Intensive Care Medicine

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Clinicolaboratory Study of 25 Fatal Cases of COVID-19 in Wuhan

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Take-home message

These findings offer new insights into the characteristics of non-survivors with COVID-19 which may facilitate identification of patients at high risk of deterioration or death. The pathogenesis of fatal cases might involve an uncontrolled release of immune mediators, a 'cytokine storm'.

In December 2019, cases of pneumonia associated with a novel 2019 coronavirus emerged in Wuhan (Hubei Province, China) [1]. The causative agent was subsequently named SARS-CoV-2 and the resulting disease COVID-19. As of 17 March 2020, 80894 cases of COVID-19 were reported in China of which 3237 (4.00%) were fatal. In Wuhan, 2490 (4.98%) of 50005 cases died. In addition, 98218 cases from 104 countries outside of China were laboratory-confirmed, of which 4189 (4.27%) were fatal. A previous study suggested that the condition of 11 (11%) patients worsened in a short period of time and they died of multiple organ failure [2], while Wang et al. [3] reported that 4.3% of COVID-19 cases were fatal. A national study of 1099 patients with COVID-19 found that 55 patients (5.00%) were admitted to an intensive care unit and 15 (1.36%) succumbed to the infection [4]. It is important to emphasize that most patients studied previously were hospitalized and thus the full spectrum of COVID-19 severity is still being elucidated [1-4]. We aimed to further explore the clinicolaboratory characteristics, hospital complications, and treatments of 25 fatal cases of COVID-19. The clinicolaboratory characteristics of survivors (N=149) and non-survivors were also compared.

This was a single-center retrospective analysis. All consecutive fatal cases of COVID-19 admitted to Wuhan University Zhongnan Hospital from 3 January to 24 February 2020, were included. COVID-19 was confirmed using throat swab samples by real-time RT-PCR [3, 5]. Epidemiological, clinical and laboratory data as well as information on treatments received, hospital complications and causes of death were collected. Blood samples were collected at admission. The study was approved by the Ethics Committee of Wuhan University Zhongnan Hospital and informed consent was waived by the Ethics Committee.

Twenty-five fatal COVID-19 cases were included. The median age of these patients was 70 years (interquartile range [IQR]: 64–80 years) and 19 (76.0%) were men. The median time from onset of symptoms to hospital admission and death was 7 days (IQR: 1–10 days) and 19 days (IQR: 13–26 days),

respectively. As shown in Table 1, fatal cases were older (70 years, IQR: 64–80 years vs. 51 years, IQR: 37–62 years), disproportionately male (76.0% vs. 40.3%), and more often suffered from comorbidities (64.0% vs. 24.2%; cardiovascular and cerebrovascular diseases: 32.0% vs. 7.4%) compared with non-fatal cases. Fatal cases were also more likely to be admitted to intensive care units (36.0% vs. 10.7%) and had higher medical expenses (53745 CNY, IQR: 30286–112268 CNY vs. 14507 CNY, IQR: 8813–27617 CNY).

During the study period, 174 patients (all COVID-19-positive hospital admissions) had an outcome (death or discharge). Thus, the case fatality rate was 14.4% (95% confidence interval: 9.2–19.6%). The most common cause of death was multiple organ dysfunction syndrome (56.0%). Cardiac arrest (20.0%), respiratory failure (16.0%) and acute respiratory distress syndrome (16.0%) were other causes of death (Table 1). Acute respiratory distress syndrome (shock), secondary bacterial infection and acute cardiac/kidney/liver injury were common during hospitalization. Most patients were treated with methylprednisolone (76.0%), invasive mechanical ventilation (68.0%) and oseltamivir (64.0%). Fatal cases experienced hospital complications and received aggressive treatment strategies more often than non-fatal cases (Table 1). Interestingly, fatal cases were treated more often with oseltamivir and methylprednisolone, but less often with umifenovir (Table 1).

Serum levels of interleukin-6, C-reactive protein and D-dimer were higher in non-survivors than in survivors, while lymphocyte counts were lower (Table 1, Figure 1). Nearly all fatal cases had abnormal coagulation, and 24 (96.0%) fatal cases showed elevated D-dimer levels. All fatal cases showed evidence of cytokine abnormalities and establishment of an inflammatory state as demonstrated by elevated interleukin-6 and C-reactive protein levels.

In summary, COVID-19 mortality is more common in older male patients with comorbidities and is mainly caused by multiple organ dysfunction syndrome. The roles of hypercoagulability and pathological inflammatory states should not be ignored. Similarly, other literature recently published in this population also showed that the increasing odds of in-hospital death associated with older age, the presence of underlying diseases, elevated inflammatory and d-dimer greater than 1 μg/ml on admission

[6-7].

