CLINICAL CHARACTERISTICS AND RISK OF DEATH OF 194 PATIENTS WITH SEVERE COVID-19

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ABSTRACT

Background and Purpose*: Corona Virus Disease 2019 (COVID-19) is a highly contagious disease which continuously and rapidly circulating around the world now. The patients with severe COVID-19 have relatively high mortality. Therefore, there is an urgent need for methods to assess mortality risk in patients with COVID-19 accurately.*

Materials and methods: *We conducted a retrospective study focusing on the clinical characteristics of 194 confirmed cases of severe COVID-19. Personal information, clinical data and laboratory information of patients with COVID-19 were collected by consulting case records so as to investigate the risk of death related to COVID-19.*

Results: *In the 194 patients with COVID-19, there was no difference in prevalence between men and women. Comorbidities (such as hypertension, cerebral infarction) associated with severe clinical features and mortality are prevalent in non-survivors. 86.1% of patients with severe COVID-19 had fever and 46.9% coughed, and the proportion of chest tightness, airlessness and dyspnea in non-survivors was significantly higher than that in survivors. There were multiple laboratory indicator differences between survivors and non-survivors. Non-survivors had significantly lower lymphocyte count (including T lymphocyte). Changes in liver (aspartate aminotransferase, AST), kidney [Urea, creatinine (Cr)], and heart [lactate dehydrogenase (LDH), creatine kinase (CK), B-type natriuretic peptide (BNP)] damage markers, coagulation, and inflammation indicators in severe patients were related to their risk of death. Multivariable logistic regression model revealed that age (OR 1.082, 95% CI 1.024-1.357), interleukin-6 (IL-6). (OR 1.568, 95% CI 1.149-2.138), D-dimer (OR 1.327, 95% CI 1.087-1.621) were associated significantly with risk of death, whereas CD4 count was associated with a lower risk (OR 0.972, 95% CI 0.953-0.992).*

Conclusion: *This study found that age, IL-6, D-dimer and CD4 counts are closely related to mortality risk in patients with severe COVID-19, and they are useful in assessing the prognosis of patients.*

Keywords: *COVID-19, patient; severe, clinical characteristics, mortality risk.*

DOI: 10.19193/0393-6384_2020_6_578

Received *November 30, 2019;* ***Accepted*** *January 20, 2020*

Introduction

COVID-19 is a highly contagious disease with high mortality (3-15%)[1-3], while severe patients are more likely to die. Although previous studies have summarized the clinical characteristics, diagnosis, and treatment of COVID-19, few studies have investigated the risk of death of COVID-19 patients. So it is urgent to predict mortality risk accurately to improve the prognosis of patients. In this study, we retrospectively summarized the epidemiological and clinical characteristics of 194 severe patients who died of COVID-19 to investigate the risk of death related to COVID-19 infection.

Materials and methods

Overall research design

We conducted a retrospective study focusing on the clinical characteristics of confirmed cases of severe COVID-19 in east hospital of Renmin Hospital of Wuhan University from 25 January 2020 to 10 March 2020. Laboratory confirmation of SARS-CoV-2 infection was performed by our hospital or the local health authority where the patient has visited. Identification of Severe patients and Critical patients was achieved by reviewing and analysing admission logs and histories and laboratory test results from all available electronic medical records and patient care resources.

Our research has been approved by the ethics committee of Renmin Hospital of Wuhan University (No.WDRY2020-K019). This was a retrospective case series study and no patients were involved in the study design, setting the research questions, or the outcome measures directly. So, the requirement of patients for written informed consent was waived.

Personal information and clinical data of patients included in the study were collected, by consulting case records. Personal information included sex, age, epidemiological history, and comorbidities. Clinical data included symptoms from onset to hospital admission, clinical presentation, vital signs, and disease outcomes.

Admission evaluation

All patients were evaluated and clinically typed upon admission, according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia version 7 (trial)"[4].

Specific clinical types included:

• Mild: mild clinical symptoms, no pneumonia manifestations on imaging;

• Common: fever, respiratory tract infection symptoms, and so on, with imaging indicating pneumonia;

• *Severe (any of the following conditions):*

• Respiratory distress, respiratory rate (RR) ≥30 breaths/min;

• Oxygen saturation ≤93% at rest;

• Partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 mmHg (1 mmHg = 0.133 kPa);

• *Critical (any of the following conditions):*

• Respiratory failure and a requirement for mechanical ventilation;

• Shock;

• Concomitant failure of other organs and requirement for intensive care unit (ICU) monitoring and treatment.

