



Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

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Summary

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Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

Methods In this retrospective, multicentre cohort study, we included all adult inpatients (≥ 18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.

Findings 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95% CI 1.03–1.17, per year increase; $p=0.0043$), higher Sequential Organ Failure Assessment (SOFA) score (5.65, 2.61–12.23; $p<0.0001$), and d-dimer greater than 1 $\mu\text{g/mL}$ (18.42, 2.64–128.55; $p=0.0033$) on admission. Median duration of viral shedding was 20.0 days (IQR 17.0–24.0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

Interpretation The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 $\mu\text{g/mL}$ could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

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Introduction

In December, 2019, Wuhan city, the capital of Hubei province in China, became the centre of an outbreak of pneumonia of unknown cause. By Jan 7, 2020, Chinese scientists had isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV), from these patients with virus-infected pneumonia,^{1,2} which was later designated coronavirus disease 2019 (COVID-19) in February, 2020, by WHO.³

Although the outbreak is likely to have started from a zoonotic transmission event associated with a large seafood market that also traded in live wild animals, it soon became clear that efficient person-to-person transmission was also occurring.⁴ The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing

asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death, with many patients being hospitalised with pneumonia in Wuhan.^{5–7} Although some case series have been published, many patients in these series remained hospitalised at time of publication. To our knowledge, no previous studies have been done among patients with definite outcomes. The estimation of risk factors for severe disease and death in these earlier case series are therefore not very robust. Additionally, details of the clinical and virological course of illness have not yet been well described.

Here, we present details of all patients admitted to the two designated hospitals in Wuhan—Jinyintan Hospital and Wuhan Pulmonary Hospital—with laboratory-confirmed COVID-19 and a definite clinical

Research in context

Evidence before this study

We searched PubMed on Feb 23, 2020, for articles that documented the risk factors of mortality and viral shedding in patients with coronavirus disease 2019 (COVID-19), resulting from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the search terms ("novel coronavirus" OR "SARS-CoV-2" OR "COVID-19") AND ("death" OR "mortality" OR "viral shedding") with no language or time restrictions. Age, comorbidities, lymphocytopenia and elevated alanine aminotransferase, d-dimer, creatine kinase, high-sensitivity cardiac troponin I, prothrombin time, and disease severity were reported to be associated with intensive care unit admission. However, no published works were found about the risk factors of mortality for adult patients with COVID-19. One study compared the sensitivity of SARS-CoV-2 RNA detection in throat and nasopharyngeal swab in 17 patients with COVID-19.

Added value of this study

In this retrospective cohort study of adult inpatients in two hospitals in Wuhan, China, we found increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95% CI 1.03–1.17; $p=0.0043$), higher Sequential Organ Failure Assessment (SOFA) score (5.65, 2.61–12.23; $p<0.0001$), and d-dimer levels greater than $1.0 \mu\text{g/mL}$ (18.42, 2.64–128.55; $p=0.0033$) on admission. Duration of viral shedding ranged between 8 and 37 days. The median duration of viral shedding was 20.0 days (IQR 17.0–24.0) in survivors, but continued until death in fatal cases.

Implications of all the available evidence

Older age, elevated d-dimer levels, and high SOFA score could help clinicians to identify at an early stage those patients with COVID-19 who have poor prognosis. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

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outcome (death or discharge) as of Jan 31, 2020. We aim to explore risk factors of in-hospital death for patients and describe the clinical course of symptoms, viral shedding, and temporal changes of laboratory findings during hospitalisation.

Methods

Study design and participants

This retrospective cohort study included two cohorts of adult inpatients (≥ 18 years old) from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China). All adult patients who were diagnosed with COVID-19 according to WHO interim guidance were screened, and those who died or were discharged between Dec 29, 2019 (ie, when the first patients were admitted), and Jan 31, 2020, were included in our study. Since these two hospitals were the only designated hospitals for transfer of patients with COVID-19 from other hospitals in Wuhan until Feb 1, 2020, our study enrolled all adult inpatients who were hospitalised for COVID-19 and had a definite outcome (dead or discharged) at the early stage of the outbreak.

Before Jan 11, 2020, SARS-CoV-2 RNA detection results were not available in the electronic medical records, from which data for this study were obtained retrospectively; therefore, this study includes 29 of the 41 patients originally reported on.⁵

The study was approved by the Research Ethics Commission of Jinyintan Hospital (KY-2020-01.01) and the requirement for informed consent was waived by the Ethics Commission as described previously.⁵

Data collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a standardised data collection

form, which was a modified version of the WHO/International Severe Acute Respiratory and Emerging Infection Consortium case record form for severe acute respiratory infections. All data were checked by two physicians (FZ and ZL) and a third researcher (GF) adjudicated any difference in interpretation between the two primary reviewers.

