Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study

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ABSTRACT The aim of this study was to identify factors associated with the death of patients with COVID-19 pneumonia caused by the novel coronavirus SARS-CoV-2.

All clinical and laboratory parameters were collected prospectively from a cohort of patients with COVID-19 pneumonia who were hospitalised to Wuhan Pulmonary Hospital (Wuhan City, Hubei Province, China) between 25 December 2019 and 7 February 2020. Univariate and multivariate logistic regression was performed to investigate the relationship between each variable and the risk of death of COVID-19 pneumonia patients.

In total, 179 patients with COVID-19 pneumonia (97 male and 82 female) were included in the present prospective study, of whom 21 died. Univariate and multivariate logistic regression analysis revealed that age ⩾65 years (OR 3.765, 95% CI 1.146–17.394; p=0.023), pre-existing concurrent cardiovascular or cerebrovascular diseases (OR 2.464, 95% CI 0.755–8.044; p=0.007), CD3+CD8+ T-cells ⩽75 cells·µL^{-1} (OR 3.982, 95% CI 1.132–14.006; p<0.001) and cardiac troponin I ⩾0.05 ng·mL^{-1} (OR 4.077, 95% CI 1.166–14.253; p<0.001) were associated with an increase in risk of mortality from COVID-19 pneumonia. In a sex-, age- and comorbid illness-matched case–control study, CD3+CD8+ T-cells ⩽75 cells·µL^{-1} and cardiac troponin I ⩾0.05 ng·mL^{-1} remained as predictors for high mortality from COVID-19 pneumonia.

We identified four risk factors: age ⩾65 years, pre-existing concurrent cardiovascular or cerebrovascular diseases, CD3+CD8+ T-cells ⩽75 cells·µL^{-1} and cardiac troponin I ⩾0.05 ng·mL^{-1}. The latter two factors, especially, were predictors for mortality of COVID-19 pneumonia patients.

Introduction

In December 2019, a new contagious disease, named COVID-19 pneumonia and caused by a novel coronavirus (SARS-CoV-2), emerged in Wuhan City, Hubei Province, China, and is now spreading across international borders [1–3]. By 12 February 2020, 189 medical teams consisting of 21 569 doctors and nurses from 29 provinces of China had been sent to Hubei Province to deal with COVID-19 pneumonia [4]. The ongoing COVID-19 pneumonia pandemic is currently not under control, with a high risk of spread in China and globally. As of 22 March 2020, a total of 307 297 confirmed cases had been reported in at least 169 countries [5]. Unfortunately, the effect of the outbreak of COVID-19 pneumonia and the ultimate scope are unclear, as the situation is rapidly evolving [6, 7]. As a matter of fact, the fear of the ongoing COVID-19 epidemic was and is playing a major role in the economic and social consequences.

In the first published cohort of 41 patients with COVID-19 pneumonia from Wuhan Jinyintan Hospital, six (14.6%) patients worsened in a short period of time and died of multiple organ failure [8]; when the cohort size expanded to 99 cases, 11 (11.1%) patients died [9]. In another Wuhan cohort of hospitalised patients with COVID-19 pneumonia, the overall mortality was 4.3% (six out of 138) [10]. The findings from these three previous studies suggested that older age and underlying comorbidities were associated with disease severity or death of COVID-19 pneumonia patients [8–10]. Between 25 December 2019 and 7 February 2020, a total of 179 adult patients with COVID-19 pneumonia were hospitalised to Wuhan Pulmonary Hospital, a special hospital for isolating and treating patients with infectious diseases. As of 24 March 2020, 158 patients had been discharged and the remaining 21 had died. In the present study, we sought to identify the clinical and laboratory parameters associated with mortality of patients with COVID-19 pneumonia.

Methods

Patients

This study was conducted in accordance with the approved guidelines of the Institutional Review Board of Wuhan Pulmonary Hospital (wufeilunli-2020-02). The need for written informed consent from each patient was waived since we prospectively collected and analysed all data from each patient according to the policy for public health outbreak investigation of emerging infectious diseases issued by the National Health Commission of the People's Republic of China.

