Original Article

Factors associated with duration of hospital stay and complications in patients with COVID-19

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Background: Medical resources have been exhausted in many countries because of the current worldwide pandemic of coronavirus disease 2019 (COVID-19). The identification of factors influencing the length of hospital stay (LOS) and complications may have the potential to guide decisions regarding resource allocation as well as significantly and safely reduce adverse outcomes in patients with COVID-19.

Methods: Demographic, clinical, and laboratory test data of 285 patients with COVID-19 were extracted to describe the characteristics and to identify factors associated with LOS and complications during hospitalization.

Results: The median LOS was 18 days (IQR 14–24), 90 patients developed complications during the hospitalization. Factors associated with prolonged LOS and complications included older age (≥60 years) (OR =2.00, 95% CI, 1.18–3.40 for LOS; OR =2.24, 95% CI, 1.32–3.80 for complications), and higher levels of (increases by 1 interquartile range) neutrophil counts (OR =1.60, 95% CI, 1.18–2.17; OR =1.30, 95% CI, 1.03–1.64), C-reactive protein (CRP) (OR =1.49, 95% CI, 1.09–2.05; OR =1.70, 95% CI, 1.25–1.31) and D-dimer (OR =1.37, 95% CI, 1.04–1.81; OR =1.25, 95% CI, 1.02–1.55).

Conclusions: During the COVID-19 pandemic, the priority for clinical practices is to identify people with a high risk of progressing to poor clinical outcomes. We found that advanced age, higher levels of neutrophil counts, CRP and D-dimer were potential predictors for both longer LOS and elevated risk of adverse complications.

Keywords: Coronavirus disease 2019 (COVID-19); risk factors; length of stay; complications

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people globally (1). This disease was later designated coronavirus disease 2019 (COVID-19). Due to the high infectivity of SARS-CoV-2, the number of infections is surging rapidly and many countries have begun to experience outbreaks (2,3).

As the epicenter of the pandemic in the last two months, China has implemented extraordinary measures to meet the challenge of COVID-19 and an increasing number of patients are being cured. However, the prognosis of this highly infectious disease is still not well investigated. Further, no antiviral drugs with definite effects have been identified thus far (4); therefore, the main therapeutic strategy still focuses on symptomatic support. Notably, although most of the patients had nonsevere disease on admission, some of them showed poor treatment efficacy during hospitalization and developed various complications such as electrolyte disturbance, acute respiratory distress syndrome (ARDS) or multiple organ failure. Although several previous studies have introduced the epidemiological and clinical features of patients with COVID-19, they were based on relatively small numbers of patients with relatively severe conditions in the city of Wuhan, and more importantly, factors associated with clinical outcomes have not been well explored (5–7).

The present study included patients admitted to a hospital based in Guangzhou, Guangdong, China, with laboratory-confirmed COVID-19. We aimed to explore factors associated with length of hospital stay (LOS) and development of adverse complications after hospital admission. Most patients included in the present study had nonsevere disease on admission, which is similar to the real-world situation (8). This study may provide new insight into the clinical management of this disease. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jphe-20-74).

Methods

Patients

The present study was a retrospective cohort study. A total of 285 consecutive adult patients (age ≥18 years) with a diagnosis of COVID-19 were recruited at Guangzhou Eighth People's Hospital. The admission dates ranged from January 20 to March 04, 2020. Guangzhou Eighth People's Hospital is one of the designated hospitals for the admission of patients with COVID-19 in Guangzhou, Guangdong, China. The diagnostic criteria of COVID-19 were based on the New Coronavirus Pneumonia Prevention and Control Program (7th edition) (9). Specifically, those who met the following criteria were considered positive: (I) patients with positive SARS-CoV-2 detection by quantitative real-time reverse-transcriptase polymerase-chain-reaction (qRT-PCR) of samples from the respiratory tract; (II) patients with relevant clinical symptoms (fever or respiratory symptoms); and (III) patients with typical changes on chest radiology. Throat swab samples were collected for the detection of SARS-CoV-2 viral nucleic acids by qRT-PCR. qRT-PCR assays were performed according to the guidelines recommended by the World Health Organization (WHO) (10). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional ethics board of Guangzhou Eighth People's Hospital approved the research and granted a waiver for informed consent from the patients in this study.