Laboratory procedures

Methods for laboratory confirmation of SARS-CoV-2 infection have been described elsewhere.⁵ Briefly, four institutions—the Chinese Center for Disease Control and Prevention, the Chinese Academy of Medical Science, the Academy of Military Medical Sciences, and the Wuhan Institute of Virology, Chinese Academy of Sciences—were responsible for SARS-CoV-2 detection in respiratory specimens by next-generation sequencing or real-time RT-PCR methods. From Jan 11, 2020, SARS-CoV-2 RNA were detected by local Centers for Disease Control and Prevention, local health institutions, and Jinyintan Hospital and Wuhan Pulmonary Hospital. Throat-swab specimens were obtained for SARS-CoV-2 PCR re-examination every other day after clinical remission of symptoms, including fever, cough, and dyspnoea, but only qualitative data were available. The criteria for discharge were absence of fever for at least 3 days, substantial improvement in both lungs in chest CT, clinical remission of respiratory symptoms, and two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart.

Routine blood examinations were complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes, interleukin-6 (IL-6), serum ferritin, and

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56.0 (46.0–67.0)	69.0 (63.0–76.0)	52.0 (45.0–58.0)	<0.0001
Sex	0.15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Exposure history	73 (38%)	14 (26%)	59 (43%)	0.028
Current smoker	11 (6%)	5 (9%)	6 (4%)	0.21
Comorbidity	91 (48%)	36 (67%)	55 (40%)	0.0010
Hypertension	58 (30%)	26 (48%)	32 (23%)	0.0008
Diabetes	36 (19%)	17 (31%)	19 (14%)	0.0051
Coronary heart disease	15 (8%)	13 (24%)	2 (1%)	<0.0001
Chronic obstructive lung disease	6 (3%)	4 (7%)	2 (1%)	0.047
Carcinoma	2 (1%)	0	2 (1%)	0.37
Chronic kidney disease	2 (1%)	2 (4%)	0	0.024
Other	22 (12%)	11 (20%)	11 (8%)	0.016
Respiratory rate >24 breaths per min	56 (29%)	34 (63%)	22 (16%)	<0.0001
Pulse ≥125 beats per min	2 (1%)	2 (4%)	0	0.024
Systolic blood pressure <90 mm Hg	1 (1%)	0	1 (1%)	0.53
Fever (temperature ≥37.3°C)	180 (94%)	51 (94%)	129 (94%)	0.94
Cough	151 (79%)	39 (72%)	112 (82%)	0.15
Sputum	44 (23%)	14 (26%)	30 (22%)	0.55
Myalgia	29 (15%)	8 (15%)	21 (15%)	0.93
Fatigue	44 (23%)	15 (28%)	29 (21%)	0.33
Diarrhoea	9 (5%)	2 (4%)	7 (5%)	0.67
Nausea or vomiting	7 (4%)	3 (6%)	4 (3%)	0.40
SOFA score	2.0 (1.0–4.0)	4.5 (4.0–6.0)	1.0 (1.0–2.0)	<0.0001
qSOFA score	1.0 (0.0–1.0)	1.0 (1.0–1.0)	0.0 (0.0–1.0)	<0.0001
CURB-65 score	0.0 (0.0–2.0)	2.0 (1.0–3.0)	0.0 (0.0–1.0)	<0.0001
0–1	141/188 (75%)	16 (30%)	125/134 (93%)	<0.0001*
2	32/188 (17%)	23 (43%)	9/134 (7%)	..
3–5	15/188 (8%)	15 (28%)	0/134	..
Disease severity status	<0.0001
General	72 (38%)	0	72 (53%)	..
Severe	66 (35%)	12 (22%)	54 (39%)	..
Critical	53 (28%)	42 (78%)	11 (8%)	..
Time from illness onset to hospital admission, days	11.0 (8.0–14.0)	11.0 (8.0–15.0)	11.0 (8.0–13.0)	0.53
Laboratory findings				
White blood cell count, × 10 ⁹ per L	6.2 (4.5–9.5)	9.8 (6.9–13.9)	5.2 (4.3–7.7)	<0.0001
<4	32 (17%)	5 (9%)	27 (20%)	<0.0001*
4–10	119 (62%)	24 (44%)	95 (69%)	..
>10	40 (21%)	25 (46%)	15 (11%)	..
Lymphocyte count, × 10 ⁹ per L	1.0 (0.6–1.3)	0.6 (0.5–0.8)	1.1 (0.8–1.5)	<0.0001
<0.8	77 (40%)	41 (76%)	36 (26%)	<0.0001
Haemoglobin, g/L	128.0 (119.0–140.0)	126.0 (115.0–138.0)	128.0 (120.0–140.0)	0.30

(Table 1 continues on next page)

procalcitonin. Chest radiographs or CT scan were also done for all inpatients. Frequency of examinations was determined by the treating physician.