Laboratory examinations

Throat swab specimens collected from all patients at admission were tested by real time polymerase chain reaction for SARS-CoV-2 RNA within three hours. Virus detection was repeated twice every 24 hours. Laboratory tests data were collected on admission including complete blood count, serum biochemistry, coagulation function, D-dimer, identification of other respiratory pathogens [such as influenza A virus (H1N1, H3N2, H7N9), influenza B virus, parainfluenza virus, respiratory syncytial virus, cytomegalovirus, and adenovirus, chlamydia, and mycoplasma], procalcitonin, C-reactive protein, blood gas analysis, CT scanning, immunological.

Statistical analysis

Continuous variables were presented as mean ± standard deviation with normal distribution and median (Q1, Q3) while those with non-normal distribution. We expressed categorical variables as numbers (%). Independent t-tests, Mann-Whitney U-test, χ^2 test, or Fisher's exact test were used to compare differences between survivors and non-survivors where appropriate. To explore the risk factors associated with in-hospital death, univariable and multivariable logistic regression models were used.

Considering the total number of deaths (n=88) in our study and to avoid overfitting in the model, six variables were chosen for multivariable analysis on the basis of clinical constraints and linear correlation analysis. All statistical analyses were performed using IBM SPSS Statistics software package (version 24). A two-sided P value of less than 0.05 was considered statistically significant.

Results

General characteristics and clinical presentations

We included 194 adult patients admitted with COVID-19 in east hospital of Renmin Hospital of Wuhan University from 25 January 2020 to 10 March 2020, 88 of whom died during hospitalization and 106 were discharged. Patients discharged and died were divided into survival group and non-survival group. The average age was 66.0 years of the 194 patients and patients in non-survivor group were older than those in survivor group (70.5 vs 58.4, p<0.001), but there was no difference in gender composition. After a median of 10 days incubation patients were hospitalized, the survival group stays with a median time of 18 days while the non-survival group with a median time of only 6 days (Table 1). Whether survivors or non-survivors, fever was the most common symptom on admission (86.8% vs 85.2%, p=0.717), followed by cough and chest congestion. There was no difference in the proportion of some symptoms like cough, sputum, myalgia, fatigue, vomiting or diarrhea, while chest congestion, anhelation, dyspnea, was observed much more in non-survivor group with P value less than 0.05 (Table 1). Hypertension was the most common comorbidity (39.7%) in the patients and presented more than half in non-survivors

(54.5%). Cerebral infarction, chronic obstructive lung disease was also more common in those died in hospital, whereas, diabetes, coronary heart disease, liver dysfunction, chronic kidney disease, carcinoma was similar (Table 1).