Data collection

A group of experienced clinicians, epidemiologists and medical students collected information from the electronic medical record system by using a structured data collection form. The collected information included epidemiological, clinical, and outcome data. Two researchers (J.Z.Z. & R.Z.) independently reviewed and analyzed the data, and discrepancies were solved by discussion with a third researcher (F.R.L.).

Routine blood hematologic and biochemical tests to detect complete blood counts, coagulation profiles, renal and liver functioning, creatine kinase, lactate dehydrogenase (LDH), electrolytes, myocardial enzymes, C-reactive protein (CRP), and procalcitonin were carried out when necessary during hospitalization. Chest radiography or computed tomography (CT) were also performed for all inpatients. All laboratory data were obtained from the clinical laboratory of Guangzhou Eighth People's Hospital.

Definitions

Based on the recommendations by the National Health Commission (11), patients were discharged from the hospital once the following conditions were met simultaneously: (I) body temperature remained to normal for more than 3 days; (II) respiratory symptoms improved significantly; (III) acute

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exudative lesions were significantly improved on pulmonary imaging; and (IV) nucleic acid tests of sputum, throat swab and other respiratory samples were negative twice in a row (the sampling time was at least 24 hours apart). The degree of severity of the disease was defined according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) (9). Electrolyte disturbance was defined as an electrolyte concentration that was outside the normal range. ARDS was defined based on the Berlin definition (12). Secondary infection was diagnosed when patients showed clinical symptoms or signs of bacteremia and had positive culture results for a new pathogen in lower respiratory tract specimens or blood samples (5). Acute kidney injury (AKI) was diagnosed based on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (13). Myocardial damage was defined if abnormalities were observed on electrocardiography and echocardiography (5). Other complications were defined mainly according to related examinations and clinicians' consensus after discussion.

Statistical analysis

The main analysis was performed with the data collected on admission, unless otherwise specified. Continuous variables and categorical variables were described by medians (interquartile ranges, IQRs) and frequencies (percentages, %). Differences were tested by using the chi-square test or Fisher's exact test for categorical variables, as appropriate, and the Mann-Whitney U test for continuous variables. To compare the baseline characteristics between groups, patients were stratified based on the median LOS (<18 and ≥18 days) and whether they had developed complications during hospitalization. Binary logistic regression models were performed, with the prolonged LOS (≥18 days) as the outcome, after the exclusion of 1 patient who had died and 4 patients who were still hospitalized. Logistic models were also used to estimate the magnitude of the associations between factors and risk of developing complications. Associations were estimated in terms of per interquartile range increases for continuous variables. All the models were run with adjustment for age (age ≥60 years or not). Variables fulfilling the following criteria were not examined in the regression models: (I) between-group variables that were nonsignificant; and (II) variables with a high risk of bias (e.g., recall bias, reverse causation) such as exposure history, treatment, etc. Sample sizes varied due to missing data.

All statistical analyses were conducted using STATA, version 14 (StataCorp). All P values were 2-tailed, with statistical significance set at α of 0.05.

Results

Epidemiology and clinical features

The median age of the patients was 48 years (IQR 35–62), and 128 (44.9%) patients were male. The median time from illness onset to hospital admission was 3 days (IQR, 2–7), and the median LOS was 18 days (IQR 13–25). Of these patients, 131 (46.0%) had an LOS shorter than 18 days, 90 (31.6%) developed one or more adverse complications, 84 (29.5%) were residents of Wuhan or around; 95 (33.3%) had visited Wuhan or areas around the city and 100 (35.1%) had never been to Wuhan but had contacted with Wuhan residents or other infected patients. Overall, 88 patients (31.4%) had one or more coexisting illnesses. The most commonly self-reported symptoms on admission were fever (67.7%), followed by dry cough (56.0%), expectoration (20.7%), chills (20.4%) and fatigue (13.0%). A total of 261 (95.6%) patients initially had findings of bilateral infiltrates on radiographic imaging; 6 (2.1%) patients were classified as severe on admission. Other baseline characteristics were presented in (*Table 1*).

