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The prognostic value of IL-8 for the death of severe or critical patients with COVID-19

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Abstract

Inflammation has been believed to contribute to coronavirus disease 2019 (COVID-19). Risk factors for death of COVID-19 pneumonia have not yet been well established.

In this retrospective cohort study, we included the deceased patients in COVID-19 specialized ICU with laboratory-confirmed COVID-19 from Guanggu hospital area of Tongji Hospital from February 8th to March 30th. Demographic, clinical, laboratory, and outcome data were extracted from electronic medical records using a standard data collection form. We used Spearman rank correlation and Cox regression analysis to explore the risk factors associated with in-hospital death, especially the association between inflammatory cytokines and death.

A total of 205 severe/critical COVID-19 pneumonia patients were admitted in the COVID-19 specialized ICU and 75 deceased patients were included in the final analysis. The median age of the deceasing patients was 70 years (IQR 65–79). The common symptoms were fever (78.9%), cough (70.4%), and expectoration (39.4%). The BNP and CRP levels were far beyond the normal reference range. In the Spearman rank correlation analysis, IL-8 was found to be significantly associated with the time from onset to death ($r_s = -0.30$, $P = .034$) and that from admission to death ($r_s = -0.32$, $P = .019$). Cox regression showed after adjusting age and sex, IL-8 levels were still significantly associated with the time from onset to death ($P = .003$) and that from admission to death ($P = .01$).

IL-8 levels were associated with in-hospital death in severe/critical COVID-19 patients, which could help clinicians to identify patients with high risk of death at an early stage.

Abbreviations: BNP = brain natriuretic peptide, CKMB = creatine kinase isoenzyme, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, ICU = intensive care unit, IL-10 = interleukin-10, IL-6 = interleukin-6, IL-8 = interleukin-8, IQR = interquartile ranges, SpO2 = pulse oxygen saturation, WBC = white blood cells, WHO = World Health Organization.

Keywords: coronavirus disease 2019, interleukin-8, inflammation, in-hospital death, severe/critical

1. Introduction

In December 2019, a series of viral pneumonia cases emerged in Wuhan City, the capital of Hubei Province, China.[1] Later a novel coronavirus, Severe Acute Respiratory Syndrome-Coronavirus-2 was isolated by Chinese scientists, which was designated coronavirus disease 2019 (COVID-19) by World Health Organization (WHO).[2,3] The outbreak of COVID-19 pneumonia in the world has affected more than 19 million patients, becoming one of the most serious hazards to global health.

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All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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As reported, patients with COVID-19 were characterized by fever, myalgia or fatigue, dry cough, radiological signs or acute respiratory distress, reduced or normal white blood cells, lymphopenia and failure to resolve over 3 to 5 days of antibiotic treatment.[4] Several authors have explored the risk factors for mortality of COVID-19 patients and found older age, high Sepsis-related Organ Failure score, and D-dimer greater than 1 μg/L were associated with poor prognosis.[5] For the pathogenesis of COVID-19 pneumonia, it was thought that inflammation had played an important role in it.[4] Especially in severely ill patients, sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS) are common complications resulting from the cytokine storms.[6] Zhou et al reported interleukin-6 (IL-6) was clearly elevated in non-survivors compared with survivors, however without an association with in-hospital death for COVID-19 patients.[5] Moreover, there has been short of studies on inflammatory biomarkers for the prognosis of COVID-19 patients, especially for those presenting with severe or critical pneumonia. And the estimation of risk factors for severe disease and death in such cases are not very robust.

Therefore, aiming to explore risk factors of in-hospital death for severe or critical COVID-19 patients, we presented the details of the deceasing patients in the COVID-19 specialized intensive care unit (ICU) of Guanggu hospital area of Tongji Hospital in Wuhan and evaluated the association between inflammatory cytokines and death.

2. Methods

2.1. Study design and participants

This retrospective cohort study included 75 dead adult patients (≥18 years old) in the COVID-19 specialized ICU of Guanggu hospital area of Tongji Hospital from February 8th to March 30th. Patients admitted in this hospital were severe or very severe cases. All the patients were diagnosed as COVID-19 pneumonia according to WHO interim guidance with positive results of COVID-19 RNA detection. The patients who fulfilled shortness of breath with respiratory rate ≥30/minutes, finger pulse oxygen saturation (SpO2) ≤93%, partial pressure of oxygen (PaO_2)/fraction of inspiration (FiO_2) ≤300 mm Hg, or respiratory failure with requirement of mechanical ventilation, shock, combination of dysfunction of other organs with requirement of ICU care were admitted to the COVID-19 specialized ICU. The study was approved by the Research Ethics Commission of Tongji Hospital and the requirement for informed consent was waived by the Ethics Commission as described previously.[4]

2.2. Data collection

Demographic, clinical, laboratory, and outcome data were extracted from electronic medical records using a standard data collection form. All data were checked by 2 physicians and a third physician adjudicated any difference in interpretation between the 2 primary interviewers.

