Identification of Risk Factors for in-Hospital Death of COVID - 19 Pneumonia

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Research

Abstract

Objective: To examine the clinical characteristics and identify independent risk factors for in-hospital mortality of 2019 novel coronavirus (COVID-19) pneumonia.

Methods: A total of 156 patients diagnosed with COVID-19 pneumonia at the central Hospital of Wuhan from January 29, 2020, to March 20, 2020 were enrolled in this single-centered retrospective study. Their epidemiological parameters, clinical presentations, underlying diseases, laboratory test results and disease outcomes were collected and analyzed.

Results: The median age of enrolled patients was 66. Underlying diseases were identified in 101 patients, with hypertension being the most common one, followed by cardiovascular disease and diabetes. The most common symptoms identified upon admission were fever, cough, dyspnea and fatigue. Compared to survival cases, patients who dead during hospitalization had higher plasma levels of D-dimer, creatinine, creatine kinase, lactate dehydrogenase, lactate and lower percentage of lymphocytes (LYM [%]), platelet count and albumin levels. Most enrolled patients received anti-biotics and anti-viral treatment. In addition, 60 patients received corticosteroid and 51 received intravenous immunoglobulin infusion. 44 patients received noninvasive ventilation, 19 received invasive ventilation. Respiratory failure was the most frequently observed complication (106 [67.9%]), followed by sepsis (103 [66.0%]), acute respiratory distress syndrome (ARDS) (67 [42.9%]) and septic shock (50 [32.1%]).

Multivariable regression suggested that advanced age (OR [odds ratio]= 1.059, 95% CI [confidence interval]: 1.011-1.110, P= 0.016) and elevated lactate level upon admission (OR= 2.411, 95% CI: 1.177-4.941, P= 0.016) were independent risk factors for in-hospital mortality for COVID-19 infection. Meanwhile, increased LYM (%) at admission (OR= 0.798, 95% CI: 0.728-0.876, P< 0.001) indicated a better prognosis.

Conclusions: In this study, we discovered that age, LYM (%) and lactate level upon admission were independent factors that could influence in-hospital mortality rate.

Introduction

Since it first identified, the 2019 novel coronavirus (COVID-19) has relentlessly spread all over the world and infected almost a million people as of April 2, 2020 and taken 45,526 lives [1, 2]. The COVID-19 is the seventh member of the notorious coronavirus family [3]. Compared with the 10% fatal rate in SARS-CoV infection [4] and 37% in MERS-CoV infection [5], the mortality rate of COVID-19 seems to be lower and has been estimated around 1–5% [2]. However, the COVID-19 has a higher reproduction number (RO) and much more contagious than its precursors so the overall impact to the global health is enormous. The clinical symptoms of COVID-19 infection are generally mild, and most patients have good prognosis. However, the conditions can deteriorate in about 10–20% of all patients who often required to be transferred to intensive care unit (ICU) and suffered from a very high mortality rate [6].

Due to its latent onset, it is important to early identify patients with increased mortality rate so clinical treatment can be adjusted before disease progression. Even though numerous reports have been published about COVID-19, studies that focusing on identifying such risk factors are still needed. Here in this retrospective analysis, we identified several risk factors that associated with death in COVID-19 patients and assessed the effectiveness of currently treatment strategies.

Methods And Materials

A total of 156 patients diagnosed with COVID-19 at the Wuhan Central hospital from January 29, 2020, to March 20, 2020 were included in this single-centered retrospective study. The Ethics Committee of Wuhan Central hospital approved this study and waived the individual inform consent due to the retrospective nature of the study.

Epidemiology parameters, clinical presentations, laboratory results and disease outcomes of enrolled patients were collected and reviewed by two independent designated researchers. The blood tested was measured in each patient upon admission or the first available date.

The diagnosis was made following the Chinese COVID-19 management guideline (7th Edition) [7]. More specifically, the diagnosis criteria for the suspected patients required confirmation real-time PCR tests for COVID-19 nucleic acid on patients' throat swabs and/or bronchoalveolar lavage fluid (BALF).

Corticosteroid therapy (methylprednisolone 40–120 mg per day) was given to some patients as indicated. Antibiotics and Oseltamivir were empirically applied to all patients. Oxygen support (nasal cannula, high oxygen flow, noninvasive assisted ventilation, and mechanical ventilation) was applied to patients as needed.