Patients with longer LOS (LOS ≥18 days) were older, had higher peak temperatures during hospitalization and were more likely to have underlying comorbidities than patients with shorter LOS (<18 days). In addition, patients with longer LOS tended to report dyspnea more often than those with shorter LOS. Patients who developed one or more complications appeared to be older, have longer LOS and have higher degrees of disease severity than patients without any complications. They were also more likely to have comorbidities, including hypertension, cardiovascular disease (CVD) and cancer; and reported dry cough, myalgia, and dyspnea more often than those without complications (*Table 1*).

Laboratory findings

Table 2 summarizes the laboratory findings. Many patients had the following hematologic abnormalities at presentation (only ratios ≥10% were shown): leukopenia [16.6%, white blood cell (WBC) count $<3.5\times10^9$ cells/L], neutropenia (16.2%, neutrophil count $<1.8\times10^9$/L), anemia (36.9%, hemoglobin level <130 g/L), lymphopenia

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Table 1 Baseline clinical characteristics of 285 patients with COVID-19

Characteristics	All patients (n=285)	Length of hospital stay			Complications		
		<18 days (n=131)	≥18 days (n=154)	P value	Yes (n=90)	No (n=195)	P value
Age, y	48 [35–62]	43 [31–57]	53 [41–63]	<0.001	55 [38–66]	33 [45–59]	<0.001
Men	128 (44.9)	51 (38.93)	74 (49.66)	0.071	41 (45.56)	87 (44.62)	0.882
Length of hospital stay, days	18 [13–25]	13 [11–16]	24 [21–28]	<0.001	21 [16–28]	17 [12–23]	<0.001
<18 days	131 (45.96)	–	–	–	30 (22.90)	101 (77.10)	0.004
≥18 days	154 (54.04)	–	–	–	60 (38.96)	94 (61.04)	
Any complications	90 (31.58)	30 (22.90)	58 (38.93)	0.004	–	–	
Duration from illness onset to first admission, days	3 [1.5–7]	3 [1–7]	4 [2–7]	0.663	4 [2–7]	3 [1–7]	0.428
Severity							
Nonsevere	279 (97.89)	130 (99.24)	149 (96.75)	0.625	85 (94.44)	194 (99.49)	0.013
Severe	6 (2.11)	1 (0.76)	5 (3.25)		5 (5.56)	1 (0.51)	
Contact history							
Never been to Wuhan but had contact with Wuhan residents or other infected patients	100 (35.1)	49 (37.4)	51 (33.12)	0.287	28 (31.11)	72 (36.92)	0.552
Recently visited Wuhan or surrounding areas	95 (33.3)	45 (34.35)	50 (32.47)		30 (33.33)	65 (33.33)	
Living in Wuhan or surrounding areas	84 (29.47)	37 (28.24)	47 (30.52)		31 (34.44)	53 (27.18)	
Others	6 (2.11)	0 (0)	6 (3.90)		1 (1.11)	5 (2.56)	
Comorbidities							
Any comorbidity	88 (31.43)	32 (24.43)	55 (35.71)	0.016	42 (46.67)	46 (24.21)	0.000
Hypertension	51 (17.89)	18 (13.74)	33 (21.43)	0.069	27 (30.00)	24 (12.31)	0.000
Diabetes	24 (8.42)	7 (5.34)	16 (10.39)	0.101	11 (12.22)	13 (6.67)	0.116
Liver disease	23 (8.07)	8 (6.11)	14 (9.09)	0.307	11 (12.22)	12 (6.15)	0.080
Lung disease	19 (6.67)	10 (7.63)	9 (5.84)	0.597	8 (8.89)	11 (5.64)	0.307
CVD	18 (6.32)	6 (4.58)	11 (7.14)	0.327	13 (14.44)	5 (2.56)	0.000
Kidney disease	8 (2.81)	3 (2.29)	4 (2.59)	0.571	5 (5.56)	3 (1.54)	0.114
Cancer	3 (1.08)	0 (0)	2 (1.29)	0.499	3 (3.37)	0 (0)	0.032
Symptoms							
Fever	193 (67.7)	84 (64.12)	106 (68.83)	0.210	64 (71.11)	129 (66.15)	0.405
Dry cough	159 (56.0)	72 (55.38)	82 (53.25)	0.953	59 (65.56)	100 (51.55)	0.027
Expectoration	59 (20.7)	23 (17.56)	34 (22.08)	0.275	25 (27.78)	34 (17.44)	0.045
Chills	58 (20.4)	27 (20.61)	30 (19.48)	0.921	23 (25.56)	35 (17.95)	0.138
Fatigue	37 (13.0)	18 (13.74)	19 (12.34)	0.807	16 (17.78)	21 (10.77)	0.102
Myalgia	34 (11.9)	15 (11.45)	19 (12.34)	0.739	16 (17.78)	18 (9.23)	0.039
Dyspnea	30 (10.5)	7 (5.34)	22 (14.29)	0.010	16 (17.78)	14 (7.18)	0.007
Headache	27 (9.5)	14 (10.69)	13 (8.44)	0.579	9 (10.00)	18 (9.23)	0.837
Pharyngalgia	25 (8.8)	11 (8.4)	14 (9.09)	0.770	6 (6.67)	19 (9.74)	0.393
Dizziness	16 (5.6)	7 (5.34)	9 (5.84)	0.505	8 (8.89)	8 (4.10)	0.103
Anorexia	14 (4.9)	7 (5.34)	7 (4.55)	0.805	6 (6.67)	8 (4.10)	0.352
Diarrhea	11 (3.9)	6 (4.58)	5 (3.25)	0.599	5 (5.56)	6 (3.08)	0.332
Nausea	10 (3.5)	4 (3.05)	6 (3.89)	0.755	3 (3.33)	7 (3.59)	0.091
Vomiting	5 (1.8)	3 (2.29)	2 (1.29)	0.668	1 (1.11)	4 (2.05)	0.495
Abdominal pain	3 (1.1)	0 (0)	3 (1.95)	0.250	2 (2.22)	1 (0.51)	0.235