Items	Total (n=194)	Survivors (n=106)	Non-survivors (n=88)	Statistics	P value
Age, years	66.0 (56.0-75.0)	58.4±12.7	70.5±11.8	-6.343	<0.001
Sex					
Female	87 (44.8%)	51(48.1%)	36(40.9%)	-	-
Male	107 (55.2%)	55 (51.9%)	52 (59.1%)	1.204	0.273
Incubation period, days	10 (8-14)	10 (7-14)	10 (8-14)	-0.590	0.55
Length of stay, days	10 (6-17)	18 (14-23)	6 (4-9)	-9.568	<0.001
Symptoms					
Fever	167 (86.1%)	92 (86.8%)	75 (85.2%)	0.131	0.717
Cough	91 (46.9%)	47 (44.3%)	44 (50.0%)	0.811	0.368
Sputum	46 (23.7%)	23 (21.7%)	23 (26.1%)	0.487	0.485
Chest congestion	70 (36.1%)	22 (20.8%)	48 (54.5%)	19.100	<0.001
Anhelation	50 (25.8%)	19 (17.9%)	31 (35.2%)	8.742	0.003
Dyspnea	30 (15.5%)	11 (10.4%)	19 (21.6%)	5.132	0.023
Myalgia	8 (4.1%)	6 (5.7%)	2 (2.3%)	1.706	0.257
Fatigue	51 (26.3%)	26 (24.5%)	25 (28.4%)	0.408	0.523
Vomiting	8 (4.1%)	5 (47.2%)	3 (3.4%)	0.284	0.709
Diarrhoea	26 (13.4%)	13 (12.3%)	13 (14.8%)	0.416	0.519
Comorbidity					
Hypertension	77 (39.7%)	29 (27.4%)	48 (54.5%)	17.569	<0.001
Cerebral infarction	7 (3.6%)	0	7 (8.0%)	6.559	0.015
Diabetes	26 (13.4%)	12 (11.3%)	14 (15.9%)	0.715	0.398
Coronary heart disease	32 (16.5%)	15 (14.2%)	17 (19.3%)	0.868	0.352
Chronic obstructive lung disease	7 (3.6%)	0	7 (8.0%)	6.559	0.015
Liver dysfunction	10 (5.2%)	6 (5.7%)	4 (4.5%)	0.024	1.000
Chronic kidney disease	7 (3.6%)	2(1.9%)	5(5.7%)	1.029	0.448
Carcinoma	9 (4.8%)	5 (4.7%)	4 (4.5%)	0.024	1.000
Laboratory findings					
White blood cell count, $\times10^9$perL	6.2 (4.5-9.7)	5.1 (3.9-6.3)	8.4 (5.5-12.4)	-5.939	<0.001
Neutrophil, $\times10^9$per L	4.9 (3.2-8.8)	3.7 (2.6-4.6)	7.4 (4.5-11.1)	-6.466	<0.001
Lymphocyte count, $\times10^9$per L	0.8 (0.5-1.0)	1.0 (0.7-1.2)	0.6(0.4-0.9)	-5.736	<0.001
Monocytex 10^9per L	0.4 (0.3-0.5)	0.43 (0.30-0.55)	0.37 (0.24-0.50)	-1.648	0.099
CRP, mg/L	63.1 (20.0-120.6)	28.7 (7.7-76.4)	95.0 (58.9-166.5)	-6.103	<0.001
PCT, ng/mL	0.12 (0.05-0.27)	0.06 (0.04-0.10)	0.20 (0.12-0.49)	-7.528	<0.001
CD3, per μL	411.0 (241.0-596.0)	540.0 (425.3-785.8)	272.0 (162.0-411.0)	-7.297	<0.001
CD4, per μL	241.0 (140.0-375.0)	348.5 (235.5-515.5)	165.0 (101.0-280.0)	-6.782	<0.001
CD8, per μL	121.0 (64.0-210.0	175.0 (121.5-261.5)	73.5 (43.3-135.0)	-6.772	<0.001
CD4/CD8	1.9 (1.4-2.9)	1.9 (1.4-2.7)	2.2 (1.5-3.1)	-1.639	0.101
IL-6, pg/mL	16.2 (4.8-38.8)	5.1 (1.9-11.4)	39.0 (20.0-128.0)	-8.423	<0.001
Albumin, g/L	35.0±4.8	36.9±4.8	33.6±4.3	4.424	<0.001
ALT, U/L	25.0 (18.0-41.0)	29.0 (17.0-37.0)	24.0 (19.0-42.0)	-0.094	0.925
AST, U/L	31.0 (22.0-47.0	24.0 (19.0-36.0)	39.5 (26.3-60.8)	-4.738	<0.001
Urea, mmol/L	6.0 (4.0-10.0)	4.3 (3.3-5.8)	9.0 (5.7-13.2)	-6.592	<0.001
Creatinine,μmol/L	70.0 (51.0-84.0	63.0 (48.0-73.0)	76.5 (55.3-97.0)	-3.589	<0.001
Lactate dehydrogenase, U/L	370.0 (266.0-546.0	271.0 (220.0-340.0)	495.0 (374.5-642.5)	-8.028	<0.001
Creatine kinase, U/L	70.0 (45.0-126.0)	56.0 (37.0-84.0)	90.0 (60.8-189.3)	-4.176	<0.001
PH	7.42 (7.38-7.46)	7.41 (7.38-7.45)	7.42 (7.36-7.47)	-0.169	0.866
PO_2, mmHg	59.0 (48.0-81.0)	73.0 (57.0-92.0)	53.0 (45.0-64.5)	-4.840	<0.001
PCO_2, mmHg	38.0 (33.0-42.3)	39.0 (37.0-44.0)	35.0 (30.3-41.0)	-3.177	0.001
BNP, pg/mL	391.9 (112.6-998.4)	110.4 (45.7-280.0)	817.0 (409.7-1653.0)	-7.918	<0.001
D-dimer, μg/L	1.8 (0.7-12.3	0.8 (0.4-1.6)	8.9 (2.5-20.6)	-8.056	<0.001

Table 1: Demographic, clinical, laboratory findings of patients on admission.