An interferon-γ-related cytokine storm may be involved in immunopathological damage in SARS patients [8]. In addition, SARS patients with early-stage disease, especially those with subsequent poor outcomes, had very high numbers of tumor necrosis factor-α- and interleukin-6-producing cells in the blood [9]. Previous studies also reported that fatal cases of COVID-19 had higher levels of clotting factors and cytokines [1-3, 7]. We speculate that the pathogenesis of fatal cases might involve uncontrolled release of immune mediators (i.e., a 'cytokine storm'). Ruan et al. [6] also suggested that COVID-19 mortality might be due to virus-activated "cytokine storm syndrome" or fulminant myocarditis [6]. Tocilizumab (a monoclonal antibody targeting the interleukin-6 receptor) had been used to treat cytokine storm syndrome [10] and a clinical trial to assess its use in COVID-19 patients has been registered. These findings offer new insights into the characteristics of fatal cases of COVID-19, which may help identify patients at high risk of severe disease or death. The limitations of this study are listed in the supplementary material.

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Concept and design: Cao, Hu, Yu, Tu, Liu

Acquisition, analysis, or interpretation of data: Cao, Hu, Yu, Tu, Liu

Drafting of the manuscript: Cao, Tu, Liu

Critical revision of the manuscript for important intellectual content: Hu, Yu.

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Data Availability Data available can be obtained from the corresponding author**.**

A Consent for publication Not applicable.

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Figure legends

Figure 1. Blood levels of biomarkers in non-survivors and survivors of COVID-19. (A) levels of lymphocyte in non-survivors and survivors; (B) levels of interleukin-6 in non-survivors and survivors; (C) levels of C reaction protein in non-survivors and survivors; (D) levels of D-dimer in non-survivors and survivors. All data are medians and interquartile ranges (IQR), with dot plots representing all values.

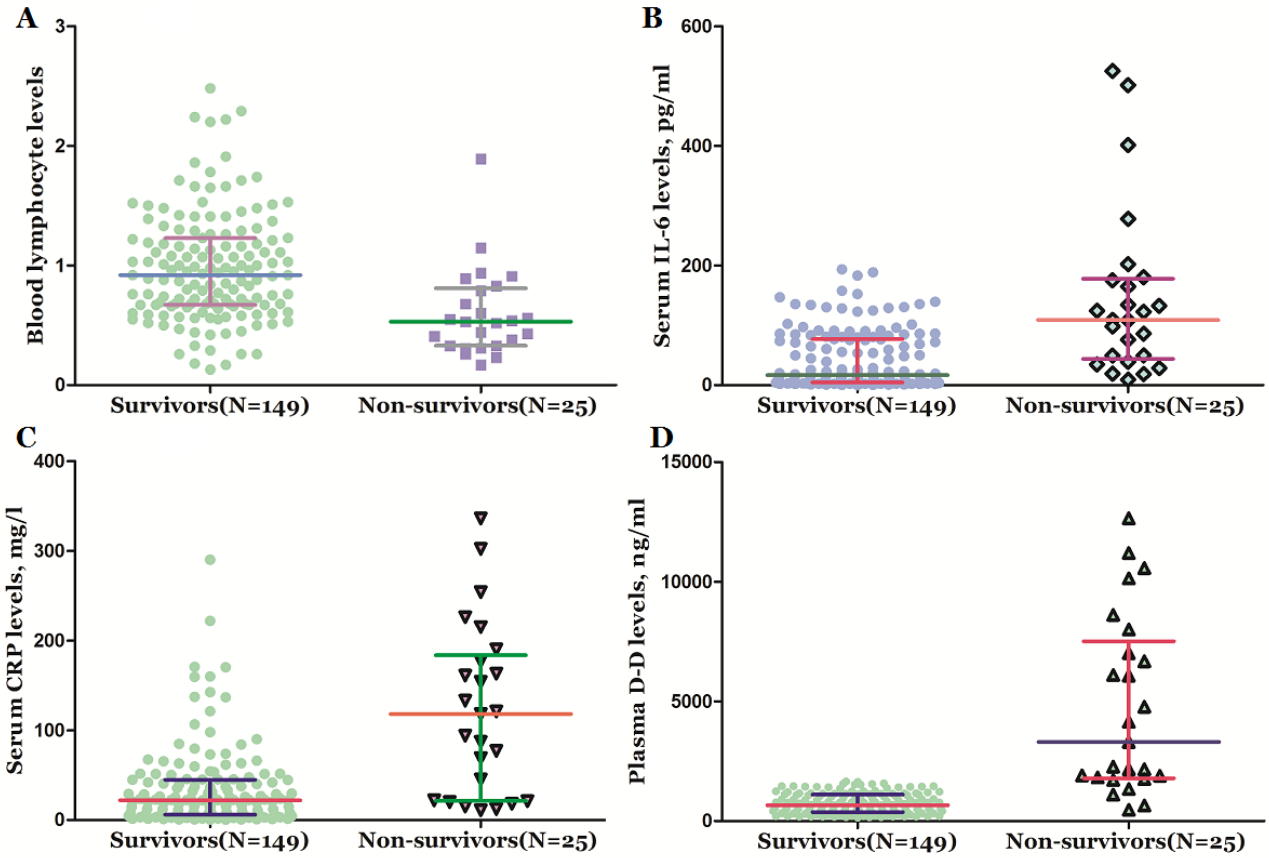

Table 1: Baseline characteristics and laboratory results of included cases of COVID-19†