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	All patients (n=285)	Length of hospital stay			Complications		
		<18 days (n=131)	≥18 days (n=154)	P value	Yes (n=90)	No (n=195)	P value
Vital signs							
Temperature, ℃	36.9 [36.6–37.4]	36.9 [36.6–37.2]	36.90 [36.6–37.5]	0.295	36.9 [36.6–37.3]	36.8 [36.5–37.6]	0.383
Peak temperature during hospitalization, ℃	37.7 [37.2–38.5]	37.3 [37.0–37.9]	38.0 [37.3–38.8]	0.000	37.9 [37.2–38.7]	37.6 [37.1–38.4]	0.058
Pulse rate, beats/min	84 [78–92]	84 [78–90]	84 [78–93]	0.763	84 [78–93]	84 [78–92]	0.689
Respiratory rate, breaths/min	20 [18–20]	20 [18–20]	20 [18–20]	0.905	20 [18–20]	20 [18–20]	0.554
Systolic blood pressure, mmHg	125 [117–135]	124 [116–132]	125 [119–139]	0.138	126 [118–146]	124 [117–132]	0.055
Diastolic blood pressure, mmHg	80 [74–87]	80 [75–88]	80 [72–87]	0.564	81.5 [76–89]	80 [74–87]	0.276
Bilateral involvement of CR	261 (95.60)	114 (94.21)	143 (96.62)	0.342	88 (98.88)	173 (94.02)	0.111
Therapy							
Antiviral	222 (77.89)	102 (77.86)	117 (75.9)	0.894	74 (82.22)	148 (75.90)	0.232
Antibiotic	220 (77.19)	95 (72.52)	122 (79.2)	0.061	75 (83.33)	145 (74.36)	0.093
Hormone	59 (20.70)	18 (13.74)	39 (25.3)	0.010	32 (35.56)	27 (13.85)	0.000
Vasoactive drug	7 (2.46)	3 (2.29)	2 (1.29)	0.668	6 (6.67)	1 (0.51)	0.005
Treatment in hospital							
Oxygen inhalation	189 (66.32)	71 (54.20)	113 (73.4)	<0.001	66 (73.33)	123 (63.08)	0.089
Ventilator support	30 (10.53)	3 (2.29)	24 (15.6)	<0.001	23 (256.56)	7 (3.59)	<0.001
Hydrogen and oxygen atomizer	12 (4.21)	1 (0.76)	11 (7.14)	0.006	11 (7.14)	1 (0.76)	0.007
ECMO	3 (1.05)	0 (0)	1 (0.65)	0.532	3 (3.33)	0 (0)	0.031
CRRT	3 (1.05)	0 (0)	1 (0.65)	0.532	3 (3.33)	0 (0)	0.031