Between 25 December 2019 and 7 February 2020, a single-centre case cohort of 179 consecutive patients with confirmed and probable COVID-19 pneumonia was hospitalised to Wuhan Pulmonary Hospital; these patients were all included in the present study. The probable and definite diagnosis of COVID-19 pneumonia was established according to the case definition established by World Health Organization interim guidance [11].

Data collection and analysis

The information for all patients, including demographic data, clinical characteristics, laboratory parameters and outcomes, were collected prospectively. Two researchers independently reviewed the data collection forms to double-check the collected data.

Descriptive statistics included frequency analysis (percentages) for categorical variables and mean±SD or median and interquartile range for continuous variables. Comparisons were determined by t-test or Mann–Whitney U-test for continuous variables, as appropriate, and by the use of the Chi-squared test or Fisher exact test for categorical variables. Univariate and multivariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters and the risk of death. The backward conditional method was used to select imaging variables entering the scoring system. The statistical significance level was set at 0.05 (two-tailed). All analyses were conducted with MedCalc (MedCalc Software Ltd, Ostend, Belgium) and SPSS version 23.0 (IBM, Armonk, NY, USA) statistical software.

Results

Clinical data

This report describes a COVID-19 pneumonia cohort of 179 patients who were hospitalised to Wuhan Pulmonary Hospital between 25 December 2019 and 7 February 2020, of whom 136 (76%) were diagnosed definitely as having COVID-19 pneumonia with a positive SARS-CoV-2 test result; the remaining 43 (24%) were diagnosed clinically. The mean±SD time between onset of symptoms and hospitalisation was 9.7±4.3 days. The mean±SD age was 57.6±13.7 years (range 18–87 years), and 97 (54.2%) were men (table 1). Of 179 patients, 21 (11.7%) worsened in a short period of time and died of multiple organ failure, especially respiratory failure and heart failure, and the mean±SD duration from admission to death was 13.7±8.3 days (range 3–33 days) (supplementary table S1).

TABLE 1 Demographics and clinical presentation in patients with COVID-19 pneumonia

Characteristics	Total	Deceased	Survivors	p-value
Patients	179	21	158	
Age years	57.6±13.7	70.2±7.7	56.0±13.5	<0.001
Sex				0.642
Male	97 (54.2)	10 (47.6)	87 (55.1)	
Female	82 (45.8)	11 (52.4)	71 (44.9)	
Underlying diseases				
Hypertension	58 (32.4)	13 (61.9)	45 (28.5)	0.005
Cardiovascular or cerebrovascular diseases	29 (16.2)	12 (57.1)	17 (10.8)	<0.001
Diabetes	33 (18.4)	6 (28.6)	27 (17.1)	0.231
Chronic digestive disorders	21 (11.7)	4 (19.0)	17 (10.8)	0.279
Tuberculosis	8 (4.5)	0 (0)	8 (5.1)	0.599
Chronic hepatic or renal insufficiency	4 (2.2)	2 (9.5)	2 (1.3)	0.068
Peripheral vascular disease	4 (2.2)	2 (9.5)	2 (1.3)	0.068
Malignancy	4 (2.2)	1 (4.8)	3 (1.9)	0.396
Symptoms				
Fever	177 (98.9)	21 (100)	156 (98.7)	1.000
Dry cough	146 (81.6)	14 (66.7)	132 (83.5)	0.074
Dyspnoea	89 (49.7)	18 (85.7)	71 (44.9)	<0.001
Fatigue	71 (39.7)	13 (61.9)	58 (36.7)	0.033
Sputum production	55 (30.7)	12 (57.1)	43 (27.2)	0.010
Gastrointestinal symptoms	39 (21.8)	8 (38.1)	31 (19.6)	0.087
Myalgia	34 (19.0)	7 (33.3)	27 (17.1)	0.083
Headache	17 (9.5)	5 (23.8)	12 (7.6)	0.033
Haemoptysis	10 (5.6)	0 (0)	10 (6.3)	0.609
Systolic blood pressure mmHg		NA	122.4±18.6	
Diastolic blood pressure mmHg		NA	77.9±10.0	
Temperature °C				0.156
<37.3	109 (60.9)	16 (76.2)	93 (58.9)	
⩾37.3	70 (39.1)	5 (23.8)	65 (41.1)	
Respiratory rate breaths·min^{-1}	20.0 (20.0–21.0)	20.0 (20.0–34.5)	20.0 (20.0–21.0)	0.016
Heart rate beats·min^{-1}	86.0 (78.0–100)	94.0 (78.0–109.5)	85.5 (78.0–99.3)	0.150

