Systemic Inflammation and Clinical Outcomes in COVID-19: a retrospective study

Meijia Wang
Tongji Hospital
Zhenli Huang
Tongji Hospital
Kun Tang
Tongji Hospital
Pengfei Gao
the First Affiliated Hospital of Henan University of Science and Technology
Yanjiao Lu
Tongji Hospital
Shanshan Wang
Tongji Hospital
Tao Wang
Tongji Hospital
Jungang Xie
Tongji Hospital
Jianping Zhao (zhaojp88@126.com)
Tongji Hospital https://orcid.org/0000-0001-9159-4235

Research

Keywords: COVID-19, systemic inflammation, clinical outcomes

Posted Date: May 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27267/v1

Abstract

Background COVID-19 causes epidemics and pandemics worldwide, but the role of pathophysiological parameters particularly systemic inflammation in COVID-19 has not been understood. We aimed to investigate clinical outcomes in view of systemic inflammation in COVID-19.

Methods In this retrospective study, the demographic and clinical data of 225 confirmed COVID-19 cases on admission at Tongji Hospital from January 28 to February 15, 2020, were extracted and analyzed. These patients were categorized by inflammation state on the basis of the expression of inflammatory factors or classified as severe and non-severe according to 2019 *American Thoracic Society* / *Infectious Disease Society of America* guidelines.

Results: Among 225 patients with confirmed COVID-19, 155 patients (68.9%) categorized into hyperinflammation group and 70 (31.1%) were non- hyperinflammation group. Compared to non-hyperinflammation group, hyperinflammation group more frequently had chest tightness/dyspnea and lymphopenia, aberrant multiple indexes of organ function including the heart, liver, kidney, and coagulation, with higher level of C-reactive protein (hsCRP) as well as interleukin (IL)-6, IL-8, tumour necrosis factor α (TNF-α), etc. Hyperinflammation group were more likely to admit to intensive care unit (ICU) (52.3% vs 5.7%), receive ventilation (84.5% vs 10.0%) and be with higher mortality (44.5% vs 5.7%) than non-hyperinflammation group. The mortality of severe patients with hyperinflammation (60/99, 60.6%) was significantly higher than without hyperinflammation (2/20, 10.0%). Non-severe patients with hyperinflammation even tended to have higher mortality (9/56, 16.1%) than those in severe cases without hyperinflammation (2/20, 10%).

Conclusion: Excessive systemic inflammation was correlated highly with poor clinical outcomes in COVID-19, particularly in severe cases. Non-severe patients with hyperinflammation even tended to have higher mortality than those in severe cases without hyperinflammation.

Trial registration: This is a retrospective observational study without a trial registration number.

Background

The newly emergent human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), first detected in Wuhan, China[1, 2]. The virus belongs to the same genus as SARS-CoV and Middle Eastern respiratory syndrome coronavirus (MERS-CoV), causing epidemics and pandemics[3, 4]. However, SARS-CoV-2 is more infectious than SARS-CoV and MERS-CoV with more than 1130000 cases having been confirmed worldwide as of April 5, 2020, according to the World Health Organization (WHO)[5]. Initial reports from China and Italy suggest high mortality and stressed intensive care unit (ICU) capacity[6, 7]. There is no specific antiviral treatment available for COVID-19 currently, and therefore further researches into the pathogenesis of human coronavirus (hCoVs) infection are imperative for identifying appropriate therapeutic targets[8].

The pathological features of COVID-19 greatly resemble those seen in SARS and MERS coronavirus infection[9–11]. From previous studies, the clinical deterioration of hCoVs infection may result from a combination of direct virus-induced cytopathic effects and immunopathology induced by excessive systemic inflammation or a “cytokine-storm”[12–14]. Consistent with these findings, accumulating evidence suggests different levels of inflammatory cytokines (e.g. IL-2R, IL-6 and IL-8) were observed between severe and non-severe patients[15–17]. Predictors of fatality from a recent retrospective study included elevated ferritin, interleukin (IL)-6 and high-sensitivity C-reactive protein (hsCRP), suggesting that COVID-19 progression might be due to virally driven hyperinflammation[18]. It’s a well-known fact that excessive systemic inflammation could induce varying degrees of lung injury, associated with clinical symptoms and disease progression[19–21]. But until now, the role of excessive systemic inflammatory responses in COVID-19 has not been fully illuminated. Notably, the argument of corticosteroid treatment for COVID-19 persists[18, 22–25]. It’s no doubt that corticosteroid treatment could suppress systemic inflammation, but the outcomes of corticosteroid treatment were conflicting[26], partly due to systemic inflammation heterogeneity in COVID-19 patients[23]. Furthermore, systemic inflammation biomarkers, such as hsCRP, IL-2, IL-6, IL-8, IL-10, tumour necrosis factor α (TNF-α), have been approved to be predictors for disease progression and remission[27–31]. Nevertheless, the association between systemic inflammation and clinical outcomes of COVID-19 has not been elucidated so far.

In this study, we intended to investigate the clinical outcomes in view of systemic inflammation in COVID-19. According to the grade of systemic inflammation, characterized by hsCRP, IL-6, IL-8 and TNF-α, we classified 225 patients with COVID-19 admitted to Tongji Hospital into subgroup to explore clinical course and outcomes. Our findings will facilitate understanding the pathogenesis of COVID-19 and improving clinical strategies against the disease.

Methods

Study participants and data collection

A total of 376 patients with COVID-19 were recruited retrospectively at Tongji hospital from January 25 to February 15, 2020, 151 of whom were excluded due to the lack of laboratory tests of cytokines and hsCRP. Tongji Hospital, the largest comprehensive medical treatment center of the central China, was urgently reconstructed and has been assigned by Chinese government as a specific hospital for the treatment of severe patients with COVID-19. Because of the urgency of data extraction, complete random sampling could not be applied. COVID-19 was diagnosed on the basis of the WHO interim guidance[32] and the confirmed case was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens[33]. As of 5 April 2020, 73 of the 225 patients had died, with a mortality rate of up to 32.4%, and 139 patients had recovered and been discharged. The remaining 13 patients were still in hospital and receiving medical care. The study was performed in accordance with Tongji Hospital Ethics Committee (TJ-IRB20200353). Written informed consent was waived by the Ethics Commission owing to the rapid emergence of this infectious disease.

