3,10.9)	5.6 (4.1,6.7)	0.010
Cr (umol/L), median (Q1, Q3)	80.0 (62.5,105.0)	67.0 (55.0,74.5)	0.035
Medicine therapy			
Arbidol	8 (57.1%)	27 (71.1%)	0.538
Lianhua Qingwen	7 (50.0%)	18 (47.4%)	0.866
Xuebijing	3 (21.4%)	7 (18.4%)	1.000
Oseltamivir	4 (28.6%)	9 (23.7%)	1.000
Ribavirin	3 (21.4%)	10 (26.3%)	1.000

Thymosin /Thymalfasin	3 (21.4%)	10 (26.3%)	1.000
Gamma globulin	6 (42.9%)	11 (28.9%)	0.538
Antibacterial treatment	14 (100%)	24 (63.2%)	0.021
Anti-fungus treatment	1 (7.1%)	1 (2.6%)	0.470
Hormone treatment	5 (35.7%)	13 (34.2%)	1.000
Complications			
ARDS	2 (14.3%)	0 (0)	0.069
Pulmonary embolism	2 (14.3%)	0 (0)	0.069
Impaired renal function	2 (14.3%)	1 (2.6%)	0.173
Impaired liver function	0 (0)	1 (2.6%)	1.000
Multiple organ failure			
Oxygen therapy	14 (100%)	35 (92.1%)	0.555
High flow oxygen therapy	7 (50.0%)	8 (21.1%)	0.089
Non-invasive ventilator	7 (50.0%)	1 (2.6%)	0.000
Tracheal intubation	1 (7.1%)	0 (0)	0.269
ECMO	1 (7.1%)	0 (0)	0.269

SD: Standard Deviation; WBC: white blood cell; ALB: albumin; GLB: globulin; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation.

Table 5. Multivariate analysis for the risk of severe events

Clinical Factors	*P*	HR	95%CI
Age (reference: ≤70 years old)	0.020	7.859	1.376,44.875
Gender (reference: female)	0.827	0.864	0.232,3.215
Lymphocyte count (reference: ≥ 0.8×10^9/L)	0.002	27.429	3.336,225.530
Co-morbidities (reference: no)	0.479	1.931	0.312,11.953
D-Dimer	0.690	0.991	0.948,1.036

Figures

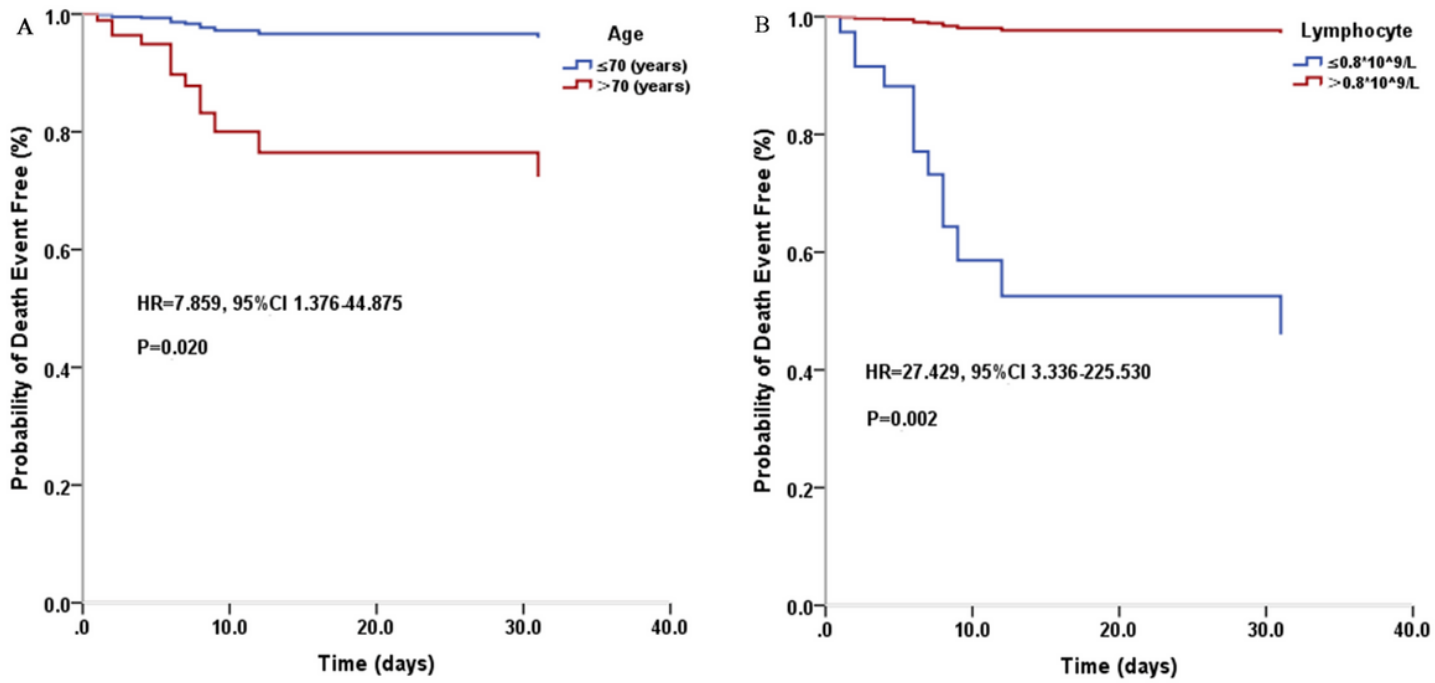

Figure 1

Kaplan-Meier curve of risk factors for developing severe events. (A) COPD patients who over 70 years old or aged 70 and under. (B) COPD patients who lymphocyte counts 0.8*10^9 and below or lymphocyte count higher than 0.8*10^9.