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. NA: not available.

As shown in table 1, the patients in the deceased group were much older than those in the survivor group (70.2±7.7 years *versus* 56.0±13.5 years; p<0.001). We noted that more patients in the deceased group had hypertension (61.9% *versus* 28.5%; p=0.005) and cardiovascular or cerebrovascular diseases (57.1% *versus* 10.8%; p<0.001), and that there was no difference in the incidence of diabetes, chronic digestive disorders, tuberculosis, chronic hepatic or renal insufficiency, peripheral vascular disease or malignancy between the two groups (all p>0.05).

Very similarly to the findings reported in the previous studies [8–10, 12], we noted that the top five common symptoms included fever (98.9% of the patients), dry cough (81.6%), dyspnoea (49.7%), fatigue (39.7%) and sputum production (30.7%) on admission among the total population (table 1). Except for dyspnoea, fatigue, sputum production and headache, which were more frequently present in the deceased group than in the survivor group (85.7% *versus* 44.9% (p<0.001), 61.9% *versus* 36.7% (p=0.033), 57.1% *versus* 27.2% (p=0.010) and 23.8% *versus* 7.6% (p=0.033), respectively), other kinds of symptoms were similar in the two groups. Patients in the deceased group had a higher respiratory rate than those in the survivor group (p=0.016); there was no difference in heart rate.

Laboratory findings

Potentially due to the presence of secondary bacterial infection, as suggested by higher concentrations of C-reactive protein and procalcitonin, the deceased had more white blood cells and neutrophils than did the survivors (table 2). In fact, lung secondary bacterial infections were documented at a late stage of disease in 10 of the 21 deceased patients, and the aetiological spectrum included *Klebsiella pneumoniae*, *Staphylococcus*, *Acinetobacter baumannii* and *Escherichia coli*. As expected, the deceased had reduced lymphocytes compared to the survivors. One remarkable finding was that absolute numbers of CD3+CD8+ T-cells, but not CD3+CD4+ T-cells, were significantly reduced in the deceased compared to the survivors.