Definitions

Fever was defined as axillary temperature of at least 37.3°C. Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock.⁵ Secondary infection was diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteraemia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples after admission.⁵ Ventilator-associated pneumonia was diagnosed according to the guidelines for treatment of hospital-acquired and ventilator-associated pneumonia.⁸ Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines⁹ and acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition.¹⁰ Acute cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, high-sensitivity cardiac troponin I) were above the 99th percentile upper reference limit, or if new abnormalities were shown in electrocardiography and echocardiography.⁵ The illness severity of COVID-19 was defined according to the Chinese management guideline for COVID-19 (version 6.0).¹¹ Coagulopathy was defined as a 3-second extension of prothrombin time or a 5-second extension of activated partial thromboplastin time. Hypoproteinaemia was defined as blood albumin of less than 25 g/L. Exposure history was defined as exposure to people with confirmed SARS-CoV-2 infection or to the Wuhan seafood market.

Statistical analysis

Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney U test, χ^2 test, or Fisher's exact test to compare differences between survivors and non-survivors where appropriate. To explore the risk factors associated with in-hospital death, univariable and multivariable logistic regression models were used. Considering the total number of deaths (n=54) in our study and to avoid overfitting in the model, five variables were chosen for multivariable analysis on the basis of previous findings and clinical constraints. Previous studies have shown blood levels of d-dimer and Sequential Organ Failure Assessment (SOFA) scores to be higher in critically ill or fatal cases, whereas lymphopenia and cardiovascular disease have been less commonly observed in non-critical or surviving patients with SARS-CoV-2 infection.^{5,6,12} Similar risk factors, including older age, have been reported associated with adverse clinical outcomes in adults with SARS and Middle East respiratory syndrome (MERS).^{3,13} Some laboratory findings, including alanine aminotransferase (ALT), lactate dehydrogenase, high-sensitivity cardiac

troponin I, creatine kinase, d-dimer, serum ferritin, and IL-6, might be unavailable in emergency circumstances. Therefore, we chose lymphocyte count, d-dimer, SOFA score, coronary heart disease, and age as the five variables for our multivariable logistic regression model.

We excluded variables from the univariable analysis if their between-group differences were not significant, if their accuracy was unconfirmed (eg, exposure, which was self-reported), if the number of events was too small to calculate odds ratios, and if they had colinearity with the SOFA score.

We compared patient characteristics between the two hospitals and used a generalised linear model to adjust for possible differences in patients' characteristics and treatment between the two study centres.

A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using the SAS software (version 9.4), unless otherwise indicated.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors (BC and HC) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

813 adult patients were hospitalised in Jinyintan Hospital or Wuhan Pulmonary Hospital with COVID-19 before Jan 31, 2020. After excluding 613 patients that were still hospitalised or not confirmed by SARS-CoV-2 RNA detection as of Jan 31, 2020, and nine inpatients without available key information in their medical records, we included 191 inpatients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) in the final analysis. 54 patients died during hospitalisation and 137 were discharged. The median age of the 191 patients was 56.0 years (IQR 46.0–67.0), ranging from 18 years to 87 years, and most patients were male (table 1). Comorbidities were present in nearly half of patients, with hypertension being the most common comorbidity, followed by diabetes and coronary heart disease (table 1). The most common symptoms on admission were fever and cough, followed by sputum production and fatigue (table 1). Lymphocytopenia occurred in 77 (40%) patients. 181 (95%) patients received antibiotics and 41 (21%) received antivirals (lopinavir/ritonavir; table 2). Systematic corticosteroid and intravenous immunoglobulin use differed significantly between non-survivors and survivors (table 2). The comparison of characteristics, treatment, and outcomes of patients from the two hospitals are shown in the appendix (pp 2–4).

The median time from illness onset (ie, before admission) to discharge was 22.0 days (IQR 18.0–25.0), whereas the median time to death was 18.5 days (15.0–22.0; table 2). 32 patients required invasive mechanical ventilation, of