Data including demographic data, clinical symptoms, radiological characteristics, laboratory findings, treatment and outcomes as well as mortality were collected from patients' electronic medical records. The data were monitored up to 5 April 2020. Comorbidities were determined based on patient's self-report on admission and sorted according to the organ systems (i.e. respiratory, cardiovascular, digestive and endocrine). For patients with smoking history, the amount of smoking, the years of smoking history and the years of smoking cessation were individually collected. The clinical classifications of patients as having severe or non-severe COVID-19 are established based on the 2019 *American Thoracic Society / Infectious Disease Society of America* guidelines[34], taking into account its global acceptance for severity stratification of community-acquired pneumonia although lacking of validation in patients with viral pneumonia. Briefly, severe cases denoted at least one major criterion (Septic shock with need for vasopressors, or respiratory failure requiring mechanical ventilation), or three or more minor criteria (respiratory rate being 30 times per minute or greater, oxygen index being 250 or lower, multiple lobe infiltration, delirium or loss of consciousness, blood urea nitrogen level being 20 mg/dl or greater, blood leukocyte count being 4,000 per deciliter or lower, blood platelet count being 100,000 per deciliter or lower, body temperature being lower than 36 degrees, hypotension necessitating vasoactive drugs for maintaining blood pressure). All the data collection forms were reviewed independently by three independent researchers.

Definition of hyperinflammation

Serum inflammatory markers (including cytokines, acute-phase reactants, etc.) were used to evaluate the systemic inflammation, and accumulating evidences suggested that severe COVID-19 might encounter cytokine storm syndrome[24, 35]. Assessment of infection-related biomarkers and serum cytokines of patients with COVID-19 on admission indicated that levels of hsCRP, IL-2R, IL-6, IL-8, IL-10, and TNF-α were markedly elevated, especially in severe cases[15, 17]. Some researchers and physicians considered very high levels of hsCRP (> 10 mg/L) may represent nonspecific inflammation, and elevated hsCRP and pro-inflammatory cytokines (including IL-6, IL-8 and TNF-α) levels in community-acquired pneumonia (CAP) were indicative of hyperinflammatory state and associated with clinical outcomes[36, 37]. Systemic inflammation processes are complex, therefore it is unlikely that a single ideal factor will ever be found. A combination of several factors may be more effective, but this requires further evaluation[38]. Based on above, predictive factors we selected to reflect systemic inflammation were assessed in each patient and included hsCRP, IL-6, IL-8 and TNF-α. For each factor, cut points used to define a high level were as following: IL-6 ≥ 7.0 pg/mL, IL-8 ≥ 62 pg/mL, TNF-α ≥ 8.1 pg/mL, hsCRP > 10 mg/L. Patients were classified as having either a positive or negative hyperinflammation (positive hyperinflammation indicates elevation in two or more factors, negative hyperinflammation indicates elevation in one or no factors).

Laboratory measurements

Pharyngeal swab specimens of patients were collected for the SARS-CoV-2 viral nucleic acid detection using RT-PCR assay performed by the clinical laboratory from Tongji Hospital. Detailed protocol was described elsewhere[39].

Clinical laboratory investigation, included a complete blood count, a coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), infection-related biomarkers, anti-SARS- CoV-2 antibodies, detection of different pathogens (include mycoplasma pneumoniae, chlamydia pneumoniae, influenza A virus, influenza B virus, adenovirus) and cytokine tests were collected for each patient. Cytokines including IL-6, IL-8 (also known as CXCL8) and TNF-α were assessed in serum samples drawn shortly after hospital admission by Chemiluminescence Immunoassay (CLIA) performed on a fully automated analyzer (Immulite 1000, DiaSorin Liaison, Italy or Cobas e602, Roche Diagnostics, Germany) for all patients according to the manufacturer's instructions. IL-6 kit (#05109442190) was purchased from Roche Diagnostics, Germany. IL-8 kit (#LK8P1) and TNF-α kit (#LKNF1) were purchased from DiaSorin (Vercelli, Italy). All medical laboratory data were generated by the clinical laboratory of Tongji hospital. Frequency of examinations was determined by the treating physician. The laboratory data for some patients were missing due to the absence of types of tests or delayed results.

Statistical Analysis

We described the categorical variables as frequency rates and percentages, and continuous variables median and interquartile range (IQR) values. Unpaired 2-sided Student's t test was used for continuous variables when the data were normally distributed; otherwise, the Mann-Whitney test was used. The frequencies of categorical variables were compared using the $\chi 2$ test and Fisher's exact test as appropriate. All statistical analyses and graphs were generated and plotted using SPSS (version 21.0) and GraphPad Prism version 7.0 software (GraphPad Software Inc). The tests with p value less than 0.05 was considered statistically significant.

Results

Demographics and baseline characteristics of patients with COVID-19

A total of 225 patients diagnosed as COVID-19 were included in this study. According to the definition described in the methods, 225 patients were divided into 155 patients in the hyperinflammation group and 70 patients in the non-hyperinflammation group. As shown in Table 1, the median age of 225 patients was 67 (IQR 57.0–74.0) years, and the mean age of hyperinflammation group was 68 (IQR 58.0–75.0) years, which was similar with non-hyperinflammation group (median [IQR],65 [57.0–73.0] years). About half (50.7%) of patients were female. Male was more predominant in hyperinflammation group (93, 60%) than in non-hyperinflammation group (18, 25.7%). All patients are residents of Wuhan, but no patients had direct exposure history of Huanan wet markets or wildlife animals. Overall, 55 (24.4%) patients had a history of close contact with previously confirmed COVID-19. Few patients had a current or former smoking history, which might be inaccurate due to the large number of patients and endangered state of most patients on admission. Hypertension, diabetes, and cardiovascular disease were the most common comorbidities among hyperinflammation group (72 [46.5%], 39 [25.5%], and 24 [15.5%]) and

non-hyperinflammation group (26 [37.1%], 10 [14.3%], and 8 [11.4%]). Only six patients with COPD were identified and all were in hyperinflammation group.

Table 1
Characteristics of patients with COVID-19

	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Age, years-median (IQR)	67.0(57.0–74.0)	68.0(58.0–75.0)	65.0(57.0–73.0)	0.1211
Sex-No. (%)				
Female	114(50.7)	62(40.0)	52(74.3)	< 0.0001
Male	111(49.3)	93(60.0)	18(25.7)	..
Exposure history-No. (%)	55(24.4)	41(26.5)	14(20.0)	0.3202
Smoked-n/N (%)				
Never	210/222(94.6)	142/152(93.4)	68/70(97.1)	0.5111*
Current	5/222(2.3)	4/152(2.6)	1/70(1.4)	..
Former	7/222(3.2)	6/152(3.9)	1/70(1.4)	..
Comorbidity-No. (%)				
Hypertension	98(38.4)	72(46.5)	26(37.1)	0.2453
Diabetes	49(19.2)	39(25.2)	10(14.3)	0.0813
Cardiovascular disease	32(12.5)	24(15.5)	8(11.4)	0.5374
Malignancy†	7(2.7)	7(4.5)	0(0.0)	0.1020
Chronic kidney disease	7(2.7)	6(3.9)	1(1.4)	0.4398
Chronic obstructive lung disease	6(2.4)	6(3.9)	0(0.0)	0.1850
Asthma	2(0.8)	0(0.0)	2(2.9)	0.0958
Interstitial lung disease	0(0.0)	0(0.0)	0(0.0)	> 0.9999
Tuberculosis	4(1.6)	4(2.6)	0(0.0)	0.3129

COVID-19 = coronavirus disease 2019, IQR = interquartile range.