Laboratory findings

Blood routine examination showed the non-survivor group had more white blood cell and neutrophil count but less lymphocyte count. As for T lymphocyte such as CD3, CD4, CD8 count were all less than survivor group (all p<0.001). Inflammatory indicators such as C-reactive protein (CRP), procalcitonin (PCT), IL-6 were significantly higher in non-survivor group with all p value less than 0.001. Non-survivors had even less albumin (33.6 vs 36.9, p<0.001), moreover had much AST, Urea and Creatinine. Cardiac parameters indicated non-survivor group had poor hart function with much higher lactate dehydrogenas (495.0 vs 271.0), creatine kinase (90.0 vs 56.0) and BNP (817.0 vs 110.4). Arterial blood gas analysis showed PO^2 and PCO^2 was lower in non-survivor group with p value less than 0.05. Non-survivors had much higher D-dimer (8.9 vs 0.8, p<0.001) (Table 1).

Risk factors associated with in-hospital death for COVID-19 patients

In univariable analysis, odds of in-hospital death was higher in patients with hypertension. Age, white blood cell count, CRP, PCT, IL-6, AST, urea, creatinine, lactate dehydrogenase, creatine kinase, BNP, D-dimer were all associated with death while lymphocyte count, CD3, CD4, CD8 count, albumin had negative correlation (Table 2).

Variables	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age, years	1.082 (1.051-1.114)	<0.001	1.179 (1.024-1.357)	0.022
Hypertension	4.067 (2.075-7.968)	<0.001	-	-
White blood cell count, $\times10^9$perL	1.336 (1.188-1.501)	<0.001	-	-
Lymphocyte count, $\times10^9$ per L	0.098 (0.036-0.265)	<0.001	-	-
CRP, mg/L	1.017 (1.010-1.023)	<0.001	-	-
PCT, ng/mL	2.443 (1.089-5.480)	0.030	-	-
CD3, per μL	0.994 (0.993-0.996)	<0.001	-	-
CD4, per μL	0.992 (0.989-0.995)	<0.001	0.972 (0.953-0.992)	0.005
CD8, per μL	0.990 (0.986-0.994)	<0.001	-	-
IL-6, pg/mL	1.147 (1.089-1.209)	<0.001	1.568 (1.149-2.138)	0.005
Albumin, g/L	0.852 (0.788-0.922)	<0.001	-	-
AST, U/L	1.021 (1.005-1.037)	0.011	0.986 (0.965-1.006)	0.168
Urea, mmol/L	1.257 (1.127-1.402)	<0.001	-	-
Creatinine, μmol/L	1.023 (1.009-1.037)	0.001	1.013 (0.981-1.046)	0.425
Lactate dehydrogenase, U/L	1.013 (1.009-1.017)	<0.001	-	-
Creatine kinase, U/L	1.010 (1.004-1.016)	0.001	-	-
BNP, pg/mL	1.000 (1.000-1.001)	0.017	-	-
D-dimer, μg/L	1.279 (1.162-1.408)	<0.001	1.327 (1.087-1.621)	0.006

Table 1: Risk factors associated with in-hospital death.

154 patients with complete data for all variables (67 non-survivors and 84 survivors) were included in the multivariable logistic regression model. To avoid overfitting in the model, six variables were chosen to enter the model on the basis of clinical constrain and linear correlation analysis. We found that age (OR 1.082, 95% CI 1.024-1.357), IL-6 (OR 1.568, 95% CI 1.149-2.138), D-dimer (OR 1.327, 95% CI 1.087-1.621) were associated significantly with risk of death, whereas CD4 count was associated with a lower risk (OR 0.972, 95% CI 0.953-0.992) (Table 2).

Discussion

In the present study, we investigated the epidemiology and clinical characteristics of patients with severe COVID-19 and found some independent predictors related to fatal outcome. It presents the status of mortality risk in patients with COVID-19.