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
Anaemia	29 (15%)	14 (26%)	15 (11%)	0.0094
Platelet count, $\times 10^9$ per L	206.0 (155.0–262.0)	165.5 (107.0–229.0)	220.0 (168.0–271.0)	<0.0001
<100	13 (7%)	11 (20%)	2 (1%)	<0.0001
Albumin, g/L	32.3 (29.1–35.8)	29.1 (26.5–31.3)	33.6 (30.6–36.4)	<0.0001
ALT, U/L	30.0 (17.0–46.0)	40.0 (24.0–51.0)	27.0 (15.0–40.0)	0.0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0.0015
Creatinine >133 μ mol/L	8/186 (4%)	5 (9%)	3/132 (2%)	0.045
Lactate dehydrogenase, U/L	300.0 (234.0–407.0)	521.0 (363.0–669.0)	253.5 (219.0–318.0)	<0.0001
>245	123/184 (67%)	53 (98%)	70/130 (54%)	<0.0001
Creatine kinase, U/L	21.5 (13.0–72.4)	39.0 (19.5–151.0)	18.0 (12.5–52.1)	0.0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0.038
High-sensitivity cardiac troponin I, pg/mL	4.1 (2.0–14.1)	22.2 (5.6–83.1)	3.0 (1.1–5.5)	<0.0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0.0001
Prothrombin time, s	11.6 (10.6–13.0)	12.1 (11.2–13.7)	11.4 (10.4–12.6)	0.0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0.016*
≥ 16	11/182 (6%)	7 (13%)	4/128 (3%)	..
D-dimer, μ g/mL	0.8 (0.4–3.2)	5.2 (1.5–21.1)	0.6 (0.3–1.0)	<0.0001
≤ 0.5	55/172 (32%)	4 (7%)	51/118 (43%)	<0.0001*
>0.5 to ≤ 1	45/172 (26%)	6 (11%)	39/118 (33%)	..
>1	72/172 (42%)	44 (81%)	28/118 (24%)	..
Serum ferritin, μ g/L	722.0 (377.2–1435.3)	1435.3 (728.9–2000.0)	503.2 (264.0–921.5)	<0.0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0.0008
IL-6, pg/mL	7.4 (5.3–10.8)	11.0 (7.5–14.4)	6.3 (5.0–7.9)	<0.0001
Procalcitonin, ng/mL	0.1 (0.1–0.1)	0.1 (0.1–0.5)	0.1 (0.1–0.1)	<0.0001
<0.1	114/164 (70%)	19/51 (37%)	95/113 (84%)	<0.0001*
≥ 0.1 to <0.25	30/164 (18%)	16/51 (31%)	14/113 (12%)	..
≥ 0.25 to <0.5	6/164 (4%)	3/51 (6%)	3/113 (3%)	..
≥ 0.5	14/164 (9%)	13/51 (25%)	1/113 (1%)	..
Imaging features				
Consolidation	112 (59%)	40 (74%)	72 (53%)	0.0065
Ground-glass opacity	136 (71%)	44 (81%)	92 (67%)	0.049
Bilateral pulmonary infiltration	143 (75%)	45 (83%)	98 (72%)	0.090

Data are median (IQR), n (%), or n/N (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. * χ^2 test comparing all subcategories.

Table 1: Demographic, clinical, laboratory, and radiographic findings of patients on admission

whom 31 (97%) died. The median time from illness onset to invasive mechanical ventilation was 14.5 days (12.0–19.0). Extracorporeal membrane oxygenation was used in three patients, none of whom survived. Sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock (table 2). Half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in ten (31%) of 32 patients requiring invasive mechanical ventilation. The frequency of complications were higher in non-survivors than survivors (table 2).

See Online for appendix

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Treatments*				
Antibiotics	181 (95%)	53 (98%)	128 (93%)	0.15
Antiviral treatment	41 (21%)	12 (22%)	29 (21%)	0.87
Corticosteroids	57 (30%)	26 (48%)	31 (23%)	0.0005
Intravenous immunoglobulin	46 (24%)	36 (67%)	10 (7%)	<0.0001
High-flow nasal cannula oxygen therapy	41 (21%)	33 (61%)	8 (6%)	<0.0001
Non-invasive mechanical ventilation	26 (14%)	24 (44%)	2 (1%)	<0.0001
Invasive mechanical ventilation	32 (17%)	31 (57%)	1 (1%)	<0.0001
ECMO	3 (2%)	3 (6%)	0	0.0054
Renal replacement therapy	10 (5%)	10 (19%)	0	<0.0001
Outcomes				
Sepsis	112 (59%)	54 (100%)	58 (42%)	<0.0001
Respiratory failure	103 (54%)	53 (98%)	50 (36%)	<0.0001
ARDS	59 (31%)	50 (93%)	9 (7%)	<0.0001
Heart failure	44 (23%)	28 (52%)	16 (12%)	<0.0001
Septic shock	38 (20%)	38 (70%)	0	<0.0001
Coagulopathy	37 (19%)	27 (50%)	10 (7%)	<0.0001
Acute cardiac injury	33 (17%)	32 (59%)	1 (1%)	<0.0001
Acute kidney injury	28 (15%)	27 (50%)	1 (1%)	<0.0001
Secondary infection	28 (15%)	27 (50%)	1 (1%)	<0.0001
Hypoproteinaemia	22 (12%)	20 (37%)	2 (1%)	<0.0001
Acidosis	17 (9%)	16 (30%)	1 (1%)	<0.0001
ICU admission	50 (26%)	39 (72%)	11 (8%)	<0.0001
ICU length of stay, days	8.0 (4.0–12.0)	8.0 (4.0–12.0)	7.0 (2.0–9.0)	0.41
Hospital length of stay, days	11.0 (7.0–14.0)	7.5 (5.0–11.0)	12.0 (9.0–15.0)	<0.0001
Time from illness onset to fever, days	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.16
Time from illness onset to cough, days	1.0 (1.0–3.0)	1.0 (1.0–1.0)	1.0 (1.0–4.0)	0.30
Time from illness onset to dyspnoea, days	7.0 (4.0–9.0)	7.0 (4.0–10.0)	7.0 (4.0–9.0)	0.51
Time from illness onset to sepsis, days	9.0 (7.0–13.0)	10.0 (7.0–14.0)	9.0 (7.0–12.0)	0.22
Time from illness onset to ARDS, days	12.0 (8.0–15.0)	12.0 (8.0–15.0)	10.0 (8.0–13.0)	0.65
Time from illness onset to ICU admission, days	12.0 (8.0–15.0)	12.0 (8.0–15.0)	11.5 (8.0–14.0)	0.88
Time from illness onset to corticosteroids treatment, days	12.0 (10.0–16.0)	13.0 (10.0–17.0)	12.0 (10.0–15.0)	0.55
Time from illness onset to death or discharge, days	21.0 (17.0–25.0)	18.5 (15.0–22.0)	22.0 (18.0–25.0)	0.0003
Duration of viral shedding after COVID-19 onset, days	20.0 (16.0–23.0)	18.5 (15.0–22.0)†	20.0 (17.0–24.0)	0.024

Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: Treatments and outcomes

In univariable analysis, odds of in-hospital death was higher in patients with diabetes or coronary heart disease (table 3). Age, lymphopenia, leucocytosis, and elevated ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6,

prothrombin time, creatinine, and procalcitonin were also associated with death (table 3).

We included 171 patients with complete data for all variables (53 non-survivors and 118 survivors) in the multivariable logistic regression model. We found that older age, higher SOFA score, and d-dimer greater than 1 µg/mL at admission were associated with increased odds of death (table 3). When adjusting for study centre, our generalised linear model showed similar results (appendix p 5).

For survivors, the median duration of viral shedding was 20.0 days (IQR 17.0–24.0) from illness onset, but the virus was continuously detectable until death in non-survivors (table 2; figure 1). The shortest observed duration of viral shedding among survivors was 8 days, whereas the longest was 37 days. Among 29 patients who received lopinavir/ritonavir and were discharged, the median time from illness onset to initiation of antiviral treatment was 14.0 days (IQR 10.0–17.0) and the median duration of viral shedding was 22.0 days (18.0–24.0). The median duration of viral shedding was 19.0 days (17.0–22.0) in patients with severe disease status and 24.0 days (22.0–30.0) in patients with critical disease status.

Major laboratory markers were tracked from illness onset (figure 2). Baseline lymphocyte count was significantly higher in survivors than non-survivors; in survivors, lymphocyte count was lowest on day 7 after illness onset and improved during hospitalisation, whereas severe lymphopenia was observed until death in non-survivors. Levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6 were clearly elevated in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration (figure 2). In non-survivors, high-sensitivity cardiac troponin I increased rapidly from day 16 after disease onset, whereas lactate dehydrogenase increased for both survivors and non-survivors in the early stage of illness, but decreased from day 13 for survivors.

Median time from illness onset to dyspnoea was similar in survivors and non-survivors, with a median duration of dyspnoea of 13.0 days (9.0–16.5) for survivors (table 2; figure 1). In survivors, the median duration of fever was 12.0 days (8.0–13.0) and cough persisted for 19.0 days (IQR 12.0–23.0; figure 1). 62 (45%) survivors still had cough on discharge and 39 (72%) non-survivors still had cough at the time of death. The dynamic profiles of fever, cough, and dyspnoea are shown in the appendix (p 6). Sepsis developed at a median of 9.0 days (7.0–13.0) after illness onset among all patients, followed by ARDS (12.0 days [8.0–15.0]), acute cardiac injury (15.0 days [10.0–17.0]), acute kidney injury (15.0 days [13.0–19.5]), and secondary infection (17.0 days [13.0–19.0]). The initiation time and duration of systematic corticosteroid use was also similar between the two groups. Among non-survivors, the median time from illness onset was 10.0 days (7.0–14.0) to sepsis, 12.0 days (8.0–15.0) to ARDS, 14.5 days (9.5–17.0) to acute cardiac injury, and

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Demographics and clinical characteristics				
Age, years*	1.14 (1.09–1.18)	<0.0001	1.10 (1.03–1.17)	0.0043
Female sex (vs male)	0.61 (0.31–1.20)	0.15
Current smoker (vs non-smoker)	2.23 (0.65–7.63)	0.20
Comorbidity present (vs not present)				
Chronic obstructive lung disease	5.40 (0.96–30.40)	0.056
Coronary heart disease	21.40 (4.64–98.76)	<0.0001	2.14 (0.26–17.79)	0.48
Diabetes	2.85 (1.35–6.05)	0.0062
Hypertension	3.05 (1.57–5.92)	0.0010
Respiratory rate, breaths per min				
≤24	1 (ref)
>24	8.89 (4.34–18.19)	<0.0001
SOFA score	6.14 (3.48–10.85)	<0.0001	5.65 (2.61–12.23)	<0.0001
qSOFA score	12.00 (5.06–28.43)	<0.0001
Laboratory findings				
White blood cell count, × 10 ⁹ per L				
<4	0.73 (0.26–2.10)	0.56
4–10	1 (ref)
>10	6.60 (3.02–14.41)	<0.0001
Lymphocyte count, × 10 ⁹ per L*	0.02 (0.01–0.08)	<0.0001	0.19 (0.02–1.62)	0.13
ALT, U/L				
≤40	1 (ref)
>40	2.87 (1.48–5.57)	0.0018