TABLE 2 Laboratory findings in patients with COVID-19 pneumonia

Characteristics	Total	Deceased	Survivors	p-value
Patients	179	21	158	
White blood cells ×10^9 cells·L^{-1}	5.3 (3.9–7.8)	8.9 (4.8–13.1)	5.1 (3.8–7.3)	0.003
Neutrophils ×10^9 cells·L^{-1}	4.0 (2.7–6.6)	7.7 (3.0–11.5)	3.9 (2.6–6.1)	0.007
Lymphocytes ×10^9 cells·L^{-1}	0.8 (0.6–1.1)	0.7 (0.5–0.8)	0.8 (0.6–1.1)	0.046
T-cell subsets				
CD3$^+$CD4$^+$ cells·µL^{-1}	114.3 (62.9–195.3)	68.0 (55.1–148.8)	128.3 (73.5–201.7)	0.066
CD3$^+$CD8$^+$ cells·µL^{-1}	75.5 (45.5–125.0)	47.9 (25.4–73.8)	104.5 (58.5–142.7)	0.001
C-reactive protein mg·L^{-1}	39.8 (20.6–97.8)	86.4 (37.9–105.5)	36.0 (19.3–91.0)	0.012
Procalcitonin ng·mL^{-1}	0.1 (0.0–0.2)	0.1 (0.1–0.5)	0.1 (0.0–0.2)	0.013
Cardiac troponin I ng·mL^{-1}	0.0 (0.0–0.1)	0.1 (0.0–0.8)	0.0 (0.0–0.0)	<0.001
Myoglobin ng·mL^{-1}	36.9 (18.4–124.0)	162.0 (48.5–342.8)	32.3 (15.5–60.3)	<0.001
Brain natriuretic peptide pg·mL^{-1}	645.0 (110.0–1504.0)	970.0 (620.5–3531.0)	390.0 (58.0–1118.5)	0.004
Albumin g·L^{-1}	33.2 (30.7–36.4)	33.2 (31.2–35.6)	33.0 (30.6–38.1)	0.764
Total bilirubin µmol·L^{-1}	8.9 (6.6–12.5)	9.6 (8.3–16.3)	8.7 (6.5–12.3)	0.146
Direct bilirubin µmol·L^{-1}	2.5 (1.8–3.9)	3.1 (2.3–6.1)	2.4 (1.8–3.8)	0.101
Alanine aminotransferase U·L^{-1}	22.0 (15.0–40.0)	27.0 (20.0–37.0)	22.0 (14.0–40.5)	0.233
Aspartate aminotransferase U·L^{-1}	30.0 (19.0–43.0)	40.0 (27.0–61.5)	27.5 (19.0–42.0)	0.010
γ-Glutamyltranspeptidase U·L^{-1}	29.0 (17.0–52.5)	23.0 (16.5–42.0)	29.0 (17.0–54.5)	0.518
Creatinine µmol·L^{-1}	66.5 (55.8–82.0)	95.0 (63.0–112.0)	65.0 (55.0–80.0)	0.001
D-dimer mg·L^{-1}	0.5 (0.3–1.7)	1.1 (0.4–10.5)	0.5 (0.3–1.2)	0.011
Prothrombin time s	13.7 (12.4–15.4)	13.9 (12.3–16.3)	13.7 (12.4–15.2)	0.758
Activated partial thromboplastin time s	35.6 (31.0–39.4)	37.8 (30.8–41.5)	35.3 (30.9–39.1)	0.383
P_{aO_2} mmHg	72.0 (57.0–88.0)	56.0 (49.0–71.0)	74.5 (59.0–92.0)	0.001
P_{aCO_2} mmHg	37.0 (33.0–41.0)	34.0 (29.0–41.0)	37.0 (34.0–41.0)	0.068
P_{aO_2}:F_{IO_2} mmHg	249.6±106.1	185.5±64.8	261.5±108.2	0.002

Data are presented as n, median (interquartile range) or mean±SD, unless otherwise stated. P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; F_{IO_2}: inspiratory oxygen fraction.

Compared to the patients in the survivor group, those in the deceased group underwent more frequent and more severe heart injury, as all laboratory parameters reflecting heart function, including cardiac troponin I, myoglobin and brain natriuretic peptide, were all significantly elevated in the deceased (tables 2 and 3). The deceased were more susceptible to hepatic or renal insufficiency, and to respiratory failure, indicated by the elevation of aspartate aminotransferase or creatinine, and the reduction of arterial oxygen tension (P_{aO_2}) and the ratio of P_{aO_2} to inspiratory oxygen fraction (F_{IO_2}).