2.3. Laboratory procedures

Methods for laboratory confirmation of COVID-19 infection have been described elsewhere.[4] Diagnosis of COVID-19 was made according to WHO guidance. Novel coronavirus tests were performed in the Guanggu hospital area of Tongji Hospital in Wuhan. Throat-swab specimens were obtained for COVID-19 examination. All patients admitted to the COVID-19 specialized ICU had positive results of COVID-19 examination by real-time reverse transcription-polymerase chain reaction. Routine blood examinations were done at the second morning after admission, including the analysis of creatine kinase isoenzyme (CKMB), myoglobin, troponin I (cTnl), brain natriuretic peptide (BNP), hepatic and renal functions, C-reactive protein (CRP), and complete blood counts. The examination of the inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-1β (IL-1β), interleukin-2 receptor (IL-2R), and tumor necrotic factor-α (TNF-α), was done as soon as the patients were admitted. The levels of the cytokines were analyzed for the assessment of relationship with prognosis of COVID-19 pneumonia.

2.4. Clinical data collection

The illness onset time was defined as the time when the symptoms appeared and the admission time was defined as the time when the patients were admitted to the COVID-19-specialized ICU. Symptoms of cough, fever, chest discomfort, fatigue, diarrhea, and expectoration were recorded. Fever was defined as axillary temperature of at least 37.3 °C. Signs of body temperature and SpO2 were recorded. In-hospital death was collected for all the admitted patients in the COVID-19 specialized ICU.

2.5. Statistical analysis

Data were presented as medians (interquartile ranges, IQR) for continuous variables and number (percentages) for categorical variables. The correlations between the time from onset to death, the time from admission to death and laboratory findings were evaluated by Spearman rank correlation analyses. Cox regression was conducted to evaluate the effects of laboratory findings on the time from onset to death and time from admission to death. A two-sided $P < .05$ was considered statistically significant. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

3. Results

A total of 205 severe or critical COVID-19 pneumonia patients were admitted in the COVID-19 specialized ICU in the Guanggu hospital area between February 8 and March 30. And a total of 75 patients experiencing death were included in the final analysis. The median age of the deceasing patients was 70 years (IQR 65–79), ranging from 35 years to 88 years, and 72% of the patients were male. The most common symptoms were fever (78.9%) and cough (70.4%). Expectoration was the third common symptom (39.4%) in those patients. The median time from onset to death was 19 days (IQR 3.5–29.5) and that from admission to death was 3 days (IQR 3–13). The BNP level (median: 1032 and IQR: 424–2653) and CRP level (median: 114 and IQR: 55–156) were far beyond the normal reference ranges. And the estimated glomerular filtration rate (eGFR) (76, 53–91) was significantly below the normal reference range (Table 1). The other laboratory indicators, including alanine transaminase, aspartate transaminase, white blood cells (WBC), and lymphocytes were basically within the normal reference ranges.

In the Spearman rank correlation analysis, IL-8 was found to be significantly associated with the time from onset to death ($r_s = -0.30$, $P = .034$) (Table 2). Also, the Spearman rank

Table 1

Baseline characteristics of the dead patients in the COVID-19 specialized ICU.

Demographics and clinical characteristics*		
Age (years)	70	65–79
Male (n, %)	54	72
Cough (n, %)	50	70.4
Fever (n, %)	56	78.9
Chest discomfort (n, %)	14	19.7
Fatigue (n, %)	21	29.6
Diarrhea (n, %)	10	14.3
Expectoration (n, %)	28	39.4
Duration 1 (days)†	19	13.5–29.5
Duration 2 (days)‡	3	3-13
Body temperature (℃)	36.8	36.5–37.6
Pulse oxygen saturation (%)	92	86-97
Creatine kinase isoenzyme (ng/ml)	2.5	1.2–4.6
Myoglobin (ng/ml)	157.2	93.1–331.9
Troponin I (pg/ml)	35.3	11.7–276.7
Brain natriuretic peptide (pg/ml)	1032	424–2653
Alanine transaminase (IU/L)	26	18–43
Aspartate transaminase (IU/L)	40	26–58
Creatinine (μmol/L)	82	66–115
Uric acid (mmol/L)	280	201–394
Estimated glomerular filtration rate (ml/minutes/1.73 m^2)	76	53–91
C-reactive protein (mg/L)	114	55–156
Procalcitonin (ng/ml)	0.32	0.15–0.66
White blood cell ($\times 10^{12}$)	8.66	6.19–12.99
lymphocyte ($\times 10^{12}$)	0.65	0.46–0.90