(Table 3 continues in next column)

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
(Continued from previous column)				
Creatinine, μmol/L				
≤133	1 (ref)
>133	4.39 (1.01–19.06)	0.048
Lactate dehydrogenase, U/L				
≤245	1 (ref)
>245	45.43 (6.10–338.44)	0.0002
Creatine kinase, U/L				
≤185	1 (ref)
>185	2.56 (1.03–6.36)	0.043
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)
>28	80.07 (10.34–620.36)	<0.0001
D-dimer, μg/mL				
≤0.5	1 (ref)	..	1 (ref)	..
>0.5	1.96 (0.52–7.43)	0.32	2.14 (0.21–21.39)	0.52
>1	20.04 (6.52–61.56)	<0.0001	18.42 (2.64–128.55)	0.0033
Prothrombin time, s				
<16	1 (ref)
≥16	4.62 (1.29–16.50)	0.019
Serum ferritin, μg/L				
≤300	1 (ref)
>300	9.10 (2.04–40.58)	0.0038
IL-6, pg/mL*	1.12 (1.03–1.23)	0.0080
Procalcitonin, ng/mL*	13.75 (1.81–104.40)	0.011

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

Table 3: Risk factors associated with in-hospital death

17.0 days (13.0–19.0) to secondary infection (figure 1; table 2). Among survivors, secondary infection, acute kidney injury, and acute cardiac injury were observed in one patient each, occurring 9 days (acute kidney injury), 14 days (secondary infection), and 21 days (acute cardiac injury) after illness onset.

The median time from dyspnoea to intubation was 10.0 days (IQR 5.0–12.5) for patients who received invasive mechanical ventilation and the time from invasive mechanical ventilation to occurrence of ventilator-associated pneumonia was 8.0 days (2.0–9.0; figure 1).

Discussion

This retrospective cohort study identified several risk factors for death in adults in Wuhan who were

hospitalised with COVID-19. In particular, older age, d-dimer levels greater than 1 μg/mL, and higher SOFA score on admission were associated with higher odds of in-hospital death. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, and lactate dehydrogenase and lymphopenia were more commonly seen in severe COVID-19 illness. Sustained viral detection in throat samples was observed in both survivors and non-survivors.

Previously, older age has been reported as an important independent predictor of mortality in SARS and MERS.^{14,15} The current study confirmed that increased age was associated with death in patients with COVID-19. Previous studies in macaques inoculated with SARS-CoV found that older macaques had stronger host innate responses to virus infection than younger adults, with an