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. Percentages may not total 100 because of rounding. P values were calculated by unpaired 2-sided Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. *χ^2 test comparing all subcategories.

† Included in this category is any type of cancer.

	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Bronchiectasis	1(0.4)	0(0.0)	1(1.4)	0.3111
Chronic hepatitis B	3(1.2)	3(1.9)	0(0.0)	0.5540
Others	64(25.1)	46(29.7)	18(25.7)	0.6327
Respiratory rate breath, per min-median (IQR)	22.0(20.0–26.0)	22.0(20.0–28.0)	20.0(20.0–25.0)	0.0054
< 24, n/N (%)	134/222(60.4)	85/152(55.9)	49(70.0)	0.0119*
24–30, n/N (%)	56/222(25.2)	38/152(25.0)	18(25.7)	..
≥ 30, n/N (%)	32/222(14.4)	29/152(19.1)	3/70(4.3)	..
Heart rate, beat per min-median (IQR)	85.0(78.0-101.0)	87.0(78.0-103.0)	82.0(76.0–96.0)	0.0899
> 100, n/N (%)	58/224(25.9)	45/154(29.2)	13/70(18.6)	0.1019
Percutaneous oxygen saturation, %-median (IQR)	95.0(90.0–97.0)	93.0(85.0–97.0)	96.0(92.0–98.0)	0.0002
≤ 93%, n/N (%)	90/224(40.2)	72/154(46.8)	18/70(25.7)	0.0032
Systolic pressure, mmHg-median (IQR)	134.0(120.0-150.0)	134.0(121.0-152.0)	134.0(120.0-144.3)	0.2615
Diastolic pressure, mmHg-median (IQR)	80.0(73.0–89.0)	80.0(71.0–90.0)	81.0(74.0–86.0)	0.8798
COVID-19 = coronavirus disease 2019, IQR = interquartile range.				
Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. Percentages may not total 100 because of rounding. P values were calculated by unpaired 2-sided Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. *χ^2 test comparing all subcategories.				
† Included in this category is any type of cancer.				

Respiratory rates, heart rates, systolic pressure, and diastolic pressure were similar in the two groups, but patients with hyperinflammation more frequently developed tightness/dyspnea (respiratory rate > 30 breaths per minute (19 [19.1%]vs 3 [4.3%]). Percutaneous oxygen saturation on admission were lower in patients with hyperinflammation (median [IQR], 93.0 [85.0–97.0], %) than those with non-hyperinflammation (median [IQR], 96.0 [92.0–98.0], %). Seventy two (46.8%) hyperinflammatory patients and 18 (25.7%) non-hyperinflammatory patients had percutaneous oxygen saturation of 93% or below.

Clinical symptoms of patients with COVID-19

Symptoms of the patients on admission are shown in Table 2. The most common symptoms at onset of illness were fever (193 [85.8%]), followed by chest tightness/dyspnea (177 [78.7%]) and cough (170 [75.6%]). Less common symptoms were chills, sore throat, fatigue, myalgia, sputum, gastrointestinal symptoms (nausea or vomiting, anorexia, abdominal pain, diarrhea), headache, dizziness and unconscious. Fever were the most prevalent symptoms in both hyperinflammation (136 [87.7%]) and non-hyperinflammation group (57 [81.4%]), and the proportions in the two groups were comparable. No difference was identified for the occurrence rates of most symptoms between the two groups, but chest tightness/dyspnea were much more common in patients with hyperinflammation (131 [84.5%]) than those with non-hyperinflammation (46 [65.7%]), and sputum were more commonly observed in patients with non-hyperinflammation (13 [18.6%] vs 12 [7.7%]).

Table 2
Clinical symptoms of patients with COVID-19

Clinical symptoms-No. (%)	Total	Hyperinflammation		
	(n = 225)	Yes(n = 155)	No(n = 70)	P value
Fever	193(85.8)	136(87.7)	57(81.4)	0.2209
Chills	21(9.3)	13(8.4)	8(11.4)	0.4665
Chest tightness/dyspnea	177(78.7)	131(84.5)	46(65.7)	0.0025
Sore throat	11(4.9)	6(3.9)	5(7.1)	0.3239
Cough	170(75.6)	116(74.8)	54(77.1)	0.7410
Chest pain	8(3.6)	4(2.6)	4(5.7)	0.2591
Sputum	25(11.1)	12(7.7)	13(18.6)	0.0221
Fatigue	93(41.3)	67(43.2)	26(37.1)	0.4650
Myalgia	39(17.3)	24(15.5)	15(21.4)	0.3414
Gastrointestinal symptoms				
Nausea or vomiting	18(8.0)	11(7.1)	7(10.0)	0.4397
Anorexia	21(9.3)	17(11.0)	4(5.7)	0.3216
Diarrhea	61(27.1)	44(28.4)	17(24.3)	0.6274
Abdominal pain	6(2.7)	4(2.6)	2(2.9)	> 0.9999
Headache	19(8.4)	12(7.7)	7(10.0)	0.6082
Unconscious	6(2.7)	6(3.9)	0(0.0)	0.1085
Dizziness	8(3.6)	8(5.2)	0(0.0)	0.0601

Data are n (%). Percentages may not total 100 because of rounding. P values were calculated by Fisher's exact test.

Laboratory and radiologic findings on admission in patients with COVID-19

Hyperinflammation group presented with significantly higher white blood cell count (median [IQR], 7.3 [5.1–10.5] vs 5.9 [4.4–7.8], x10^9/L) and neutrophil counts (median [IQR], 5.7 [4-9.4] vs 3.9 [2.6–5.8], x10^9/L) and clearly lower lymphocyte counts (median [IQR], 0.7 [0.5–0.9 vs 1.2 [0.9–1.5], x10^9/L) and platelet (median [IQR], 180 [132.8-248.3 vs 253.5 [193.8-327.5], x10^9/L) than non-hyperinflammation group (Table 3). Hemoglobin in hyperinflammation group was slightly lower than in non-hyperinflammation group (median [IQR], 129.0 [117.0-139.0] vs 124.0 [113.0-134.0], g/L). Red blood cell

counts of the two groups were similar. Hyper-inflammation group also had significantly longer prothrombin time (median [IQR], 14.5 [13.8–15.7] vs 13.6 [13.2–14.4], seconds), longer activated partial thromboplastin time (median [IQR], 40.2 [36–44] vs 37.5 [34.8–41.5], seconds), and a significant higher level of D-dimer (median [IQR], 2.5 [1.1–21] vs 1.4 [0.6–2.3], μg/ml).