Data are presented as the median [interquartile range] or n (%). CVD, cardiovascular disease; CR, chest radiographs; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

(31.7%, lymphocyte count <1.1×10^9 cells/L), hypokalemia (17.3%, potassium <3.3 mmol/L), thrombocytopenia (11.2%, platelet count <125×10^9 cells/L), D-dimerization (83.0%, D-dimer >500 mg/L); prolonged activated partial thromboplastin time (APTT) (68.5%, >37 seconds). Levels of the following enzymes and proteins were elevated: procalcitonin (≥0.1 ng/mL) in 49.3% of patients, LDH (>243 U/L) in 23.0%, aspartate aminotransferase (AST) (>40 U/L) in 12.7%, elevated CRP levels (≥10 mg/L) in 38.4%. Analbuminaemia (albumin <40 g/L) was also observed in 49.2% of the patients. Other analytes were largely within the normal range.

Those with LOS longer than 18 days had higher WBC counts, neutrophil counts, D-dimer, alanine aminotransferase (ALT), AST, creatinine, LDH, CRP; lower platelet counts and, sodium; and longer APTTs than those with LOS shorter than 18 days. Higher D-dimer, ALT, AST, LDH, CRP and platelet counts, albumin, and sodium were observed among those who developed complications, compared with those who did not. Serial monitoring of laboratory measures showed that during hospitalization, patients had longer LOS or those with complications generally experienced significant increases in the incidence of abnormal blood biochemical parameters, compared with those with shorter LOS or those who had no complications (Table S1).

Clinical courses and outcomes

During hospitalization, all patients received either antibiotic therapy, antiviral therapy, hormonal therapy, vasoactive drug therapy, or a combination of the above based on clinical experience. The median time from admission to the development of any complication was 13 days (IRQ 8–21). Twenty (7.0%) patients were admitted to the intensive care unit (ICU), and 3 (1.1%) patients received extracorporeal

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Table 2 Initial laboratory tests result of patients with COVID-19