Definitions

Fever was defined as an axillary temperature above 37.3°C. Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock [8]. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition [9]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition (KDIGO) guideline [10]. The acute cardiac injury was diagnosed if serum levels of cardiac enzymes increased above upper limit of the normal value or new abnormalities identified in electrocardiography and echocardiography [6].

Discharge criteria was defined as: body temperature returned to normal and maintained at least three consecutive days; remission of respiratory symptoms; significant improvement on chest computed tomography (CT) scans and negative results on RNA tests on nasopharyngeal swabs obtained at least 24 hours apart.

Statistical analysis

Data was analyzed with SPSS software for windows (version 25.0 IBM Corp, Armonk, NY). Continuous variables were expressed as median and interquartile (IQR). The student t-test was applied for normally distributed continuous variables and the Mann-Whitney U test for nonnormally distributed variables. Categorical variables were compared with the χ^2 test or Fisher exact test.

To identify the risk factors associated with in-hospital death, multivariable logistic regression model (stepwise enter method) was applied. Considering the relatively low number of deaths in the cohort and in order to avoid overfitting in the model, five variables were chosen for multivariable logistic analysis based on previous studies. Advanced age and underlying cardiovascular disease had been reported to associate with adverse clinical outcomes in patients with SARS or MERS infections [11, 12]. Previous COVID-19 studies had shown that the serum levels of D-dimer and lactate were increased in patients with worse prognosis [13, 14]. In addition, lymphopenia was commonly seen in severe SARS-COV-2 infection [6, 15] and it was suggested to be associated with death in a recent COVID-19 study [16]. However, we did not observe significant difference of lymphocyte count in the death cases. Liu and colleagues [17] recently discovered that the percentage of lymphocytes (LYM [%]) was a potential predictor of COVID-19 severity. Therefore, age, whether complicated with underlying cardiovascular disease or not, LYM (%), D-dimer and lactate were chosen as the five parameters for the multivariable logistic regression model. Receiver-operating characteristic (ROC) curves were constructed to assess the diagositic value of above three laboratory test results. The optimal cutoff was first assessed by You-den's index (J = Sensitivity + Specificity − 1). STATA statistical analysis software was used to assess the difference between the areas under receiver-operating characteristic curve (AUC). $P < 0.05$ was considered statistically significant.

Results

The cohort included in this study consisted of 156 hospitalized patients diagnosed with COVID-19 pneumonia. 56 patients died during hospitalization and 100 were successfully discharged. The median age of all enrolled patients was 66 (IQR, 46.3–73.0; range, 9−99 years), and 76 (48.7%) were male. Comorbidities were present in 101 (64.7%) patients, with hypertension, cardiovascular disease and diabetes being the most common ones. The most common symptoms presented upon admission were fever (79 [50.6%]) and cough (71 [45.5%]), followed by dyspnea (28 [17.9%]) and fatigue (23 [14.7%]) (Table 1).

Table 1
Baseline characteristics of patients infected with COVID-19

	Total (n = 156)	Survivor (n = 100)	Non-survivor (n = 56)	P value[a]
Characteristics				
Age, years	66.0 (46.3−73.0)	58.0 (37.0−69.0)	72.0 (65.3−83.0)	**< 0.001**
Male	76 (48.7)	44(44.0)	32(57.1)	0.115
Underlying disease				
Cardiovascular disease	44 (28.2)	17(17.0)	27(48.2)	**< 0.001**
COPD	27 (17.3)	12(12.0)	15(26.8)	**0.019**
Chronic renal disease	15 (9.6)	4(4.0)	11(19.6)	**0.001**
Chronic liver disease	14 (9.0)	2(2.0)	12(21.4)	**< 0.001**
Cerebrovascular	22 (14.1)	9(9.0)	13(23.2)	**0.014**
Diabetes	31 (19.9)	11(11.0)	20(35.7)	**< 0.001**
Hypertension	65 (41.7)	31(31.0)	34(60.7)	**< 0.001**
Cancer	14 (9.0)	3(3.0)	11(19.6)	**< 0.001**
Initial symptoms				
Fever	79 (50.6)	56 (56.0)	23 (41.4)	0.074
Cough	71 (45.5)	45(45.0)	26(46.4)	0.864
Chest tightness	28 (17.9)	16(16.0)	12(21.4)	0.397
Asthma	30 (19.2)	22(22.0)	8(14.3)	0.241
Headache	5 (3.2)	2(2.0)	3(5.4)	0.351
Myalgia	2 (1.3)	1(1.0)	1(1.8)	1.000
Chill	4 (2.6)	4(4.0)	0(0)	0.297

Notes: Data presented as n (%) or median (IQR).