The mortality of critically ill patients with COVID-19 is considerable. Although study revealed that the X chromosome and sex hormones may reduce the infection of women by virus[5], we found no gender differences in patients who died. We observed that non-survivors were older than survivors and age (OR 1.082, 95% CI 1.024-1.357) was independently associated with mortality risk, and that has been confirmed by previous study[6, 7]. Older patients (>65 years) with comorbidities and ARDS are at increased the risk of death[8]. In this study, the proportion of patients with hypertension was as high as 39.7%, which is close to other research data[9], while it was 54.5% among non-survivors.

High levels of renin-angiotensin (RAS) is closely related to angiotensin converting enzyme 2 (ACE2), and is an important cause of hypertension[10]. New coronaviruses enter cells by binding to ACE2[11], and it replication may also be closely related to ACE2[12]. The increased concentration of ACE2 leads to inflammatory response and exudation, resulting in loss of pulmonary ventilation function and difficulty in oxygenation[13]. Dyspnea and a severe decrease in PaO_2 can directly reflect the extent of lung invasion and was a risk factor for disease progression. Therefore, hypertension patients suffering from COVID-19 may be closely related to ACE2, however, further studies are needed to confirm more related mechanisms.

SARS-CoV-2 can not only cause organ damage through direct action, but also may cause multiple organs indirectly due to inflammatory storm inducing by immune response and/or oxygen supply imbalance inducing by acute respiratory distress syndrome. Fever is one of the common manifestations of inflammation. We found that 86.1% of patients with COVID-19 had fever and the maximum body temperature at admission in non-survivors was significantly higher than in survivors, and that is similar to previous studies[2, 14].

In present study, there were multiple laboratory indicator differences between survivors and non-survivors, and the latter showed significantly lower lymphocyte count but higher white blood cell count, neutrophil count. In terms of CD3+, CD4+ and CD8+ T lymphocytes, non-survivors was also significantly lower than survivors, and CD4+ T lymphocytes count was associated with a lower risk (OR 0.972, 95% CI 0.953-0.992). These result was supported by the data from Huang et al[2] and shows that SARS-CoV-2 consumes many immune cells and inhibits the body's cellular immune function. T lymphocyte subsets are an important cell group for the function of the cellular immune system. In mice with T lymphocyte deficiency, the MERS-Cov virus cannot be eliminated[15]. Prior study have shown that lymphocytes are the main target cells of viral infections[16]. The targeted invasion of SARS-CoV-2 particles destroyed the cytoplasmic component of the lymphocyte and causes its destruction, and then led to immunosuppression. As immune deficiency is a close relative of mortality, evaluating immune condition could be conductive to monitor patient's general condition and estimate prognosis. Excessive neutrophils contributed to acute lung damage[17, 18], which may be associated with severe complication (such as ARDS) and fatality in patients with COVID-19. According to our observation, the leukocyte and neutrophil counts in non-survivors were significantly higher than those in survivors, indicating that they could be used as a reference for risk assessment of patient death, and Yu et al[7, 9] also hold similar views. IL-6, which may link to the systemic inflammatory response[19] and appeared to significantly correlate with illness severity by complementing CD8+ T cell function[16]. According to our results, the serum levels of IL-6 in non-survivors were significantly higher than those in survivors, while IL-6 (OR 1.568, 95% CI 1.149-2.138) was independently associated with mortality risk, and no similar conclusion has been found in other studies. This study found that plasma D-dimer values in non-survivors were higher than those in survivors, and elevated D-dimer (OR 1.327, 95% CI 1.087-1.621) was independently associated with mortality risk, which

was supported by previous data[6, 9]. After suffering from COVID-19, the ensuing activation of immune response and cytokine storm will induce the formation of hyaline thrombus in the small vessels of the patient's lungs and other organs and tissues[20], that may be the cause of elevated plasma D-dimer.

In this study, non-survival patients with COVID-19 had higher levels of AST, LDH, CRP, D-dimer, urea and Cr and PCT, which is basically consistent with the earlier data[14]. Studies have shown that AST, PCT, etc are independent risk factors related to the risk of death[9], but we have not found similar results, which may be due to missing data and biases in obtaining medical history and clinical data. Decreased albumin is a sign associated with poor prognosis of COVID-19, which is a finding in present study. Albumin is the most intuitive index of the nutritional status of the body. When albumin is consumed in large quantities, the body loses resistance to the virus, leading to disease progression[21]. Although virus infection does not directly increase PCT in patients, it will reduce respiratory immunity and raise the exudation of small airways and alveoli, eventually resulting in secondary bacterial infections and elevated PCT. Bacterial co-infection not only manifested with worsened outcomes, but also prolonged hospital stay, moreover there is a higher risk of death in patients with secondary bacterial infections[22].