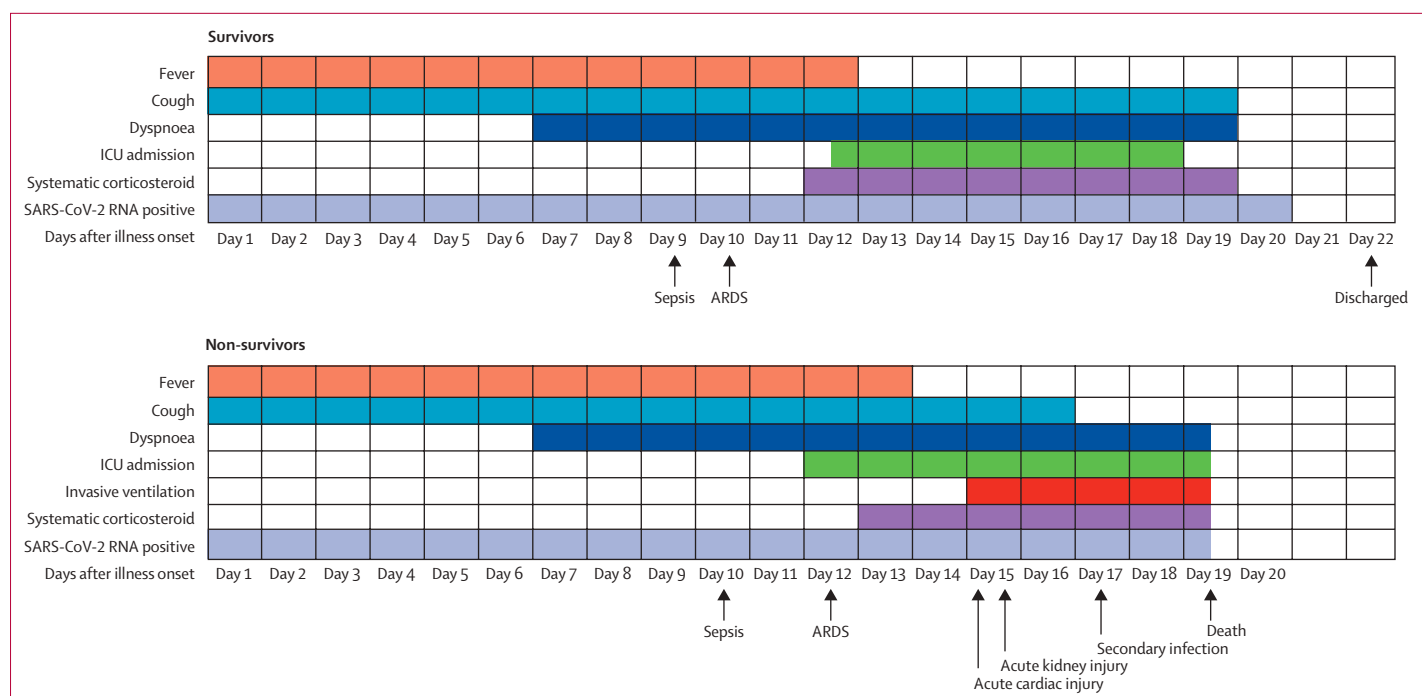


Figure 1: Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19

Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

increase in differential expression of genes associated with inflammation, whereas expression of type I interferon beta was reduced.¹⁶ The age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged proinflammatory responses, potentially leading to poor outcome.¹⁷

SOFA score is a good diagnostic marker for sepsis and septic shock, and reflects the state and degree of multi-organ dysfunction.^{18,19} Although bacterial infections are usually regarded as a leading cause of sepsis, viral infection can also cause sepsis syndrome. Previously, we determined that sepsis occurred in nearly 40% of adults with community-acquired pneumonia due to viral infection.²⁰ In the current study, we found that more than half of patients developed sepsis. Additionally, we found that more than 70% of patients had white blood cell count below 10.0×10^9 per L or procalcitonin below 0.25 ng/mL, and no bacterial pathogens were detected in these patients on admission. Sepsis was a common complication, which might be directly caused by SARS-CoV-2 infection, but further research is needed to investigate the pathogenesis of sepsis in COVID-19 illness.

Cardiac complications, including new or worsening heart failure, new or worsening arrhythmia, or myocardial infarction are common in patients with pneumonia. Cardiac arrest occurs in about 3% of inpatients with pneumonia.²¹ Risk factors of cardiac events after

pneumonia include older age, pre-existing cardiovascular diseases, and greater severity of pneumonia at presentation.²² Coronary heart disease has also been found to be associated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections.^{22–24} In this study, increased high-sensitivity cardiac troponin I during hospitalisation was found in more than half of those who died. The first autopsy of a 53-year-old woman with chronic renal failure in Jinyintan Hospital showed acute myocardial infarction (data not published; personal communication with a pathologist from the Chinese Academy of Science). About 90% of inpatients with pneumonia had increased coagulation activity, marked by increased d-dimer concentrations.²⁵ In this study, we found d-dimer greater than 1 µg/mL is associated with fatal outcome of COVID-19. High levels of d-dimer have a reported association with 28-day mortality in patients with infection or sepsis identified in the emergency department.²⁶ Contributory mechanisms include systemic pro-inflammatory cytokine responses that are mediators of atherosclerosis directly contributing to plaque rupture through local inflammation, induction of procoagulant factors, and haemodynamic changes, which predispose to ischaemia and thrombosis.^{27–29} In addition, angiotensin converting enzyme 2, the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells,^{30,31} so there is at least theoretical potential possibility of direct cardiac involvement by the virus. Of note, interstitial mononuclear inflammatory infiltrates in heart tissue has

been documented in fatal cases of COVID-19, although viral detection studies were not reported.³²

The level and duration of infectious virus replication are important factors in assessing the risk of transmission and guiding decisions regarding isolation of patients. Because coronavirus RNA detection is more sensitive than virus isolation, most studies have used qualitative or quantitative viral RNA tests as a potential marker for infectious coronavirus. For SARS-CoV, viral RNA was detected in respiratory specimens from about a third of patients as long as 4 weeks after disease onset.³³ Similarly, the duration of MERS-CoV RNA detection in lower respiratory specimens persisted for at least 3 weeks,^{34,35} whereas the duration of SARS-CoV-2 RNA detection has not been well characterised. In the current study, we found that the detectable SARS-CoV-2 RNA persisted for a median of 20 days in survivors and that it was sustained until death in non-survivors. This has important implications for both patient isolation decision making and guidance around the length of antiviral treatment. In severe influenza virus infection, prolonged viral shedding was associated with fatal outcome and delayed antiviral treatment was an independent risk factor for prolonged virus detection.³⁶ Similarly, effective antiviral treatment might improve outcomes in COVID-19, although we did not observe shortening of viral shedding duration after lopinavir/ritonavir treatment in the current study. Randomised clinical trials for lopinavir/ritonavir (ChiCTR2000029308) and intravenous remdesivir (NCT04257656, NCT04252664) in treatment of COVID-19 are currently in progress.