Abbreviations: COVID-19, Coronavirus Disease 2019; IQR, interquartile range; COPD: Chronic obstructive pulmonary disease

[a] P values indicate differences between survivors and non-survivors. $P < 0.05$ was considered statistically significant.

	Total (n = 156)	Survivor (n = 100)	Non-survivor (n = 56)	P value[a]
Nausea or vomiting	8 (5.1)	3(3.0)	5(8.9)	0.136
Fatigue	23 (14.7)	8(8.0)	15(26.8)	**0.002**
Diarrhea	2 (1.3)	1(1.0)	1(1.8)	0.359
Poor appetite	13 (8.3)	4(4.0)	9(16.1)	**0.014**
Disturbance of consciousness	4 (2.6)	0(0)	4(7.1)	**0.015**

Notes: Data presented as n (%) or median (IQR).

Abbreviations: COVID-19, Coronavirus Disease 2019; IQR, interquartile range; COPD: Chronic obstructive pulmonary disease

[a] P values indicate differences between survivors and non-survivors. P< 0.05 was considered statistically significant.

Compared with successfully discharged patients, the patients who died during hospitalization were older (72.0 years [65.3–83.0] VS 58.0 years [37.0–69.0]), and were more likely complicated with underlying diseases such as hypertension (34 [60.7%] vs 31 [31.0%]), diabetes (20 [35.7%] vs 11 [11.0%]), cardiovascular disease (27 [48.2%] vs 17 [17.0%]), cerebrovascular disease (13 [23.2%] vs 9 [9.0%]), chronic obstructive pulmonary disease (COPD) (15 [26.8%] vs 12 [12.0%]), cancer (11 [19.6%] vs 3 [3.0%]), chronic renal disease (11 [19.6%] vs 4 [4.0%]), and chronic liver disease (12 [21.4%] vs 2 [2.0%]). Compared with survivors, non-survivors were more likely to present fatigue (15 [26.8%] vs 8 [8.0%]), anorexia (9 [16.1%] vs 4 [4.0%]), and neuropsychic symptoms (4 [7.1%] vs 0) (Table 1).

In terms of laboratory tests, multiple differences between survivors and non-survivors were identified and summarized in Table 2. Specifically, non-survivors had an increased level of white blood cell (WBC) count, neutrophil count, percentage of neutrophils, D-dimer, creatinine, creatine kinase (CK) and lactate dehydrogenase (LDH), as well as higher levels of c-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6). Whereas, percentage of lymphocytes, platelet count and albumin levels were significantly lower in non-survivors. In addition, non-survivors had elevated levels of lactate and glucose, accompanied by lower levels of PaO_2/FiO_2 (Table 3).

Table 2
Laboratory findings of patients infected with COVID-19 on admission to hospital

	Total (n = 156)	Survivor (n = 100)	Non-survivor (n = 56)	P value[a]
WBC count, 10^9/L	6.2 (4.7−8.3)	5.6 (4.5−7.2)	7.8 (5.5−12.6)	**< 0.001**
Neutrophil count, 10^9/L	4.0 (3.0-6.8)	3.4 (2.5-5.0)	6.8 (4.5−11.3)	**< 0.001**
Lymphocyte count, 10^9/L	1.2 (0.7−1.7)	1.4 (1.0-1.9)	0.7 (0.5−1.1)	0.503
NEU (%), %	71.0 (58.9−84.4)	62.9 (55.3−72.4)	86.7 (76.3−91.0)	**< 0.001**
LYM (%), %	19.7 (10.5−30.6)	27.6 (18.4−33.5)	8.7 (4.7−14.3)	**< 0.001**
Hemoglobin, g/L	123.7 (114.2-136.6)	125.0 (115.5-136.3)	122.4 (113.9-135.8)	0.246
Platelet, 10^9/L	194.0 (157.0-249.0)	218.5 (172.3-259.5)	168.0 (114.0-200.0)	**< 0.001**
Total bilirubin, mmol/L	10.9 (7.5−17.2)	10.7 (7.5−14.6)	13.0 (7.5−25.6)	0.057
LDH, U/L	197.0 (159.5−279.0)	175.0 (149.0-219.0)	310.5 (201.0-479.3)	**< 0.001**
ALT, U/L	20.2 (13.5−39.5)	19.5 (13.0-37.9)	22.1 (14.7−41.5)	0.400
AST, U/L	21.7 (16.1−34.2)	18.8 (15.1−26.6)	30.0 (21.3−55.3)	**0.002**
Albumin, g/L	37.5 (33.8−42.6)	39.9 (36.5−43.3)	33.1 (29.7−33.6)	**< 0.001**
Globulin, g/L	28.7 (24.4−32.9)	28.2 (24.1−30.9)	31.5 (24.8−34.9)	**0.014**
BUN, mmol/L	4.7 (3.7−6.2)	4.2 (3.3−5.3)	6.2 (5.0-10.8)	**< 0.001**
Creatinine, μmol/L	66.1 (50.3−84.2)	64.8 (50.9−75.1)	74.2 (47.0-126.9)	**0.008**