Laboratory finding	No. of patients tested (%)	Median (IQR)
WBC, $\times10^9$/L	284	4.94 (3.99–6.31)
<3.5	47 (16.55)	3.04 (2.69–3.26)
3.5–9.5	225 (79.23)	5.35 (4.41–6.36)
>9.5	12 (4.23)	11.30 (10.15–15.12)
Neutrophil count, $\times10^9$/L	284	2.97 (2.14–4.00)
<1.8	46 (16.20)	1.50 (1.23–1.66)
1.8–6.3	221 (77.82)	3.16 (2.44–3.98)
>6.3	17 (5.99)	8.02 (6.84–11.75)
Monocytes, $\times10^9$/L	276	0.36 (0.29–0.58)
<0.1	1 (0.36)	0.08 (0.08–0.08)
0.1–0.6	252 (91.30)	0.35 (0.28–0.43)
>0.6	23 (8.33)	0.71 (0.64–0.84)
Hemoglobin, g/L	276	136 (123.5–146)
<130.0	102 (36.92)	119.5 (114.0–125.0)
130.0–175.0	172 (63.32)	143.0 (136.0–150.0)
>175.0	2 (0.72)	180.0 (177.0–183.0)
Lymphocyte count, $\times10^9$/L	284	1.37 (1.0–1.9)
<1.1	90 (31.69)	0.89 (0.74–1.00)
1.1–3.2	188 (66.20)	1.66 (1.36–2.04)
>3.2	6 (2.11)	4.17 (4.00–4.55)
Platelet count, $\times10^9$/L	276	186.5 (150.5–231.5)
<125	31 (11.23)	105.0 (91.0–115.0)
125–350	242 (87.68)	195.5 (163.0–235.0)
>350	3 (1.09)	465.0 (422.0–483.0)
APTT, s	270	39.15 (36.1–42.1)
21–37	85 (31.48)	34.7 (33.5–35.9)
>37	185 (68.52)	40.7 (39.0–43.6)
D-dimer, mg/L	276	1,090 [710–1,570]
0–500	47 (17.03)	290 [1–450]
>500	229 (82.97)	1,220 [890–1,640]
Albumin, g/L	264	40.05 (36.65–42.45)
<40.0	130 (49.24)	36.60 (34.40–38.10)
40.0–55.0	134 (50.76)	42.35 (40.80–44.50)
ALT, U/L	281	20 (14–31.3)
<9	8 (2.85)	7.15 (5.90–8.10)
9–50	247 (87.90)	19.45 (14.00–26.70)
>50	26 (9.25)	76.38 (60.30–101.00)

Table 2 (*continued*)

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Table 2 (*continued*)

Laboratory finding	No. of patients tested (%)	Median (IQR)
AST, U/L	275	19.7 (16.4–27.6)
<15	48 (17.45)	13.00 (11.65–14.05)
15–40	192 (69.82)	20.10 (17.45–25.45)
>40	35 (12.73)	55.00 (46.00–66.70)
Total bilirubin, mmol/L	274	9.58 (6.7–13.75)
<5	34 (12.41)	4.15 (3.53–4.68)
5–21	215 (78.47)	9.86 (7.41–13.09)
>21	25 (9.12)	28.10 (22.80–32.97)
Creatinine, μmol/L	265	60.4 (49–76.6)
<64	147 (55.47)	50.50 (44.30–57.20)
64–104	110 (41.51)	77.00 (71.50–83.60)
>104	8 (3.02)	118.35 (111.55–181.00)
CK, U/L	283	67 [44–104]
<40	48 (16.96)	31.0 (24.5–36.0)
40–200	213 (75.27)	72.0 (54.0–103.0)
>200	22 (7.77)	256.0 (228.0–323.0)
LDH, U/L	265	188 [152–235]
<125	15 (5.66)	115 [112–122]
125–243	189 (71.32)	172 [150–201]
>243	61 (23.02)	305 [283–376]
Procalcitonin, ng/mL	265	0.10 (0.037–30.00)
<0.1	134 (50.57)	0.04 (0.03–0.05)
≥0.1	131 (49.43)	30.00 (0.27–49.60)
Potassium, mmol/L	266	3.6 (3.3–3.89)
<3.3	46 (17.29)	3.13 (3.00–3.20)
3.3–5.0	220 (82.71)	3.70 (3.50–3.90)
Sodium, mmol/L	266	140 [138–142]
<134	11 (4.14)	130 [126–133]
134–143	229 (86.09)	140 [138–141]
>143	26 (9.77)	144 [144–145]
CRP, mg/L	276	5 (5–45.5)
<10	170 (61.59)	5 [5–5]
≥10	106 (38.41)	61.5 [36–88]

Data are presented as the median (interquartile range) or n (%). WBC, white blood cell count; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

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membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT). Eventually, 280 (98.3%) patients were discharged from the hospital and 1 (0.4%) patient died. According to our case definition, 90 (31.6%) patients developed complications during their hospital stay. Electrolyte disturbance was the most common complication (15.1%), followed by liver damage (11.9%), secondary infection (5.3%), and AKI (3.9%). Other concurrent medical conditions included respiratory failure, ARDS, disseminated intravascular coagulation (DIC), shock, myocardial damage, and atrial fibrillation, etc. (Table S2). During hospitalization, many symptoms, such as anorexia, dyspnea, nausea became increasingly prevalent, affecting up to 41.4%, 34.7%, and 25.3% of the patients, respectively (Table S3).