Our study has some limitations. First, due to the retrospective study design, not all laboratory tests were done in all patients, including lactate dehydrogenase, IL-6, and serum ferritin. Therefore, their role might be underestimated in predicting in-hospital death. Second, patients were sometimes transferred late in their illness to the two included hospitals. Lack of effective antivirals, inadequate adherence to standard supportive therapy, and high-dose corticosteroid use might have also contributed to the poor clinical outcomes in some patients. Third, the estimated duration of viral shedding is limited by the frequency of respiratory specimen collection, lack of quantitative viral RNA detection, and relatively low positive rate of SARS-CoV-2 RNA detection in throat-swabs.³⁷ Fourth, by excluding patients still in hospital as of Jan 31, 2020, and thus relatively more severe disease at an earlier stage, the case fatality ratio in our study cannot reflect the true mortality of COVID-19. Last but not least, interpretation of our findings might be limited by the sample size. However, by including all adult patients in the two designated hospitals for COVID-19, we believe our study population is representative of cases diagnosed and treated in Wuhan.

To the best of our knowledge, this is the largest retrospective cohort study among patients with COVID-19 who have experienced a definite outcome. We found that

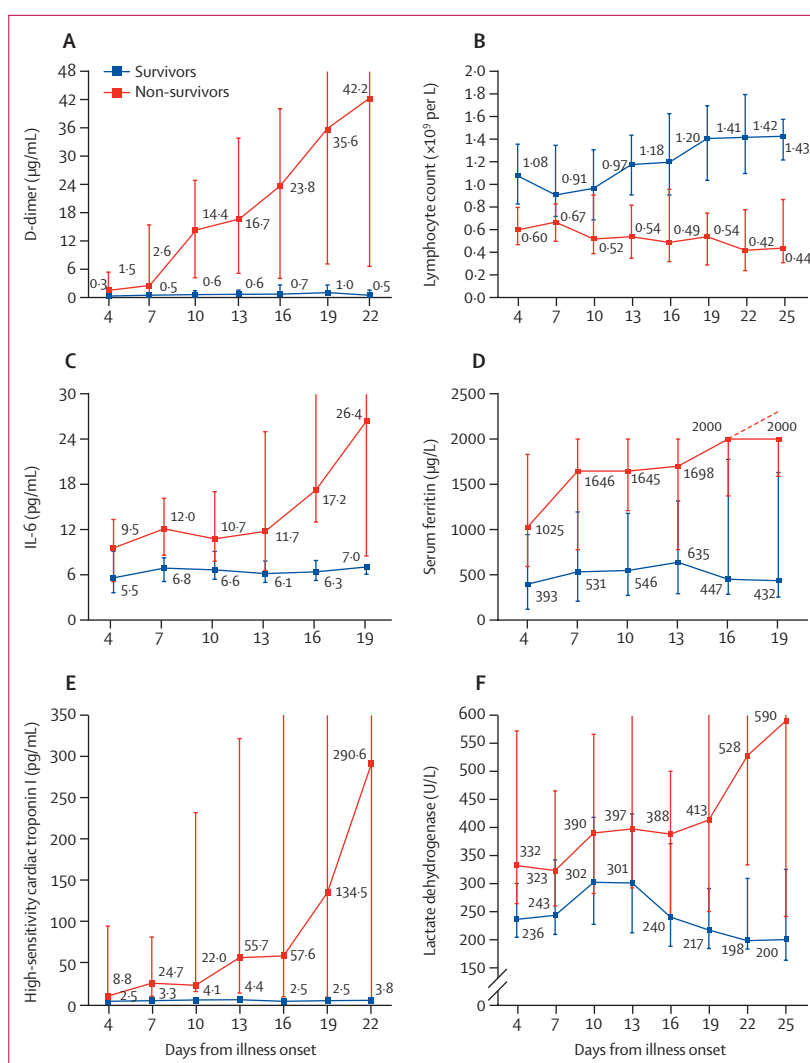


Figure 2: Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19 Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors and non-survivors were significant for all timepoints shown, except for day 4 after illness onset for d-dimer, IL-6, and high-sensitivity cardiac troponin I. For serum ferritin (D), the median values after day 16 exceeded the upper limit of detection, as indicated by the dashed line. COVID-19=coronavirus disease 2019. IL-6=interleukin-6.

older age, higher SOFA score, and elevated d-dimer at admission were risk factors for death of adult patients with COVID-19. The prolonged viral shedding provides the rationale for testing novel coronavirus antiviral interventions in efforts to improve outcomes.

Contributors

BC and HC had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BC, FZ, GF, ZL, JXi, and YL drafted the paper. BC, FZ, RD, GF, ZL, XG, HL, and YW did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. FZ, RD, GF, ZL, YL, BS, LG, YWe, XW, JXu, ST, and YZ collected the data. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

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