Notes: Data presented as n (%) or median (IQR).

Abbreviations: COVID-19, Coronavirus Disease 2019; WBC, White blood cell; NEU (%), Percentage of neutrophils; LYM (%): Percentage of lymphocytes; LDH, Lactate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CK, Creatine kinase-MB; CK-MB, Creatine kinase-MB; BNP, Brain natriuretic peptide; CRP, C-reactive protein; IL-6, Interleukin-6

[a] *P* values indicate differences between survivors and non-survivors. *P* < 0.05 was considered statistically significant.

	Total	Survivor	Non-survivor	P value[a]
	(n = 156)	(n = 100)	(n = 56)	
CK, U/L	68.0 (45.0-121.0)	63.0 (40.0−96.0)	112.8 (62.3−245.0)	**0.028**
CK-MB, U/L	1.6 (0.8−4.6)	0.9 (0.7−1.4)	4.3 (1.7−13.3)	**0.044**
troponin I, pg/ml	20.0 (4.1−57.5)	10.0 (3.0−20.0)	50.0 (22.3−115.0)	**0.013**
BNP, ng/L	118.5 (32.5-392.7)	56.8 (20.0-132.9)	374.7 (135.1-814.5)	0.069
D-dimer, mg/L	1.0 (0.4−4.6)	0.7 (0.2−1.6)	3.3 (1.2−7.8)	**0.025**
CRP, mg/L	0.9 (0.1−3.6)	0.2 (0.1−1.6)	4.1 (2.5−7.2)	**< 0.001**
Procalcitonin, ng/mL	0.06 (0.04−0.14)	0.05 (0.04−0.06)	0.37 (0.12−0.77)	**0.022**
IL-6, pg/mL	7.1 (2.4−24.7)	2.9 (1.5−7.4)	79.6 (9.6-212.5)	**0.027**
CD19+, count/μL	12.6 (9.0-18.9)	11.1 (8.6−17.0)	16.6 (10.1−19.1)	0.292
CD3+, count/μL	68.9 (57.4−75.3)	70.6 (62.0-76.7)	66.8 (54.6−71.4)	0.329
CD4+, count/μL	38.8 (34.6−46.0)	38.8 (31.4−45.2)	39.4 (36.2−52.5)	0.183
CD8+, count/μL	25.3 (19.2−32.3)	26.7 (19.6−33.9)	20.5 (13.9−30.5)	0.063
CD4/CD8	1.6 (1.1−2.3)	1.5 (1.0-2.1)	1.8 (1.2−3.9)	0.071
Notes: Data presented as n (%) or median (IQR).				
Abbreviations: COVID-19, Coronavirus Disease 2019; WBC, White blood cell; NEU (%), Percentage of neutrophils; LYM (%): Percentage of lymphocytes; LDH, Lactate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CK, Creatine kinase-MB; CK-MB, Creatine kinase-MB; BNP, Brain natriuretic peptide; CRP, C-reactive protein; IL-6, Interleukin-6				
[a] P values indicate differences between survivors and non-survivors. P< 0.05 was considered statistically significant.				