Associations between factors and LOS and adverse complications

Those with longer LOS presented with more complications than those with shorter LOS. Additionally, patients who developed complications during hospitalization tended to have longer LOS than those without complications. We used logistic regression to explore the associations of various factors with LOS and complications. Age-adjusted models revealed that the following factors were linked to both a longer LOS and complications: older age (OR =2.00, 95% CI, 1.18–3.40 for LOS; OR =2.24, 95% CI, 1.32–3.80 for complication), relatively high neutrophil counts (OR =1.60, 95% CI, 1.18–2.17; OR =1.30, 95% CI, 1.03–1.64), CRP (OR =1.49, 95% CI, 1.09–2.05; OR =1.70, 95% CI, 1.25–1.31) and D-dimer (OR =1.37, 95% CI, 1.04–1.81; OR =1.25, 95% CI, 1.02–1.55). Factors such as WBC (OR =1.44; 95% CI, 1.07–1.95) and APTT (OR =1.57; 95% CI, 1.12–2.20) were positively associated with the longer LOS but not with complications. On the other hand, comorbidities (OR =2.33; 95% CI, 1.33–4.10), elevated ALT (OR =1.25; 95% CI, 1.05–1.50), elevated AST (OR =1.49; 95% CI, 1.23–1.82) and elevated LDH (OR =1.39; 95% CI, 1.08–1.79) were significantly associated with the risk of complications but not the longer LOS (*Table 3*).

Discussion

In this retrospective cohort study, we reported the characteristics and factors associated with LOS and complications during hospitalization in patients with COVID-19 at a designated hospital in Guangzhou, Guangdong, China. In our study, a large proportion of patients had abnormal clinical conditions on admission, but most of the included patients had a favorable prognosis. We found that advanced age; relatively high neutrophil counts, CRP and D-dimer levels were associated with both prolonged LOS and elevated risk of adverse complications.

During the outbreak of COVID-19, medical resources have been exhausted in many countries. Understanding hospital LOS and factors related to LOS may provide important information to inform clinicians about patient selection, the development of strategies to reduce hospital LOS, and how to ultimately reduce resource utilization. Our study recorded a longer LOS (18 days) than some other studies in Wuhan (14,15), where the average LOS for COVID-19 patients was nearly 12 days. These differences may be because study populations in Wuhan were not representative of all cases diagnosed and treated in China. Many patients may have been transferred late in their illness to hospitals during the initial outbreak. Additionally, it is possible that a large proportion of patients in the above studies were still hospitalized at the time of publication and the shortage of medical resources led to some patients being discharged in advance to make room the new case.

So far, there have been no antiviral drugs with definite effects identified, and thus the main therapeutic strategy for COVID-19 still focuses on symptomatic support. Unlike previous studies that recorded many cases of ARDS and respiratory failure (15,16), the most common complications in this study were electrolyte disturbances, followed by liver damage, secondary infection, AKI. Electrolyte disturbances, such as hypokalemia can potentially be fatal but is amenable by relatively simple interventions. The frequent observance of electrolyte disturbances has not been reported in previous studies of COVID-19, but it is in line with the results of a few studies of Ebola patients (17). However, as electrolyte disturbance complication could be commonly observed in critically ill patients hospitalized for long periods (18), we could hardly confirm it a distinctive characteristic of patients with COVID-19. Additionally, renal dysfunction, pancreatitis and sepsis could contribute to this disorder (19). Multiple organ injury is common in patients with COVID-19. Our data showed that biomarkers of impaired organ function such as ALT, AST and LDH were elevated on admission in those patients with complications. The exact cause of organ injury remains unknown, but both the hyperinflammation and viral evasion are likely involved (20,21).