Table 3
Laboratory and radiologic findings on admission in patients with COVID-19

Findings (normal range)	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Blood routine test-median (IQR)				
White blood cell, $x10^9$/L (3.5–9.5)	6.7(4.9–9.9)	7.3(5.1–10.5)	5.9(4.4–7.8)	0.0009
Neutrophil, $x10^9$/L (1.8–6.3)	5.3(3.7–8.4)	5.7(4.0-9.4)	3.9(2.6–5.8)	< 0.0001
Lymphocyte, $x10^9$/L (1.1–3.2)	0.8(0.6–1.2)	0.7(0.5–0.9)	1.2(0.9–1.5)	< 0.0001
Red blood cell, $x10^{12}$/L (3.8–5.1)	4.1(3.7–4.5)	4.2(3.8–4.6)	4.0(3.6–4.3)	0.1218
Haemoglobin, g/L (130–175)	126.0(115.0-137.5)	129.0(117.0-139.0)	124.0(113.0-134.3)	0.0303
Platelet, $x10^9$/L (125–350)	209.5(148.0-280.5)	180.0(132.8-248.3)	253.5(193.8-327.5)	< 0.0001
Coagulation function-median (IQR)				
Prothrombin time, s (11.5–14.5)	14.3(13.5–15.3)	14.5(13.8–15.7)	13.6(13.2–14.4)	< 0.0001
Activated partial thromboplastin time, s (29.0–42.0)	38.9(35.8–43.2)	40.2(36–44)	37.5(34.8–41.5)	0.0116
D-dimer, μg/mL (< 0.5)	1.8(0.9–7.8)	2.5(1.1–21.0)	1.4(0.6–2.3)	< 0.0001
Biochemical test-median (IQR)				
Albumin, g/L (35.0–52.0)	32.1(29.5–35.2)	31.4(28.5–33.9)	35(31.6–37.9)	< 0.0001
Globulin, g/L (20.0–35.0)	35.3(32.2–39.0)	35.7(32.6–39.3)	34.4(31.1–37.7)	< 0.0001
Aspartate aminotransferase, U/L (≤ 40)	33.0(22.0-48.5)	37.0(26.5–56.5)	24.0(18.0–33.0)	< 0.0001
Alanine aminotransferase, U/L (≤ 41)	29.0(17.0–44.0)	31.0(19.0–49.0)	23.5(14.0-36.3)	0.0088
Total-bilirubin, μmol/L (≤ 26)	10.6(7.5–15.3)	11.7(8.3–17.1)	8.5(6.1–12.0)	< 0.0001
Direct-bilirubin, umol/L (≤ 8)	4.7(3.3–7.3)	5.5(3.9–8.8)	3.5(2.6–4.9)	< 0.0001
Creatinine, μmol/L (59–104)	76.0(61.0–93.0)	82.0(66.0-95.3)	62.5(54.0–80.0)	< 0.0001

Findings (normal range)	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Urea nitrogen, mmol/L (3.1-8.0)	5.6(4.1–8.4)	6.4(4.7–9.6)	4.6(3.2–5.6)	< 0.0001
Positive urinary protein-n/N (%)	96/190(50.5)	85/122(69.7)	11/68(16.2)	< 0.0001
Positive urinary occult blood-n/N (%)	67/190(35.3)	55/122(45.1)	12/68(17.6)	0.0001
Infection-related biomarkers-median (IQR)				
Procalcitonin, ng/mL (0.02–0.05)	0.09(0.04–0.28)	0.15(0.07–0.45)	0.03(0.02–0.05)	< 0.0001
Erythrocyte sedimentation rate, mm/h (0–15)	43.5(25.0-69.8)	47(27-72.3)	33.5(22-62.5)	0.0810
Ferritin, μg/L (30–400)	1093.0(548.0-1804.0)	1222.0(730.5–2014.0)	435.0(306.3-633.9)	< 0.0001
High sensitivity C-reactive protein, mg/L (< 1)	47.5(16.5-112.1)	75.5(38.3-140.2)	8.75(2.4–27.8)	< 0.0001
> 10 mg/L, No. (%)	182(80.9)	149(96.1)	33(47.1)	< 0.0001
Lactate dehydrogenase, U/L (135–225)	379.0(264.0-504.0)	442.0(305.0-601.0)	264.0(225.0-368.3)	< 0.0001
Cytokines-median (IQR) or No. (%)				
Interleukin 1β ≥ 5 pg/mL	21(9.3)	18(11.6)	3(4.3)	0.0887
Interleukin 2 receptor, U/mL (223–710)	778(470–1175)	996(632–1341)	487.5(364.5-696.8)	< 0.0001
≥ 710 U/L	124(55.1)	109(70.3)	15(21.4)	< 0.0001
Interleukin 6, pg/mL (< 7)	18.8(4.0-55.6)	37.2(16.5–93.2)	2.7(1.5–4.3)	< 0.0001
≥ 7 pg/mL	150(66.7)	145(93.5)	5(7.1)	< 0.0001
Interleukin 8, pg/mL (< 62)	12.6(6.1–26.6)	20.6(10.7–35.6)	5.2(5–10.0)	< 0.0001
≥ 62 pg/mL	20(8.9)	20(12.9)	0(0.0)	0.0006
Interleukin 10 ≥ 9.1 pg/mL	65(28.9)	63(40.6)	2(2.9)	< 0.0001

Findings (normal range)	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Tumour necrosis factor α, pg/mL (< 8.1)	8.3(5.7–11.5)	9.9(7.7–13.5)	5.3(4-6.7)	< 0.0001
≥ 8.1 pg/mL	118(52.4)	112(72.3)	6(8.6)	< 0.0001
Myocardial enzymes-median (IQR)				
Creatine kinase, U/L (≤ 190)	89.0(49.0-191.0)	107.0(54.8-222.5)	49.0(41.0-66.5)	0.0001
N-terminal pro-brain natriuretic peptide, pg/mL (< 285)	244.5(109.3-965.8)	402.0(155.5–1597.0)	179.0(75.0-467.0)	0.0001
Hypersensitive cardiac troponin I, pg/mL (≤ 15.6)	9.5(3.8–28.7)	12.1(5.6–53.2)	4.5(2.3–11.2)	< 0.0001
Myoglobin, ng/mL (≤ 106)	69.2(41.4-151.2)	87.0(51.6-175.1)	42.7(29.2–75.9)	0.0005
SARS-CoV-2 identified-median (IQR)				
IgM antibody, AU/ml (≤ 10)	44.9(17.1-124.2)	49.2(23.6-124.3)	37.8(15.2–124)	0.3894
IgG antibody, AU/ml (≤ 10)	182.3(159.2-216.6)	187.7(161.2-220.1)	177.7(157.3-210.2)	0.4156
RT-PCR assay (+)-n/N (%)	173/213(81.2)	119/143(83.2)	54/70(77.1)	0.3504
Pathogen antibody-n/N (%)	55/107(51.4)	42/81(51.9)	13/26(50.0)	> 0.9999*
Influenza A virus IgM (+)	46/107(43.0)	36/81(44.4)	10/26(38.5)	..
Influenza B virus IgM (+)	4/107(3.7)	3/81(3.7)	1/26(3.8)	..
Mycoplasma pneumoniae IgM (+)	10/107(9.3)	8/81(9.9)	2/26(7.7)	..
Chlamydia pneumoniae IgM (+)	4/107(3.7)	3/81(3.7)	1/26(3.8)	..
Adenovirus IgM (+)	1/107(0.9)	1/81(1.2)	0/26(0.0)	..
Bilateral involvement on CT-n/N (%)	175/217(80.6)	118/147(80.3)	57/70(81.4)	> 0.9999

COVID-19 = coronavirus disease 2019; IQR = interquartile range; CT = chest computed tomography; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RT-PCR = real-time polymerase chain reaction; IgM = Immunoglobulin M; IgG = Immunoglobulin G.