Table 3
Blood gas analysis of patients infected with COVID-19

	Total (n = 156)	Survivor (n = 100)	Non-survivor (n = 56)	P value[a]
Ph	7.44 (7.39−7.47)	7.43 (7.40−7.46)	7.45 (7.39−7.48)	0.970
PaO_2, mm Hg	91.0 (64.3−119.0)	95.0 (79.0-129.0)	72.0 (50.0-116.0)	**0.049**
PaO_2/FiO_2, mm Hg	195.0 (90.0-262.5)	225.0 (152.5-287.5)	117.5 (78.3-192.9)	**< 0.001**
$PaCO_2$, mm Hg	38.0 (34.0−42.0)	40.0 (35.0−45.0)	36.0 (33.0−40.0)	0.113
BE, mmol/L	1.9 (-0.7−4.1)	2.1 (-0.1−3.9)	1.2 (-1.8−4.6)	0.300
K^+, mmol/L	3.8 (3.4−4.1)	3.8 (3.5−4.2)	3.8 (3.3−4.1)	0.768
Na^+, mmol/L	140.0 (136.0-143.8)	141.0 (138.0-144.0)	137.0 (133.0-142.0)	0.641
Ca^{2+}, mmol/L	0.9 (0.7-1.0)	0.9 (0.7−1.1)	0.9 (0.7-1.0)	0.482
Lactate, mmol/L	1.7 (1.2−2.3)	1.5 (1.1−2.1)	2.0 (1.5−2.9)	**0.005**
Hematocrit, %	37.0 (32.0−41.0)	38.0 (32.5−42.0)	36.0 (30.0−40.0)	0.627
Glucose, mmol/L	6.7 (5.4−8.7)	5.9 (4.9−7.9)	7.4 (6.2−11.1)	**0.034**

Notes: Data presented as median (IQR).

Abbreviations: COVID-19, Coronavirus Disease 2019; PaO_2, Partial pressure of oxygen; PaO_2, Partial pressure of carbon dioxide; BE, Base excess

[a] P values indicate differences between survivors and non-survivors. $P < 0.05$ was considered statistically significant.

150 (96.2%) patients received antibiotics and 139 (89.1%) received antiviral treatment. Unsurprisingly, systematic corticosteroid was more commonly applied in non-survivors. 56 patients (35.9%) received high-flow nasal cannula oxygen therapy, 44 (28.2%) received non-invasive mechanical ventilation and 19 patients (12.2%) required invasive mechanical ventilation support. 6 patients (3.8%) received renal replacement therapy (RRT) and no patients were treated with extracorporeal membrane oxygenation therapy. Oxygen support (including high oxygen flow, noninvasive assisted ventilation, and mechanical ventilation) and renal replacement therapy were more commonly applied in non-survivors (Table 4).

Table 4
Treatments of patients infected with COVID-19

	Total (n = 156)	Survivor (n = 100)	Non-survivor (n = 56)	P value[a]
Antibiotics	150 (96.2)	96 (96.0)	54 (96.4)	1.000
Antiviral treatment	139 (89.1)	89 (89.0)	50 (89.3)	0.956
Corticosteroids	60 (38.5)	22 (22.0)	38 (67.9)	< 0.001
Intravenous immunoglobulin	51 (32.7)	18 (18.0)	33 (58.9)	< 0.001
High-flow nasal cannula oxygen therapy	56 (35.9)	26 (26.0)	30 (53.6)	0.001
Non-invasive mechanical ventilation	44 (28.2)	13 (13.0)	31 (55.4)	< 0.001
Invasive mechanical ventilation	19 (12.2)	1 (1.0)	18 (32.1)	< 0.001
RRT	6 (3.8)	1 (1.0)	5 (8.9)	0.023

Notes: Data presented as n (%).

Abbreviations: COVID-19, Coronavirus Disease 2019; RRT, Renal replacement therapy

[a] P values indicate differences between survivors and non-survivors. P < 0.05 was considered statistically significant.

The clinical outcomes of the enrolled 156 patients were summarized in Table 5. Unsurprisingly, non-survivor patients were more likely to develop complications compared with survivors. Respiratory failure was the most frequently developed complication (106 [67.9%]), followed by sepsis (103 [66.0%]), ARDS (67 [42.9%]), septic shock (50 [32.1%]), arrhythmia (42 [26.9%]), acute cardiac injury (26 [16.7%]), cardiac failure (24 [15.4%]), and acute kidney injury (18 [11.5%]). The median time from disease onset to admission was 10.0 days (IQR 4.3–16.0). And the median time from disease onset to discharge was 36.0 days (IQR 27.3–48.0), whereas the median time to death was 17.0 days (IQR 10.0-26.5). After comparing the time from disease onset to hospital admission and total hospital stay between non-survivors with survivors [(median time, 6.0 days [1.0–10.0] vs 14.5 days [7.0–20.0]) and (median time, 9.0 days [3.3–16.0] vs 22.0 days [16.0–29.0]) respectively], it seemed like the disease progressed more rapidly in non-survivors.