Predictors of mortality

For all demographic data, clinical presentation data and laboratory findings presented in tables 1 and 2, we initially evaluated, using univariate analysis, each variable that displayed a statistically significant difference (p<0.05) between nonsurvivors and survivors. Our analysis revealed that age ⩾65 years, hypertension, cardiovascular or cerebrovascular diseases, dyspnoea, fatigue, sputum production, headache, white blood cell count >10×10^9 cells L^{-1}, neutrophil count >6.3×10^9 cells L^{-1}, CD3$^+$CD8$^+$ T-cells ⩽75 cells·µL^{-1}, cardiac troponin I ⩾0.05 ng·mL^{-1}, myoglobin >100 ng·L^{-1}, creatinine ⩾133 µmol·L^{-1}, D-dimer ⩾0.5 mg·L^{-1} and P_{aO_2} <60 mmHg were associated with the death of patients with COVID-19 pneumonia (table 3). Of all the studied variables, P_{aO_2} ⩾80 mmHg was the only factor that was associated with patients' survival (OR 0.233, 95% CI 0.065–0.840; p=0.026). The above 16 variables were further processed using a multivariable logistic regression model, which selected four variables that were predictive of mortality, including age ⩾65 years, cardiovascular or cerebrovascular diseases, CD3$^+$CD8$^+$ T-cells ⩽75 cells·µL^{-1} and cardiac troponin I ⩾0.05 ng·mL^{-1} (table 4).

To further understand the factors that can affect the survival of COVID-19 pneumonia patients with similar age and underlying diseases, we selected 42 sex-, age- and underlying disease-matched patients from the survivors to perform a case–control study at a ratio of 2:1. As shown in supplementary table S2, there was no difference in any of the demographic and clinical presentation parameters between the deceased and the matched case–control survivors. Given that many survivors were younger people, two survivors whose age was the same or ±1 year were matched to each one deceased. Compared to the survivors, the deceased had significantly increased concentrations of procalcitonin, cardiac troponin I, myoglobin and creatinine, and significantly reduced numbers of CD3$^+$CD8$^+$ T-cells (supplementary table S3).

TABLE 3 Univariate analysis of mortality risk factors for patients with COVID-19 pneumonia

Characteristics	Deceased	Survivors	OR (95%CI)	p-value
Patients n	21	158		
Age group years				
0–49	0	31.0	0.000 (0.000–)	0.997
50–64	19.0	38.6	2.673 (0.859–8.318)	0.090
⩾65	81.0	30.4	9.740 (3.113–30.476)	<0.001
Underlying diseases				
Hypertension	61.9	28.5	4.081 (1.584–10.510)	0.004
Cardiovascular or cerebrovascular diseases	57.1	10.8	11.059 (4.068–30.063)	<0.001
Symptoms				
Dyspnoea	85.7	44.9	7.352 (2.082–25.966)	0.002
Fatigue	61.9	36.7	2.802(1.096–7.160)	0.031
Sputum production	57.1	27.2	3.566 (1.403–9.061)	0.008
Headache	23.8	7.6	3.802 (1.187–12.177)	0.025
Respiratory rate >20 breaths·min^{-1}	47.6	31.0	2.022(0.806–5.076)	0.134
White blood cells ×10^9 cells·L^{-1}				
>10	33.3	12.7	3.450 (1.242–9.580)	0.017
4–10	52.4	60.1	1.371 (0.550–3.418)	0.499
<4	14.3	27.2	0.446 (0.125–1.590)	0.213
Neutrophils ×10^9 cells·L^{-1}				
>6.3	57.1	24.7	4.068 (1.594–10.382)	0.003
1.8–6.3	33.3	65.2	0.267 (0.102–0.700)	0.071
<1.8	9.5	10.1	0.934 (0.199–4.384)	0.931
Lymphocytes <1.1×10^9 cells·L^{-1}	90.5	72.2	3.667(0.820–16.400)	0.089
CD3$^+$CD8$^+$ T-cells ⩽75 cells·μL^{-1}	78.9	40.0	5.625 (1.664–19.013)	0.005
C-reactive protein ⩾10 mg·L^{-1}	95.2	87.3	2.901 (0.368–22.878)	0.312
Procalcitonin ⩾0.5 ng·mL^{-1}	21.1	9.9	2.438 (0.631–9.414)	0.196
Cardiac troponin I ⩾0.05 ng·mL^{-1}	61.5	17.9	7.314 (1.832–29.210)	0.005
Myoglobin >100 ng·mL^{-1}	64.3	18.4	8.000 (2.157–29.671)	0.002
Brain natriuretic peptide >100 pg·mL^{-1}	94.1	67.6	7.680 (0.909–64.906)	0.061
Aspartate aminotransferase >40 U·L^{-1}	47.6	29.9	2.134 (0.848–5.373)	0.108
Creatinine ⩾133 μmol·L^{-1}	19.0	2.1	11.137 (2.296–54.028)	0.003
D-dimer ⩾0.5 mg·L^{-1}	76.2	47.9	3.474 (1.152–10.481)	0.027
P_{aO_2} mmHg				
⩾80	14.3	41.7	0.233 (0.065–0.840)	0.026
60–79	28.6	32.4	0.834 (0.298–2.334)	0.730
<60	57.1	25.9	3.810 (1.451–10.004)	0.007
P_{aO_2}:F_{IO_2} <200 mmHg	47.6	29.2	2.204 (0.854–5.684)	0.102