	Non-survivors	Survivors	P
N	25	149	-
Age, years	70(64-80)	51(37-62)	<0.001
Sex-male	19(76.0)	60(40.3)	<0.001
BMI, kg/m2	24.6(22.3-28.3)	23.6(21.6-25.6)	0.125
Temperature at admission, ℃	38.1(37.1-39.0)	38.0(37.3-38.9)	0.383
Comorbidities			
Any	16(64.0)	36(24.2)	<0.001
Hypertension	12(48.0)	25(16.8)	<0.001
Diabetes	6(24.0)	11(7.4)	0.010
Cardiovascular-cerebrovascular diseases	8(32.0)	8(7.4)	<0.001
Respiratory diseases	4(16.0)	8(7.4)	0.130
Onset of symptom to, days			
Hospital admission	7(1-10)	7(3-9)	0.381
Death or discharge	19(13-26)	20(13-27)	0.894
ICU admission	9(36.0)	16(10.7)	0.003
Cost of hospitalization, CNY	53 745(30 286-112 268)	14 507(8 813-27 617)	<0.001
Laboratory findings at admission††			
White blood cell, 109/l	6.88(4.96-13.48)	4.22(3.21-5.91)	<0.001
Elevated (>9.5)	10(40.0)	10(6.7)	<0.001
Lymphocyte, 10^9/l	0.53(0.33-0.82)	0.92(0.67-1.23)	<0.001
Reduced(<1.1X10^9/l)	23(92.0)	99(66.4)	0.010
IL-6, pg/ml	108.8(44.1-177.9)	16.8(4.4-76.9)	<0.001
Elevated(>2.9pg/ml)	25(100.0)	115(77.2)	0.017
D-dimer, ng/ml	3306(1790-7512)	660(370-1108)	<0.001
Elevated(>500ng/ml)	24(96.0)	89(59.7)	<0.001
CRP, mg/l	118(22-184)	22(6-45)	<0.001
Elevated(>10mg/l)	25(100.0)	95(63.8)	<0.001
Treatment			
Umifenovir	3(12.0)	70(47.0)	0.001
Oseltamivir	16(64.0)	61(40.9)	0.032
Lopinavir	5(20.0)	46(30.9)	0.269
Methylprednisolone	18(72.0)	71(47.7)	0.024
Noninvasive ventilation	4(16.0)	5(3.4)	0.031
Invasive mechanical ventilation	17(68.0)	2(1.3)	<0.001

ECMO	3(12.0)	3(2.0)	0.052
CRRT	7(28.0)	1(0.7)	<0.001
Complications			
Shock and/or ARDS	23(92.0)	8(5.4)	<0.001
Secondary bacterial infection	20(80.0)	6(4.0)	<0.001
Acute cardiac injury†††	18(72.0)	7(4.7)	<0.001
Acute kidney injury	19(76.0)	8(5.4)	<0.001
Acute liver injury	15(60.0)	30(20.1)	<0.001
Cause of death			
MODS	14(56.0)	-	
ARDS	2(8.0)	-	
Cardiac arrest	5(20.0)	-	
Respiratory Failure	4(16.0)	-	

†The results were presented as median (IQR) for continuous variables and number (%) for categorical variables. The different characteristics between death and survival groups were tested by Mann-Whitney U test (continuous variables) or Chi-square test (categorical variables). A two-sided a of less than 0·05 was considered statistically significant.

††We calculated the average value if one patient had multiple tests.

†††Acute cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, troponin I) were above the 99th percentile upper reference limit, or new abnormalities were shown in electrocardiography and echocardiography.

ICU, Intensive Care Unit; BMI, body mass index; CNY, China Yuan; IL-6, interleukin-6; CRP, C reaction protein; ECMO, Extracorporeal membrane oxygenation; MODS, multiple organ dysfunction syndrome; CRRT, continuous renal replacement therapy; ARDS, Acute respiratory distress syndrome

Supplementary material: study limitations

The study is limited by lack of patients with mild infections. Our hospital, located in the center of the epidemic area, is one of the major tertiary university hospitals and is responsible for the treatments for patients with severe COVID-19. In addition, this study is only a single-center retrospective analysis with 25 fatalities. Multicenter large-scale prospective study is warranted to explore the pathogenesis of fatal cases. Third, only throat swab samples had been used to test the virus of COVID-19. In fact, other samples such as blood, urine and stool also could be used. Fourth, only a single cytokine (IL-6) was measured at admission. These data do not allow us to infer anything about other cytokines levels and changes in cytokine levels over time. Further research needs to clarify these questions. We considered this as one study limitation and added. Fifth, fatal cases more often received treatment with oseltamivir and methylprednisolone, while fewer received arbidol. This is likely to be a result of clinician appreciation of severity of illness and thus willingness to apply these treatments, as it is to be an effect of these interventions on mortality. The true effects of these drugs on COVID-19 need to be verified in further clinical trials. Lastly, viral load could be used to assess treatment efficacy and disease progression. However, we did not obtain this information. This should be determined in COVID-19 in further study.