* All values are expressed as median (interquartiles) unless otherwise noted.
† Duration 1 indicates the time from onset to death.
‡ Duration 2 indicates the time from admission to death.

correlation revealed the IL-8 level was associated with the time from admission to death ($r_s = -0.32$, $P = .019$), which indicate IL-8 may be a predictor for death in severe or critical COVID-19 patients. Besides, CKMB, CRP, WBC, and SpO2 were significantly correlated to the time from admission to death (Table 3).

Table 2

The association between laboratory findings and the time from onset to death.

Laboratory findings	r_s	*P* value
Creatine kinase isoenzyme	−0.21	.10
Brain natriuretic peptide	−0.021	.88
Troponin I	−0.050	.71
Aspartate transaminase	−0.12	.38
Alanine transaminase	−0.11	.39
Creatinine	−0.17	.18
Uric acid	−0.20	.12
C-reactive protein	−0.18	.17
Procalcitonin	−0.024	.86
White blood cell	−0.18	.16
Body Temperature (the highest)	−0.24	.059
Pulse oxygen saturation (the highest)	0.22	.074
Interleukin-1β	−0.19	.18
Interleukin-2R	−0.031	.83
Interleukin-6	−0.17	.24
Interleukin-8	−0.30	.034
Interleukin-10	−0.27	.053
Tumor necrotic factor-α	−0.14	.33

Table 3

The association between inflammatory cytokines and the time from admission to death.

Laboratory findings	r_s	*P* value
Creatine kinase isoenzyme	−0.28	.029
Brain natriuretic peptide	−0.12	.39
Troponin I	−0.20	.12
Aspartate transaminase	−0.16	.21
Alanine transaminase	−0.11	.39
Creatinine	−0.065	.61
Uric acid	−0.098	0.44
C-reactive protein	−0.48	< .0001
Procalcitonin	−0.17	.19
White blood cell	−0.45	.0002
lymphocyte	0.0094	.94
Body Temperature (the highest)	−0.078	.54
Pulse oxygen saturation (the highest)	0.41	.0007
Interleukin-1β	−0.057	.68
Interleukin-2 receptor	−0.19	.18
Interleukin-6	−0.13	.34
Interleukin-8	−0.32	.019
Interleukin-10	−0.10	.45
Tumor necrotic factor-α	−0.095	.50

Considering that age and sex may influence the effect of laboratory findings on time from onset to death and time from admission to death, we further performed cox regression including age and sex as covariates. After adjusting for the effects of age and sex, CRP, WBC, SPO_2, and IL-8 had significant influence on both the time from onset to death and the time from admission to death, as shown in Table 4. CKMB and BNP levels also have significant effect on the time from admission to death.

4. Discussion

COVID-19 can cause lethal infections and has rapidly spread over more than 200 countries across the globe in about 7 months, thus an analysis of fatal cases is a public health priority. Our retrospective cohort study identified correlating factors for death in severe/critical adults in Wuhan who were hospitalized in COVID-19-specialized ICU. And we first showed in severe/critical COVID-19 patients, IL-8 levels were associated with the time from onset to death and that from admission to death, even after adjusting for the influence of age and sex, which indicated higher IL-8 levels were associated with higher odds of in-hospital death in those patients.

The pathogenesis of highly pathogenic human coronavirus is still not completely understood. And cytokine storm and viral evasion of cellular immune responses are reported to play important roles in disease severity.[7] Neutrophilia was found in both the peripheral blood[8] and lung of SARS-Cov patients.[9] And in patients with Middle East Respiratory syndrome, the severity of lung damage was associated with extensive pulmonary infiltration of neutrophils and macrophages and higher numbers of these cells in the peripheral blood.[10–12] And neutrophils are the main source of chemokines and cytokines. In patients with severe COVID-19, but not in patients with mild disease, an increase in neutrophil count and in the neutrophil-to-lymphocyte ratio usually indicates higher disease severity and poor clinical outcome.[13] IL-8 was exactly the activation factor for neutrophils. In our study, we first indicated in severe/critical COVID-19

Table 4

Effects of laboratory findings after adjusting age and sex (The tables are uploaded separately).