Data are presented as %, unless otherwise stated. P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction.

After excluding the impact of age and underlying diseases on mortality, univariate analysis indicated that CD3$^+$CD8$^+$ T-cells ⩽75 cells·μL^{-1} and cardiac troponin I ⩾0.05 ng·mL^{-1} were the only two variables that could be predictors of mortality of patients with COVID-19 pneumonia (table 5).

Discussion

The ongoing SARS-CoV-2 epidemic is the third time that a zoonotic coronavirus has crossed species to infect human populations during the past 18 years [13]. In November 2002, severe acute respiratory

TABLE 4 Multivariate logistic regression analysis of mortality risk factors for patients with COVID-19 pneumonia

Variables	OR (95% CI)	p-value
Age ⩾65 years	3.765 (1.146–17.394)	0.023
Cardiovascular or cerebrovascular diseases	2.464 (0.755–8.044)	0.007
CD3$^+$CD8$^+$ T-cells ⩽75 cells·μL^{-1}	3.982 (1.132–14.006)	<0.001
Cardiac troponin I ⩾0.05 ng·mL^{-1}	4.077 (1.166–14.253)	<0.001

TABLE 5 Univariate analysis of mortality risk factors for patients with COVID-19 pneumonia in matched case–control study

Variables	Deceased	Survivors	OR (95% CI)	p-value
Patients n	21	42		
CD3$^+$CD8$^+$ T-cells ⩽75 cells·μL^{-1}	78.9	42.9	5.000 (1.319–18.960)	0.018
Cardiac troponin I ⩾0.05 ng·mL^{-1}	61.5	18.2	7.200 (1.518–34.139)	0.013
Myoglobin >100 ng·mL^{-1}	60.0	28.6	3.750 (0.924–15.226)	0.064
Procalcitonin ⩾0.5 ng·mL^{-1}	21.1	9.1	2.667 (0.528–13.477)	0.235
Creatinine ⩾133 μmol·L^{-1}	19.0	4.8	4.706 (0.786–28.178)	0.090

Data are presented as %, unless otherwise stated.

syndrome (SARS), caused by SARS-CoV, was first found in Guangdong Province, China, and the number of SARS cases increased substantially in the next year in China and later spread globally [14], infecting 8098 people in 26 countries and killing 774 of them [15]. Between September 2012 and 20 January 2017, the outbreak of Middle East respiratory syndrome (MERS), caused by MERS-CoV, led to 1879 laboratory-confirmed cases in 27 countries, resulting in at least 659 related deaths [16]. As of midnight on 24 March 2020, the numbers of Chinese confirmed COVID-19 pneumonia cases and deaths were 81218 and 3281, respectively, indicating that the overall death rate from COVID-19 pneumonia was 4% [17].