Findings (normal range)	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. Percentages may not total 100 because of rounding. P values were calculated by unpaired 2-sided Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. *χ^2 test comparing all subcategories.				
Data were missing for erythrocyte sedimentation rate in 29 patients (12.9%), for creatine kinase in 98 patients (43.6%), for N-terminal pro-brain natriuretic peptide in 21 patients (9.3%), for hypersensitive cardiac troponin I in 14 patients (6.2%), for coagulation function in 8 patients (3.6%), for ferritin in 74 patients (32.9%).				
Data were available for myoglobin in 100 patients, for anti- SARS-CoV-2 antibody in 113 patients.				
+The antibody was positive.				

Compared with non-hyperinflammation group, hyperinflammation group were more likely to have multiple organ function damage including the liver, kidney and heart. Hyperinflammation group had significantly higher levels of aspartate aminotransferase (median [IQR], 37.0 [26.6–56.6] vs 24.0 [18.0–33.0], U/L), alanine aminotransferase (median [IQR], 31.0 [19.0–49.0] vs 23.5 [14.0-36.3], U/L), total-bilirubin (median [IQR], 11.7 [8.3–17.1] vs 8.5 [6.1–12.0], μmol/L), and direct-bilirubin (median [IQR], 5.5[3.9–8.8] vs 3.5 [2.6–4.9], μmol/L), and lower levels of albumin concentrations(median [IQR], 31.4[28.5–33.9] vs 35.0 [31.6–37.9], g/L, $P < 0.0001$). Hyperinflammation group also had evidence of higher levels of creatinine (median [IQR], 82.0 [66.0-95.3] vs 62.5 [54.0–80.0], μmol/L), urea nitrogen (median [IQR], 6.4 [4.7–9.6] vs 4.6 [3.2–5.6], mmol/L), higher proportions of positive urinary protein (85/122 [69.7%] vs 11/68 [16.2%]) and positive urinary occult blood (55/122 [45.1%] vs 12/68 [17.6%]). The levels of biomarkers indicating cardiac injury in patients with hyperinflammation were significantly higher, as hypersensitive cardiac troponin I (median [IQR], 12.1 [5.6–53.2] vs 4.5 [2.3–11.2], pg/mL) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (median [IQR], 402.0 (155.5–1597.0] vs 179.0 [75.0-467.0], pg/mL). Of patients with available data, concentrations of creatine kinase (median [IQR], 107.0 [54.8-222.5] vs 49.0 [41.0-66.5], g/L) and myoglobin (median [IQR], 87.0 [51.6-175.1] vs 42.7 [29.2–75.9], ng/L) were significantly higher in patients with hyperinflammation than cases with non-hyperinflammation.

The infection-related biomarkers, including procalcitonin (median [IQR], 0.15 [0.07–0.45] vs 0.03 [0.02–0.05], ng/mL), ferritin (median [IQR], 1222.0 [730.5–2014.0] vs 435.0 [306.3-633.9], μg/L), lactate dehydrogenase (median [IQR], 442.0[305.0-601.0] vs 264.0 [225.0-368.3], U/L), and globulin (median [IQR], 35.7 [32.6–39.3] vs 34.4 [31.1–37.7], g/L), high-sensitivity C-reactive protein (median [IQR], 75.5[38.3-140.2] vs 8.75 [2.4–27.8], mg/L) were significantly higher in hyperinflammation group. 149 (96.1%) patients with hyperinflammation and 33 (47.1%) who with non-hyperinflammation had increased concentration of hsCRP (> 10 mg/L). But erythrocyte sedimentation rate did not differ between the 2 groups.

Assessment of serum cytokines on admission revealed that levels of IL-2 receptor (IL-2R), IL-6, IL-8, IL-10, and TNF-α were significantly higher in hyperinflammation group. The concentration of IL-1β was undetectable (< 5 pg/mL) in nearly all COVID-19 patients with either hyperinflammation or non-hyperinflammation. The abnormal IL-2R (≥ 710U/L, 109 (70.3%) vs 15 (21.4%)), IL-6 (≥ 7 pg/mL, 145 (94.3%) vs 5 (7.1%)), IL-8 (≥ 62 pg/mL, 20 (12.9%) vs 0 (0%)), IL-10 (≥ 9.1 pg/mL, 63 (40.6%) vs 2 (2.9%)), and TNF-α (≥ 8.1 pg/mL, 112 (72.3%) vs 6 (8.6%)) were more common in hyperinflammation group than in non- hyperinflammation group. Besides SARS-CoV-2, nine respiratory pathogens were also detected within some patients. About half of the patients infected other pathogens, Influenza A virus was the most common (46/107, 43%). There was no difference in the risk of co-infection with other pathogens between hyperinflammation group and non-hyperinflammation group. Of the 217 patients with chest CT scan on admission, the majority (175, 80.6%) had bilateral involvement, showing typical images that were bilateral multiple ground glass opacities or consolidation (Table 3).

Treatment and outcomes in patients with COVID-19

Hypoxemia was more difficult to correct in hyperinflammation group than non-hyperinflammation group (high-flow nasal cannula oxygen therapy (35 (22.6%) vs 4 (5.7%), non-invasive mechanical ventilation (66 (42.6%) vs 4 (5.7%), invasive mechanical ventilation (65 (30.2%) vs 3 (4.3%) (Table 4). Four patients in hyperinflammation group were treated with extracorporeal membrane oxygenation (ECMO). 85 (37.8%) patients admission to intensive care unit (ICU), of whom 81 (95.3%) were with hyperinflammation, with a median time from illness onset to ICU admission was 16.0 (IQR 11.0–22.0) days for hyperinflammation group and 23.0 (IQR 17.0–26.0) days for non-hyperinflammation group.