Laboratory findings	Time from onset to death			Time from admission to death		
	Beta	Se	*P*	Beta	Se	*P*
Creatine kinase isoenzyme	-2.67×10^{-4}	0.001	.72	0.037	0.017	.03
Brain natriuretic peptide	4.83×10^{-5}	5.16×10^{-5}	.245	1.08×10^{-4}	4.54×10^{-5}	.017
Troponin I	3.57×10^{-5}	3.70×10^{-5}	.335	3.89×10^{-5}	3.60×10^{-5}	.28
Aspartate transaminase	2.71×10^{-4}	3.17×10^{-4}	.393	2.14×10^{-4}	2.82×10^{-4}	.448
Alanine transaminase	2.72×10^{-4}	4.13×10^{-4}	.511	2.89×10^{-4}	3.44×10^{-4}	.4
Creatinine	-1.44×10^{-4}	0.001	.88	-4.37×10^{-4}	0.001	.625
Uric acid	3.48×10^{-4}	0.001	.66	0.001	0.001	.318
C-reactive protein	0.004	0.002	.027	0.007	0.002	2.75×10^{-4}
Procalcitonin	0.023	0.043	.278	0.019	0.035	.592
White blood cell	0.054	0.026	.039	0.121	0.029	3.34×10^{-5}
lymphocyte	0.24	0.274	.381	0.003	0.26	.99
Body Temperature (the highest)	0.251	0.151	.096	0.321	0.199	.107
Pulse oxygen saturation (the highest)	−0.029	0.012	.017	−0.059	0.015	1.14×10^{-4}
Interleukin-1β	0.06	0.04	.12	0.025	0.033	.45
Interleukin-2 receptor	2.48×10^{-4}	1.58×10^{-4}	.12	3.24×10^{-5}	1.27×10^{-4}	.80
Interleukin-6	4.86×10^{-4}	4.31×10^{-4}	.26	1.27×10^{-4}	3.9×10^{-4}	.745
Interleukin-8	0.006	0.002	.003	0.004	0.002	.01
Interleukin-10	0.001	0.001	.25	0.001	0.001	.223
Tumor necrotic factor-α	0.003	0.02	.89	0.016	0.017	.36

patients, IL-8 might be a prognostic indicator for in-hospital death. Besides, Fei Zhou et al reported elevated levels of blood IL-6 were more commonly seen in severe COVID-19 illness, however without an association with in-hospital death.[5] We treated a severe COVID-19 patient with tocilizumab, IL-6 receptor antagonists, who eventually recovered (data has not been published). Our data indicates the association between IL-10 and the time from onset to death that is almost statistical significant ($P=.053$), while the association between IL-10 and the time from admission to death is not significant ($P=.45$). It has been believed that high levels of pro-inflammatory cytokines may lead to shock and tissue damage in multiple organs as well as extensive pulmonary pathology. The finding of IL-8 as a possible prognostic indicator for death of COVID-19 patients may provide a new way to treat COVID-19 pneumonia with anti-IL-8 therapy.

Contrary to Shoenfeld Y,[14] Lauren A, Henderson et al thought hyperinflammation in COVID-19 is not macrophage activation syndrome, with modest elevation of ferritin and focused severe end-organ disease of lung.[15] However, critically-ill COVID-19 patients often demonstrate features suggestive of cytokine storm, including fever, characteristic lab changes, and ARDS. Thus the host is immune response and tissue-focused inflammation in the lung likely plays an important role in COVID-19, which suggests it will be important to monitor hospitalized COVID-19 patients for evidence of cytokine storm. Though IL-6 were reported significantly elevated in COVID-19 patients, it has not yet been proven to be predictive of poor outcome. Our finding of IL-8 as a correlating factor for in-hospital death in severe/critical COVID-19 patients may provide a new way to evaluate and treat COVID-19 pneumonia.

There were some limitations of the present study. Firstly, due to the retrospective study design, not all laboratory tests were done for all patients, including serum ferritin. Secondly, the interpretation of the findings might be limited by the relative small sample size. Thirdly, a survivor group should be included for researchers to verify the mortality risk factors identified in the present study.

5. Conclusions

To the best of our knowledge, we first reported that IL-8 levels were associated with in-hospital death in severe/critical COVID-19 patients. Our findings may provide a new way to evaluate and treat COVID-19 pneumonia. However, more studies are needed to disentangle the risk factors for death of COVID-19 pneumonia and the underlined mechanisms.

Author contributions

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