In Wuhan City, two large-scale special hospitals, Wuhan Pulmonary Hospital and Wuhan Jinyintan Hospital, provide medical service for patients with infectious diseases. Since the outbreak of COVID-19 pneumonia, all patients in the two hospitals have been COVID-19 pneumonia cases. Usually, only those patients with severe disease from general hospitals are transferred to the special hospitals for quarantine and treatment. This was why the overall mortality of COVID-19 pneumonia in the special hospitals (11.1% in the cohort of Wuhan Jinyintan Hospital [9] and 11.7% (95% CI 7.0–16.5%) in our current cohort) seemed to be higher than that in the cohort of a general hospital (4.3%) [10]. Unfortunately, no anti-SARS-CoV-2 drugs are available for treating patients with COVID-19 pneumonia. Although no antibiotic, antifungal drug, corticosteroid or immune globulin is routinely recommended to be administered for COVID-19 pneumonia, a combination consisting of two or more of these drugs was given to all critically ill patients in the present study.

It has been documented that, although there are some similarities in the clinical features between SARS and MERS, MERS progresses to respiratory failure much more rapidly with much higher mortality than SARS, and older age and underlying illness is likely to be related to the mortality of MERS [18]. In the present study, patients in the deceased group were much older than the survivors, and univariate and multivariate logistic regression analysis revealed age ⩾65 years as a strong predictor for death from COVID-19 pneumonia. In fact, in the whole cohort of 179 COVID-19 pneumonia patients, no one died who was younger than 50 years whereas 17 (81%) of the deceased patients were older than 65 years. As expected, our analysis also revealed that underlying cardiovascular or cerebrovascular diseases contributed to high mortality from COVID-19 pneumonia.

It has been demonstrated that inactivated SARS-CoV elicits an antigen-specific recall cytotoxic T-lymphocyte response in peripheral blood mononuclear cells of recovered SARS patients, but not in patients with critical SARS or those who have died of SARS, suggesting that the latter apparently cannot generate sufficient protective immunity to eliminate SARS-CoV; their immune responses to this pathogen may have in fact exacerbated their illness [19]. In the case of MERS, several inflammatory mediators, including inducible protein-10, monocyte chemoattractant protein-1 and interleukin-6, are strongly associated with mortality [20]. Given that COVID-19 pneumonia is an emerging infectious disease, the mechanisms by which SARS-CoV-2 causes severe illness and fatal outcomes in humans are unknown. More recently, CD8$^+$ T-cells have been reported to be significantly decreased in peripheral blood in patients with COVID-19 pneumonia [21]. It has been shown for several cytokines and chemokines, such as interleukin-2, interleukin-7, interleukin-10, macrophage colony-stimulating factor, inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α and tumour necrosis factor-α, that concentrations were higher in patients with severe COVID-19 pneumonia than in those with mild disease, suggesting that SARS-CoV-2 infection damages the human immune system and results in a systematic inflammatory response [8]. One important finding in our study was that CD3$^+$CD8$^+$ T-cells, but not CD3$^+$CD4$^+$ T-cells, were tremendously reduced in the circulation in deceased patients compared to either the total survivor population or the sex-, age- and comorbid illness-matched controls. More importantly, CD3$^+$CD8$^+$ T-cells ⩽75 cells·μL^{-1} was a reliable predictor for mortality of patients with

COVID-19 pneumonia. These data indicate that progressive immune-associated injury and inadequate adaptive immune responses could be possible mechanisms by which SARS-CoV-2 causes severe illness and fatal outcomes.

On 24 March 2020, China had 4287 current cases with confirmed COVID-19 pneumonia, and 1399 (32.6%) of them were very severe cases [17]. As mentioned, the overall death rate from COVID-19 pneumonia was 4% [17], and most deceased patients were older people with underlying illness [8–10]. For a younger cohort of 1716 Chinese medical staff whose age was always <65 years all over the country, six (0.3%) died [22]. These data suggest that the majority of patients with COVID-19 pneumonia will recover from the disease, especially younger people. Our current data demonstrate that patients in the deceased group were susceptible to multiple organ failure, especially heart failure and respiratory failure. One of the best laboratory parameters reflecting heart injury for predicting mortality from COVID-19 pneumonia was cardiac troponin I, and this parameter remained valid in the sex-, age- and underlying illness-matched control analysis. Our findings suggest that, in the care of critically ill patients with COVID-19 pneumonia, a strategy for protection of vital organs should be emphasised to improve their survival. It should be noted that the elevation of cardiac troponin I in COVID-19 patients was indicative of myocardial injury that was probably secondary to severe hypoxaemia. For the patients with positive cardiac troponin I results, what we could do was to choose an appropriate respiratory support strategy to improve oxygenation and wait for the recovery of the myocardial damage.