Some limitations of this study should also be acknowledged. Firstly, the sample size was relatively small in this study, which may lead to biased results. Secondly, the retrospective single-center design leads to missing data and unavoidable biases in obtaining medical history and epidemiological data. In addition, there was lack of pregnant population.

In conclusion, our data suggest that in patients with severe COVID-19, there are multiple abnormalities in clinical features, epidemiological characteristics, and laboratory indicators, many of which can be used to assess the prognosis of patients. Moreover, age, elevated IL-6 and D-dimer at admission are independently associated with risk factors of death and CD4+ T lymphocytes count was associated with a lower risk in adult patients with COVID-19, and them can offer important information to clinicians, allowing for the recognition of mortality risk.

References

1) Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission Potential and Severity of COVID-19 in South Korea. Int J Infect Dis 2020 Apr; 93: 339-44.
2) Huang C, Wang Y, Li X, Ren L, Zhao J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15; 395(10223): 497-506.
3) Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020 Feb 15; 395(10223): 470-3.
4) Diagnosis and treatment protocol for novel coronavirus pneumonia (7rd interim edition). China NHCOTPSRO. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml
5) Jaillon S, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. Clin Rev Allergy Immunol 2019; 56(3): 308-21.
6) Zhou F, Yu T, Du RH, Fan GH, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62.
7) Shi Y, Yu X, Zhao H, Wang H, Zhao RH, et al. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Critical Care 2020; 24: 108.
8) Yang XB, Yu Y, Xu JQ, Shu HQ, Xia JA, et al. Clinical course and outcomes of critically ill patients with OCVID-19 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020 May; 8(5): 475-81.
9) Zheng Z, Peng F, Xu B, Zhao J, Liu H, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020 Aug; 81(2):e16-e25.
10) Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. Expert Rev Cardiovasc Ther 2018 Dec; 16(12): 879-87.
11) Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020 Apr 16; 181(2): 271-80.e8.
12) Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020 Sep 1; 202(5):756-9.
13) Xu Z, Shi L, Wang Y, Zhang jy, Huang L, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4): 420-2.
14) Wang D, Hu B, Hu C, Zhu FF, Liu X, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 Mar 7; 323(11): 1061-9.
15) Zhao J, Li K, Wohlford-Lenane C, Agnihothram SS, Fett C, et al. Rapid generation of a mouse model for Middle East respiratory syndrome[J]. Proc Natl Acad Sci USA 2014; 111(13): 4970-5.
16) Ho TS, Wang SM, Liu CC. Historical review of pandemic influenza A in Taiwan, 2009. Pediatr Neonatol 2010; 51(2)83-88.

17) Narasaraju T, Yang E, Samy RP, Ng HH, Poh WP, et al. Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol 2011; 179(1): 199-210.
18) Tang BM, Shojaei M, Teoh S, Meyers A, Ho J, et al. Neutrophils-related host factors associated with severe disease and fatality in patients with influenza infection. Nat Commun 2019; 10(1): 3422.
19) Gao R, Bhatnagar J, Blau DM, Greer P, Rollin DC, et al. Cytokine and chemokine profiles in lung tissues from fatal cases of 2009 pandemic influenza A (H1N1): role of the host immune response in pathogenesis. Am J Pathol 2013; 183(4): 1258-68.
20) Yao XH, Li TY, He ZC, Ping YF, Liu HW, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi 2020 May 8; 49(5): 411-7.
21) Duc S, Rainfray M, Soubeyran P, Fonck M, Blanc JF, et al. Predictive factors of depressive symptoms of elderly patients with cancer receiving first-line chemotherapy. Psychooncology 2017 Jan; 26(1): 15-21.
22) Azoulay E, Mokart D, Lambet J, Lemiale V, Rabbat A, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: ran-domized controlled trial[J]. Am J Respir Crit Care Med 2010; 182(8): 1038-46.

Funding:
This work was supported by the National Key Research and Development Plan for the Emergency Management of Novel Coronavirus Pneumonia, China (No. 2020YFC0845100) and the Wuhan Municipal Key Technology Project on Novel Coronavirus Pneumonia, China (No.2020020101010005).

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