Table 5
Outcomes of patients infected with COVID-19

	Total	Survivor	Non-survivor	P value[a]
	(n = 156)	(n = 100)	(n = 56)	
Arrhythmia	42 (26.9)	13 (13.0)	29 (51.8)	< 0.001
Sepsis	103 (66.0)	49 (49.0)	54 (96.4)	< 0.001
ARDS	67 (42.9)	17 (17.0)	50 (89.3)	< 0.001
Respiratory failure	106 (67.9)	50 (50.0)	56 (100)	< 0.001
Cardiac failure	24 (15.4)	11 (11.0)	13 (35.9)	0.043
Septic shock	50 (32.1)	9 (9.0)	41 (73.2)	< 0.001
Acute kidney injury	18 (11.5)	8 (8.0)	15 (26.8)	0.002
Acute cardiac injury	26 (16.7)	6 (6.0)	20 (35.7)	< 0.001
Onset to admission, days	10.0 (4.3−16.0)	14.5 (7.0−20.0)	6.0 (1.0−10.0)	< 0.001
Hospitalization, days	18.0 (11.0-27.8)	22.0 (16.0−29.0)	9.0 (3.3−16.0)	< 0.001
Onset to discharge or death, days	30.0 (21.0-42.8)	36.0 (27.3−48.0)	17.0 (10.0-26.5)	< 0.001
Notes: Data presented as n (%) or median (IQR).				
Abbreviations: COVID-19, Coronavirus Disease 2019; ARDS, Acute respiratory distress syndrome				
[a] P values indicate differences between survivors and non-survivors. P< 0.05 was considered statistically significant.				

Next, we analyzed variables introduced above in the methods section by multivariable logistic regression assay and discovered that age (OR [odds ratio] = 1.059, 95% CI [confidence interval]: 1.011−1.110, P= 0.016), LYM (%) at admission (OR = 0.798, 95% CI: 0.728−0.876, P< 0.001), and lactate at admission (OR = 2.411, 95% CI: 1.177−4.941, P = 0.016) were independent risk factors for in-hospital death of COVID-19 pneumonia (Table 6).

Table 6
Risk Factors Associated with in-hospital death infected with COVID-19

	OR	95% CI	P value
Age	1.059	1.011−1.110	**0.016**
Cardiovascular disease	1.835	0.554−6.073	0.320
LYM (%)	0.798	0.728−0.876	**< 0.001**
D-dimer	0.974	0.935−1.015	0.209
Lactate	2.411	1.177−4.941	**0.016**
Abbreviations: COVID-19, Coronavirus Disease 2019; OR, Odds ratio;			
CI, Confidence interval			
P< 0.05 was considered statistically significant.			

In addition, we conducted the ROC curve assay and calculated the AUC among these three indicators. We discovered that the AUC of LYM (%) was 0.903 (95% CI, 0.856−0.949), 0.792 (95% CI, 0.720−0.863) for D-dimer and of 0.651 (95% CI, 0.555−0.748) for lactate. (Fig. 1) Comparing to the other indicators, the AUC of LYM (%) was higher in predicting in-hospital death of COVID-19 pneumonia (LYM [%] VS D-dimer, P = 0.003; LYM [%] VS lactate, P < 0.001; respectively). Furthermore, we discovered that the cutoff value of LYM (%) for predicting in-hospital death was 14.7%.

Discussion

In this study we reported a cohort of 156 patients with laboratory-confirmed COVID-19 pneumonia. After carefully summarized and compared patients' clinical characteristics, we identified several risk factors for in-hospital death. In specific, our data suggested that advanced age, decreased LYM (%) and increased lactate at admission were associated with higher odds of in-hospital death. Additionally, we also found that non-survivors were older, more likely to complicate with underlying comorbidities and with a more rapidly progressed disease course.