In conclusion, we identified four predictors for high mortality among the overall population of COVID-19 pneumonia patients: age $\geqslant$65 years, pre-existing concurrent cardiovascular or cerebrovascular diseases, $CD3^+CD8^+$ T-cells $\leqslant$75 cells·μL^{-1} and cardiac troponin I $\geqslant$0.05 ng·mL^{-1}. In the sex-, age- and comorbid illness-matched case–control study, we further found that $CD3^+CD8^+$ T-cells $\leqslant$75 cells·μL^{-1} and cardiac troponin I $\geqslant$0.05 ng·mL^{-1} remained as predictors for high mortality of COVID-19 pneumonia patients with similar age and underlying diseases.

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References

1   Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727–733.
2   Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199–1207.
3   Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 2020; 395: 689–697.
4   National Health Commission of the People's Republic of China. More than 20,000 medical staff were sent to Hubei Province. www.nhc.gov.cn/xcs/yqfkdt/202002/1beb07d46d424a13a710847a2dadedfb.shtml Date last accessed: 2 March 2020.
5   Johns Hopkins University Center for Systems Science and Engineering. Wuhan coronavirus (2019-nCoV) global cases. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 Date last accessed: 22 March 2020.
6   Paules CI, Marston HD, Fauci AS. Coronavirus infections – more than just the common cold. JAMA 2020; in press [https://doi.org/10.1001/jama.2020.0757].
7   Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; in press [https://doi.org/10.1001/jama.2020.2648].
8   Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
9   Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513.
10   Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; in press [https://doi.org/10.1001/jama.2020.1585].
11   World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected Date last updated: 28 January 2020. Date last accessed: 2 March 2020.
12   Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; in press [https://doi.org/10.1056/NEJMoa2002032].

13   Perlman S. Another decade, another coronavirus. *N Engl J Med* 2020; 382: 760–762.

14   Zhong NS, Zheng BJ, Li YM, *et al.* Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 2003; 362: 1353–1358.

15   Christian MD, Poutanen SM, Loutfy MR, *et al.* Severe acute respiratory syndrome. *Clin Infect Dis* 2004; 38: 1420–1427.

16   Arabi YM, Balkhy HH, Hayden FG, *et al.* Middle East respiratory syndrome. *N Engl J Med* 2017; 376: 584–594.

17   National Health Commission of the People's Republic of China. Latest on the novel coronavirus outbreak. www.nhc.gov.cn/xcs/yqfkdt/202003/b882c06edf184fbf800d4c7957e02dad.shtml Date last accessed: 24 March 2020.

18   Hui DS, Memish ZA, Zumla A. Severe acute respiratory syndrome *vs.* the Middle East respiratory syndrome. *Curr Opin Pulm Med* 2014; 20: 233–241.

19   Chen H, Hou J, Jiang X, *et al.* Response of memory CD8^{+} T cells to severe acute respiratory syndrome (SARS) coronavirus in recovered SARS patients and healthy individuals. *J Immunol* 2005; 175: 591–598.

20   Hong KH, Choi JP, Hong SH, *et al.* Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax* 2018; 73: 286–289.

21   Liu Y, Yang Y, Zhang C, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020; 63: 364–374.

22   National Health Commission of the People's Republic of China. Press conference of the State Council of the People's Republic of China. www.nhc.gov.cn/xcs/s3574/202002/5329d7ab7af24690a1d5b66982333af3.shtml. Date last accessed: 2 March 2020.