Table 4
Treatment and outcomes in patients with COVID-19

	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Respiratory support-No. (%)				
High-flow nasal cannula oxygen therapy	39(17.3)	35(22.6)	4(5.7)	0.0020
Non-invasive mechanical ventilation	70(31.1)	66(42.6)	4(5.7)	< 0.0001
Invasive mechanical ventilation	68(30.2)	65(41.9)	3(4.3)	< 0.0001
ECMO	4(1.8)	4(2.6)	0(0.0)	0.3129
Outcomes-median (IQR)				
ICU admission- No. (%)	85(37.8)	81(52.3)	4(5.7)	< 0.0001
ICU length of stay, days ‡	9.0(5.0–20.0)	10.0(5.0–21.0)	7.0(2.0–17.0)	0.2903
Onset of symptom to admission, days	12.0(8.0–16.0)	11.0(7.0–15.0)	13.0(10.0–17.0)	0.0160
Hospital length of stay, days ‡	27.0(18.0–37.0)	25.0(15.0–37.0)	29.0(24.0–37.0)	0.0181
Time from illness onset to ICU admission, days	16.0(12.0–23.0)	16.0(11.0–22.0)	23.0(17.0–26.0)	0.1379
Time from illness onset to end-point events, days ¶	39.0(28.0–48.0)	36.0(25.0–48.0)	42.0(35.0–49.0)	0.0066
Viral shedding	173/213(81.2)	119/143(83.2)	54/70(77.1)	0.3504
Duration of viral shedding from illness onset, days ‡	26.0(21.0–36.0)	25.0(19.0–34.0)	30.0(23.0–38.0)	0.0048

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. Percentages may not total 100 because of rounding. P values were calculated by unpaired 2-sided Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. *χ^2 test comparing all subcategories.

ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.

¶The end-point events were discharge or death.

‡Detectable until death.

	Total(n = 225)	Hyperinflammation		
		Yes(n = 155)	No(n = 70)	P value
Severity-No. (%)				
Severe	119(52.9)	99(63.9)	20(28.6)	< 0.0001
Non-severe	106(47.1)	56(36.1)	50(71.4)	..
Status at data cutoff -No. (%)				
Hospitalization	13(5.8)	12(7.7)	1(1.4)	< 0.0001*
Discharge	139(61.8)	74(47.7)	65(92.9)	..
Death	73(32.4)	69(44.5)	4(5.7)	..
Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. Percentages may not total 100 because of rounding. P values were calculated by unpaired 2-sided Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. *χ^2 test comparing all subcategories.				
ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.				
¶The end-point events were discharge or death.				
‡Detectable until death.				

The median time from onset of symptoms to hospital admission was 11.0 (IQR 7.0–15.0) days, which tended to be shorter in hyperinflammation group compared with non-hyperinflammation (median [IQR], 13.0 [10.0–17.0], days). And the median time from illness onset to end-point event was shorter in hyperinflammation group (median [IQR], 36.0 [25.0–48.0] vs 42.0 [35.0–49.0], days). Median length of hospital stay was also shorter in hyperinflammation group than non-hyperinflammation group (median [IQR], 25.0 [15.0–37.0] vs 29.0 [24.0–37.0], days). For patients with hyperinflammation, the median duration of viral shedding was 25 days (IQR, 19.0–34.0) from illness onset,while it was longer in non-hyperinflammatory patients (median [IQR], 30.0 [23.0–38.0]). The virus was continuously detectable until death in non-survivors of the two groups. Of all 225 patients, 119 (52.9%) were severe pneumonia based on the 2019 *American Thoracic Society / Infectious Disease Society of America* guidelines[34], and 69.3% (99/155) patients with hyperinflammation. Whereas 92.9% (65/70) patients with non-hyperinflammation were classified as non-severe pneumonia.

None of the 225 patients were lost to follow-up during the study. Up to 5 April 2020, a primary composite end-point event occurred in 212 patients (94.2%), including 32.4% who died, 61.8% who discharged from hospital. Among the 155 patients with hyperinflammation, a primary composite end-point event occurred in 133 patients (92.3%) and 44.5% (69/155) died. The majority of patients with non-hyperinflammation are discharged (65/70, 92.9%).

Mortality of severe/non-severe patients with/without hyperinflammation

Further subanalysis suggested that most (60/73, 82.2%) of the non-survivors were severe patients with hyperinflammation. Four of 99 cases with hyperinflammation and severe COVID-19 died within 10 days after the onset of the illness, and about 73.3% (44/60) of non-survivors in hyperinflammation and severe COVID-19 group died within 30 days (Table 5). Among 225 patients, 4.0% (2 of 50) in non-severe patients without hyperinflammation, 10.0% (2 of 20) in severe patients without hyperinflammation, 16.1% (9 of 56) in non-severe patients with hyperinflammation, and 60.6% (60 of 99) severe patients with hyperinflammation with died during hospitalization (Fig. 1). Of note, the mortality of severe patients with hyperinflammation (60/99, 60.6%) was significantly higher than without hyperinflammation (2/20, 10.0%). Non-severe patients with hyperinflammation even tended to have higher mortality (9/56, 16.1%) than those in severe cases without hyperinflammation (2/20, 10%).

Table 5
Number of deaths involved and mortality of patients with severe/non-severe COVID-19 and with/without hyperinflammation

Time since onset of symptoms to end-point events, days ¶	**10**	**20**	**30**	**40**	**50**	**60**	**70**
No. of death involved							
Severe patients with hyperinflammation (n = 99)	4	22	44	55	59	60	60
Non-severe patients with hyperinflammation (n = 56)	0	2	5	7	8	8	9
Severe patients without hyperinflammation (n = 20)	0	0	2	2	2	2	2
Non-severe patients without hyperinflammation (n = 50)	0	0	2	2	2	2	2
Mortality, %							
Severe patients with hyperinflammation (n = 99)	4.0	22.2	44.4	55.6	59.6	60.6	60.6
Non-severe patients with hyperinflammation (n = 56)	0.0	3.6	8.9	12.5	14.3	14.3	16.1
Severe patients without hyperinflammation (n = 20)	0.0	0.0	10.0	10.0	10.0	10.0	10.0
Non-severe patients without hyperinflammation (n = 50)	0.0	0.0	4.0	4.0	4.0	4.0	4.0
¶The end-point events were discharge or death							

Discussion

This report provides detailed information on the association between systemic inflammation and clinical outcomes of patients with COVID-19. Among 225 patients with COVID-19, 155 (68.9%) exhibited hyperinflammation, with higher odds of ICU admission and in-hospital death. Further, subgroup analysis revealed that severe patients with hyperinflammation had the highest mortality (60.6%). Additionally, Non-severe patients with hyperinflammation even tended to have higher mortality than those in severe cases without hyperinflammation.