Wuhan Central hospital is the largest tertiary hospital around Huanan Seafood Wholesale Market area, where speculated to be ground zero for this pandemic [18−20]. As the matter of fact that most of the enrolled patents lived close to this market, our data might include a large portion of patients with so called " primary infection". To the best of our knowledge, this is the largest single-centered retrospective cohort study about patients with COVID-19 who had definite outcomes and complete disease courses. Comparing with other reports [6, 15, 16], patients included in our cohort were older and complicated with more comorbidities. It seemed like that the patients in our study were much severer when they were diagnosed and had a longer hospital stay.

Our data suggested symptoms that were more common in critically ill patient were fatigue, anorexia and neuropsychic symptoms. The onset and persistent of these symptoms might suggest an unfavorable prognosis. Time from disease onset to admission and death was much shorter for non-survivors, which might imply a more rapid disease progression.

After carefully reviewed the medical records of all enrolled patients, we found that 26.9% of patients with COVID-19 pneumonia presented with arrhythmia and 16.7% complicated with acute cardiac injuries. Further analysis indicated that the incidence of myocardial injury was much higher in non-survivors. In Li's report [21], they found at least 8% of patients with COVID-19 suffered acute cardiac injury and this ratio was 12% in Wang's research [15]. Gao et al. reported that NT-proBNP might be an independent risk factor for in-hospital death in patients with severe COVID-19 [22]. The pathogenesis of COVID-19 infection-related acute myocardial injury is still under-studied. But according to the clinical presentation and available laboratory results, we speculated that the direct assault from the virus, hypoxemia induced by pneumonia and over-reacting immune response all play important roles in the pathogenesis.

Consistently, our study confirmed that advanced age was associated with death in patients with COVID-19, as reported by Zhou and colleagues [16]. Previously, advanced age has been identified as an important predictor of mortality in SARS and MERS infection [23, 24]. Though has not been verified in mechanism studies, several reasons may contribute to this age-related vulnerability: firstly, aged patients are usually with decreased cardiopulmonary compliance and reserve thus more difficult in coping with the disequilibrium of cardiopulmonary system induced by COVID-19 infection; secondly, the immune system in aged patients are usually incompetent and has an increased risks of both under- and over-react with the virus infection [25, 26]; thirdly, aged patients have an increased risk of having comorbidities which has been proved in several studies associate with worse prognosis; finally, the diagnosis and treatments in patients with advanced ages are more likely to be delayed due to atypical symptoms. Thus, attention should be paid to COVID-19 patients with advanced ages, especially to whom having multiple comorbidities.

The multivariable logistic regression assay suggested that the decreased LYM (%) was an independent risk factor for in-hospital death and further analysis concluded that LYM (%) was a stronger indicator in predicting in-hospital death of COVID-19 pneumonia indicated by the ROC assay. Previous studies showed that lymphopenia was a risk factor for increased mortality rate for SARS and COVID-19 [16, 27]. While in our study, there was no statistical difference observed in terms of lymphopenia between survivors and non-survivors. Liu and colleagues [17] demonstrated the percentage of lymphocytes (LYM [%]) was a potential predictor of COVID-19 severity. Considering the fact that the WBC counts was significantly higher in the non-survivors in our cohort and might biased the result, we substituted the absolute lymphocyte count with the LYM [%] in the regression analysis model and repeated the assay. The decreased LYM (%) might be explained by the fact that coronavirus was able to destroy lymphocytes during an acute process. The decreased LYM% may reflect an under-activation and/or over exhausting of the immune system that consequently unable to contain COVID-19 infection.

Serum lactate was identified as another risk factor associated with in-hospital death in our study. Lactate has been used as a prognostic marker in predicting the severity and outcome of sepsis and septic shock [28]. Shankar-Hari et al. suggested in their study that the adjusted odds ratio for hospital mortality increased linearly with increasing lactate levels with lactate level > 2 mmol/L being the cutoff value for the diagnosis of septic shock [29]. This finding had been further confirmed by some recent studies [14, 30, 31]. In sepsis, patients usually experience hyperlactatemia as a consequence of tissue hypoperfusion, as well as a diminished lactate clearance rate due to dysfunction of the liver and kidney [32]. In consistent with our study, Zhou and colleagues [16] identified that sepsis and septic shock were a major complication for COVID-19 patients. Measurement of serum lactate seems to be a simple yet effective strategy to identify patients with increased risks.