Up to April 5, 2020, coronavirus disease 2019 has been confirmed in 1133758 people worldwide, carrying a mortality of approximately 5.5%, which has ultimately proven more deadly as it has spread to many more people globally[5]. Both clinical and epidemiological features of patients with COVID-19 have recently been reported[2, 6, 33, 39]. However, there is insufficient knowledge of pathophysiological parameters to understand the mechanism involved in COVID-19. According to previous studies, the immune response to pulmonary viral infections facilitates viral clearance but at the same time can produce excessive inflammation resulting in tissue damage[40]. Studies from humans who died of SARS and researches in animal models revealed an exuberant inflammation leading to lethal disease[41]. In the current study, dyspnea, chest tightness, and symptoms related to hypoxemia were more frequent in the hyperinflammation group. Correspondingly, patients with hyperinflammation more often required mechanical ventilation, indicating more prone to experience lung injury related to excessive inflammation[41, 42]. Additionally, we noted that substantial differences in abnormalities of laboratory findings between two groups, such as lymphopenia ($< 0.8 \times 10^9$/L) in patients with hyperinflammation, which might attribute to lymphocyte apoptosis caused by disordered cytokines[43]. Regarding primary outcomes, patients with hyperinflammation were more likely to become severe cases (63.9% vs 28.6%). The mortality was also greater than patients without hyperinflammation (44.5% vs 5.7%), indicating the association between excessive inflammation and outcomes of COVID-19. Notably, the length of hospital stay was shorter in the hyperinflammation group, which could be plausible because of higher mortality during the early course of diseases.

Although the exact pathophysiological mechanism underlying COVID-19 is not fully understood, a previous study showed that subjects with SARS had high levels of pro-inflammatory cytokines and chemokines that were associated with T cell depletion, the accumulation of immune cells, pulmonary inflammation, and extensive lung damage[44, 45], suggesting that the widespread lung damage associated with SARS may be caused more by an excessive inflammation than the virus itself. Consistent with these reports, a cytokine profile associated with COVID-19 disease severity was found, characterized by increased IL-2, IL-7, granulocyte colony stimulating factor (G-CSF), interferon-γ inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1A), and TNF-α[33]. In a retrospective, multicenter study of 150 confirmed COVID-19 cases, elevated hsCRP and IL-6 were shown to be predictors of fatality, which indicated that mortality might be due to virally driven hyperinflammation[18]. Here, we demonstrated that patients with hyperinflammation were associated with poor clinical outcomes, which has echoed the recently published studies in terms of the systemic inflammation in patients with COVID-19[17, 46]. Besides, the markedly dynamic escalation of mortality

during the course of disease in severe patients with hyperinflammation further confirmed that excessive inflammation contributes to the pathogenesis of COVID-19.

Unfortunately, until now, no vaccine or specific antiviral treatment for COVID-19 has proven to be effective. Given the role excessive systemic inflammatory responses may play in the mechanism of COVID-19, anti-inflammation drugs are likely to be beneficial, e.g. corticosteroids, which are widely used during the outbreaks of SARS-CoV and MERS-CoV, and are being used in patients with COVID-19[2, 47, 48]. However, there still remains controversy concerning the use of corticosteroids. Clark Russell and colleagues proposed that corticosteroids should not be used in COVID-2019-induced lung injury or shock with the available clinical evidence on corticosteroid[22]. Conversely, Lianhan Shang and colleagues pointed that existing evidence was inconclusive. After all, in severe patients, the overwhelming inflammation and cytokine-related lung injury might cause rapidly progressive pneumonia[23]. Overall, corticosteroid treatment is a double-edged sword with both anti-inflammation and immunosuppression, which does more good than harm in patients with hyperinflammation. It is reasonable to reach conflicting results in previous studies, partly because of the underrecognition of systemic inflammation heterogeneity in COVID-19 patients, particularly in severe cases[47–49]. Therefore, “personalized therapy” needs to be considered when it comes to corticosteroid. All patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends to identify the subgroup of patients for whom corticosteroid treatment could improve mortality[24].

Our study has some notable limitations. First, due to the retrospective study design, not all laboratory tests were done in all patients. Second, because the clinical observation of patients is still ongoing, some have not reached clinical end points. Third, only 225 patients with confirmed COVID-19 were included, and larger populations and multiple centers are warranted to further confirm our conclusions.

Conclusions

In conclusion, excessive inflammation has a significant correlation with poor outcomes of COVID-19. Varying degrees of systemic inflammation signify great differences in prognosis, which needs to be taken into account for treating patients with confirmed COVID-19.

Abbreviations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; MERS-CoV: Middle Eastern respiratory syndrome coronavirus; WHO: World Health Organization; ICU: Intensive care unit; hCoVs: Human coronavirus; IL: Interleukin; hsCRP: High-sensitivity C-reactive protein; TNF-α: Tumour necrosis factor α; RT-PCR: Reverse-transcriptase–polymerase-chain-reaction; CLIA: Chemiluminescence Immunoassay; IQR: Interquartile range; NT-proBNP: N-terminal pro-brain natriuretic peptide; IL-2R: IL-2 receptor; G-CSF: Granulocyte colony stimulating factor; IP-10: Interferon-γ inducible protein 10; MCP-1: Monocyte chemoattractant protein 1; MIP-1A: Macrophage inflammatory protein 1-α;

Declarations

Acknowledgments

We thank all the patients and their families involved in this study, as well as numerous doctors, nurses and civilians working together to fight against the SARS-CoV-2.

Author contributions

MW, ZH, KT and PG designed the study. MW, JZ and JX had full access to all data in the study and take responsibility for the integrity of data and the accuracy of the data analysis. MW contributed to patient recruitment, data collection, data analysis, data interpretation, literature search, and writing of the manuscript. JZ, JX and TW had roles in patient recruitment, data collection, and clinical management. MW, ZH, KT, PG, YL, and SW had roles in data analysis, and data interpretation, literature search and writing of the manuscript. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version of the manuscript.

Funding

This work was funded by Huazhong University of Science and Technology COVID-19 Rapid Response Call (2020kfyXGYJ015) and The National Major Science and Technology Project for the Control and Prevention of Major Infectious Diseases of China (2017ZX10103004). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and materials

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

Ethics approval and consent to participate

The study was performed in accordance with Tongji Hospital Ethics Committee (TJ-IRB20200353).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, et al: A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020, 382:727-733.

2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al: Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020.
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020, 579:270-273.
4. Zhang J, Litvinova M, Wang W, Wang Y, Deng X, Chen X, Li M, Zheng W, Yi L, Chen X, et al: Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. *The Lancet Infectious Diseases* 2020.
5. Coronavirus disease 2019 (COVID-19) situation report – 76. April 5, 2020 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200405-sitrep-76-covid-19.pdf?sfvrsn=6ecf0977_4. Accessed 6 Apr 2020.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 2020, 395:1054-1062.
7. Grasselli G, Pesenti A, Cecconi M: Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA* 2020.
8. Lu H: Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends* 2020, 14:69-71.
9. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, et al: Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine* 2020, 8:420-422.
10. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, Cai J, Li X, Kang W, Weng D, et al: The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol* 2003, 200:282-289.
11. Ng DL, Al Hosani F, Keating MK, Gerber SI, Jones TL, Metcalfe MG, Tong S, Tao Y, Alami NN, Haynes LM, et al: Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. *Am J Pathol* 2016, 186:652-658.
12. Cheung CY, Poon LL, Ng IH, Luk W, Sia SF, Wu MH, Chan KH, Yuen KY, Gordon S, Guan Y, Peiris JS: Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. *J Virol* 2005, 79:7819-7826.
13. Chien JY, Hsueh PR, Cheng WC, Yu CJ, Yang PC: Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. *Respirology* 2006, 11:715-722.
14. Lau SKP, Lau CCY, Chan KH, Li CPY, Chen H, Jin DY, Chan JFW, Woo PCY, Yuen KY: Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. *J Gen Virol* 2013, 94:2679-2690.
15. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, et al: Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest* 2020.

16. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al: Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
17. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS: Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020.
18. Ruan Q, Yang K, Wang W, Jiang L, Song J: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020.
19. Zhou J, Chu H, Li C, Wong BH, Cheng ZS, Poon VK, Sun T, Lau CC, Wong KK, Chan JY, et al: Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. *J Infect Dis* 2014, 209:1331-1342.
20. Guo XJ, Thomas PG: New fronts emerge in the influenza cytokine storm. *Semin Immunopathol* 2017, 39:541-550.
21. Nagata N, Iwata N, Hasegawa H, Fukushi S, Harashima A, Sato Y, Saijo M, Taguchi F, Morikawa S, Sata T: Mouse-passaged severe acute respiratory syndrome-associated coronavirus leads to lethal pulmonary edema and diffuse alveolar damage in adult but not young mice. *Am J Pathol* 2008, 172:1625-1637.
22. Russell CD, Millar JE, Baillie JK: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet* 2020, 395:473-475.
23. Shang L, Zhao J, Hu Y, Du R, Cao B: On the use of corticosteroids for 2019-nCoV pneumonia. *The Lancet* 2020, 395:683-684.
24. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ: COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020, 395:1033-1034.
25. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, et al: Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020.
26. Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med* 2005, 353:1711-1723.
27. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, Bowman ED, Engels EA, Caporaso NE, Harris CC: Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst* 2011, 103:1112-1122.
28. Beer TM, Lalani AS, Lee S, Mori M, Eilers KM, Curd JG, Henner WD, Ryan CW, Venner P, Ruether JD, et al: C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer: results from the ASCENT trial. *Cancer* 2008, 112:2377-2383.
29. Chen C, Shi L, Li Y, Wang X, Yang S: Disease-specific dynamic biomarkers selected by integrating inflammatory mediators with clinical informatics in ARDS patients with severe pneumonia. *Cell Biol Toxicol* 2016, 32:169-184.

30. Ko JH, Park GE, Lee JY, Lee JY, Cho SY, Ha YE, Kang CI, Kang JM, Kim YJ, Huh HJ, et al: Predictive factors for pneumonia development and progression to respiratory failure in MERS-CoV infected patients. *J Infect* 2016, 73:468-475.
31. Namas RA, Vodovotz Y, Almahmoud K, Abdul-Malak O, Zaaqoq A, Namas R, Mi Q, Barclay D, Zuckerbraun B, Peitzman AB, et al: Temporal Patterns of Circulating Inflammation Biomarker Networks Differentiate Susceptibility to Nosocomial Infection Following Blunt Trauma in Humans. *Ann Surg* 2016, 263:191-198.
32. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed 28 Jan 2020.
33. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020, 395:497-506.
34. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, et al: Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019, 200:e45-e67.
35. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, et al: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003, 107:499-511.
36. Chalmers S, Khawaja A, Wieruszewski PM, Gajic O, Odeyemi Y: Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: The role of inflammatory biomarkers. *World J Crit Care Med* 2019, 8:59-71.
37. Ridker PM, Cook N: Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation* 2004, 109:1955-1959.
38. Zotova NV, Zhuravleva YV, Zubova TE, Gusev EY: Integral estimation of systemic inflammatory response under sepsis. *Gen Physiol Biophys* 2020, 39:13-26.
39. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, et al: Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020, 368:m1091.
40. Yoo JK, Kim TS, Hufford MM, Braciale TJ: Viral infection of the lung: host response and sequelae. *J Allergy Clin Immunol* 2013, 132:1263-1276; quiz 1277.
41. Channappanavar R, Perlman S: Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017, 39:529-539.
42. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G: COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020.
43. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H: Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020, 5:33.

44. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, Wang H, Li Z, Zhao L, Geng J, et al: Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J Pathol* 2006, 210:288-297.
45. Okabayashi T, Kariwa H, Yokota S, Iki S, Indoh T, Yokosawa N, Takashima I, Tsutsumi H, Fujii N: Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. *J Med Virol* 2006, 78:417-424.
46. Wang Z, Yang B, Li Q, Wen L, Zhang R: Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis* 2020.
47. Stockman LJ, Bellamy R, Garner P: SARS: systematic review of treatment effects. *PLoS Med* 2006, 3:e343.
48. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, Jose J, Pinto R, Al-Omari A, Kharaba A, et al: Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* 2018, 197:757-767.
49. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, Ruddy RM, Malik B, Nelson KA, Bregstein JS, et al: A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007, 357:331-339.

Figures

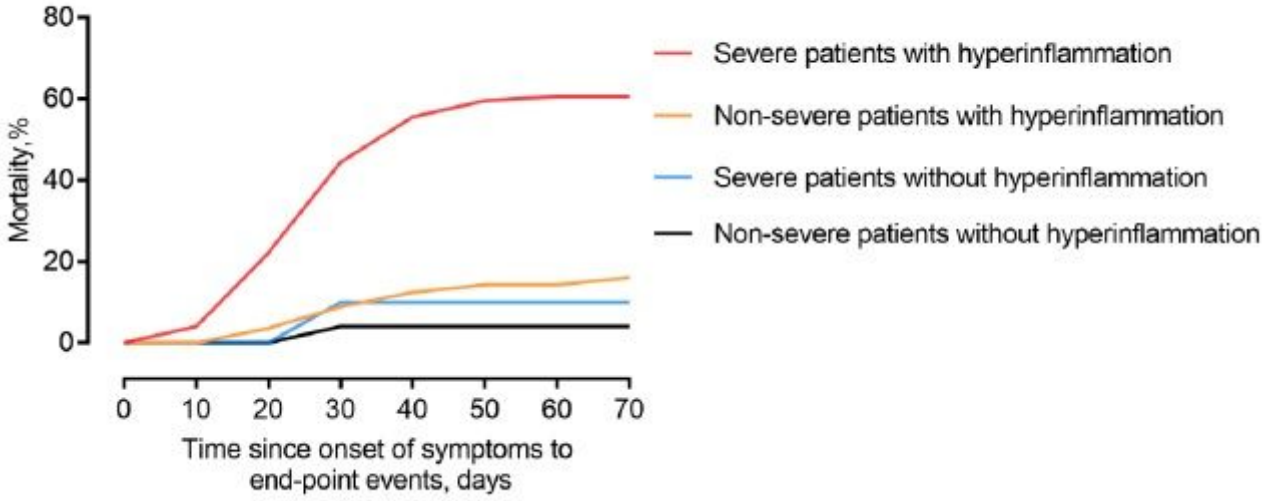

Figure 1

Mortality of severe/non-severe patients with/ without hyperinflammation