A previous study suggested that about 90% of patients with severe pneumonia had increased coagulation activity, marked by the increased D-dimer concentrations [33]. High levels of D-dimer was proved to be associated with increased mortality rate in patients with sepsis identified in the emergency room [13]. Previous research also demonstrated that D-dimer greater than 1 ug/ml was associated with fatal outcome of COVID-19 [16]. While in our study, D-dimer was not identified as an independent risk factor for in-hospital death. This discrepancy may be due to the difference of patients selection and future research includes a larger population is needed to confirm the conclusions.

Limitations

This study had several limitations. Firstly, this study was a retrospective study conducted in a single center, with a cohort that might not necessarily representable for the general population. Secondly, by excluding patients still in hospital receiving treatment as of March 20, 2020, the mortality rate in our study might be biased. Finally, the lack of more effective antiviral drugs and life support methods like extracorporeal membrane oxygenation in our hospital might contribute to the poor clinical outcomes in some severe patients.

Conclusions

Our study indicated that the non-survivors were older and with a disease course that progressed more rapidly compared to survivors. Advanced age, decreased LYM (%), and increased lactate level upon hospital admission were independent risk factors for in-hospital death of patients with COVID-19.

Abbreviations

COVID-19, 2019-novel coronavirus; OR, Odds ratio; CI, Confidence interval; LYM (%), Percentage of lymphocytes; ARDS, Acute respiratory distress syndrome; ROC, Receiver-operating characteristic; ICU, Intensive care unit; BALF, Bronchoalveolar lavage fluid; ARDS, Acute respiratory distress syndrome; KDIGO, Kidney Disease: Improving Global Outcomes; CT, Computed tomography; AUC, Areas under receiver-operating characteristic curve. MERS, Middle east respiratory syndrome; COPD, Chronic obstructive

pulmonary disease; WBC, White blood cell; CK, Creatine kinase; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin; IL-6, Interleukin-6; IQR, Interquartile range; NEU (%), Percentage of neutrophils; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CK-MB, Creatine kinase-MB; BNP, Brain natriuretic peptide; PaO2, Partial pressure of oxygen; PaCO2, Partial pressure of carbon dioxide; BE, Base excess; RRT, Renal replacement therapy

Declarations

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Authors' contributions

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have declared they have no interest.

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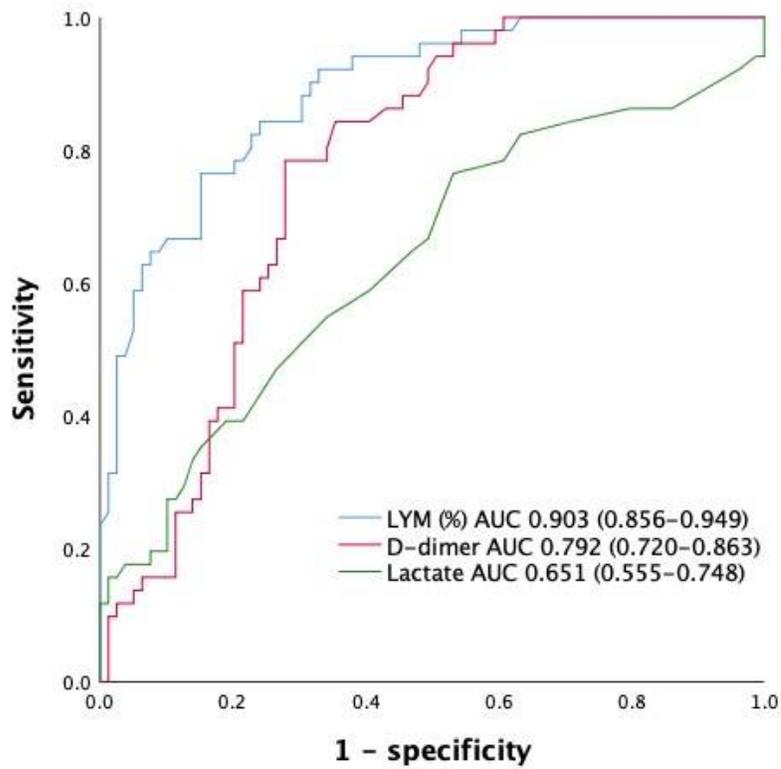
Figures

Figure 1

Receiver-operating characteristic of LYM (%), D-dimer and lactate upon hospital admission (AUC= areas under receiver-operating characteristic curve; LYM[%] = percentage of lymphocytes.)