In the present study, older age appeared to be associated

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Table 3 Factors significantly associated with prolonged hospital stay and complications

Variables	Length of hospital stay		Complications	
	OR* (95% CI)	P value	OR* (95% CI)	P value
Demographics and clinical characteristics				
Older adults (*vs.* young adults <60 y)	2.00 (1.18–3.40)	0.011	2.24 (1.32–3.80)	0.003
Men (*vs.* women)	1.62 (1.00–2.62)	0.052	1.07 (0.64–1.79)	0.784
Any comorbidity	1.56 (0.89–2.71)	0.118	2.33 (1.33–4.10)	0.003
Severe (*vs.* nonsevere)	1.99 (2320–19.99)	0.559	8.08 (0.91–72.12)	0.061
Laboratory findings				
WBC, $\times10^9$/L	1.44 (1.07–1.95)	0.017	1.25 (0.97–1.60)	0.081
Neutrophil count, $\times10^9$/L	1.60 (1.18–2.17)	0.002	1.30 (1.03–1.64)	0.025
Monocytes, $\times10^9$/L	1.27 (0.96–1.67)	0.091	0.78 (0.58–1.04)	0.089
Platelet count, $\times10^9$/L	0.75 (0.55–1.04)	0.083	0.70 (0.49–1.00)	0.053
APTT, s	1.57 (1.12–2.20)	0.009	1.25 (0.93–1.68)	0.142
Albumin, g/L	0.78 (0.55–1.10)	0.158	0.40 (0.27–0.60)	0.000
ALT, U/L	1.16 (0.96–1.39	0.118	1.25 (1.05–1.50)	0.013
AST, U/L	1.17 (0.98–1.40)	0.075	1.49 (1.23–1.82)	0.000
Sodium, mmol/L	1.02 (0.90–1.15)	0.805	0.98 (0.87–1.10)	0.740
LDH, U/L	1.23 (0.94–1.59)	0.129	1.39 (1.08–1.79)	0.010
CRP, mg/L	1.49 (1.09–2.05)	0.013	1.70 (1.25–2.31)	0.001
D-dimer, mg/L	1.37 (1.04–1.81)	0.023	1.25 (1.02–1.55)	0.035

*, adjusted for age. WBC, white blood cell count; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

with prolonged hospitalization and an increased risk of developing complications. Indeed, it is well recognized that older age is an important predictor of adverse outcomes, and previous studies of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 confirmed these findings (15,22,23). Older age may be a proxy for a deficiency in the control of viral replication and less-robust immune responses (24), potentially leading to adverse clinical outcomes (25). Prior studies have also found that comorbid diseases were the most common reasons for continued hospitalization among patients with community-acquired pneumonia (26). The poor health status of those with comorbid illnesses may lead to complications and additional treatment, leading to prolonged hospitalization.

The pathogenesis of highly pathogenic SARS-CoV-2 is still not completely understood, but virally driven hyperinflammation are thought to play important roles in disease severity (27,28). In this study, we found that increased levels of several inflammation-related factors, such as neutrophil and CRP were associated with adverse outcomes. Neutrophils are the main source of chemokines and cytokines. It has been reported that increased levels of neutrophilia were common in both the peripheral blood and lungs of patients with SARS and MERS (29–31). These abnormalities suggest that increased levels of neutrophilia may be a common characteristics of coronavirus infection. The monitor on this index should be intensified during hospitalization since various of infections are commonly related to this condition and may consequently lead to poor outcome. Moreover, clinical analysis on it should be more prudent and comprehensive. (e.g., taking the patients' status of use of corticosteroids into account owing to its confounding effects on neutrophilia). CRP is an acute-phase protein that increases with infection during virally driven hyperinflammation. A previous study demonstrated that the

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detection rate of respiratory viruses was strongly associated with CRP levels (32). As the host inflammatory response can be measured by CRP levels, CRP could also be used in clinical practice to guide viral testing and directed antiviral therapy where available (33).

Elevated D-dimer, as a degradation product of fibrinogen breakdown, could be a marker of impaired coagulation function. Therefore, the higher risk of thromboembolic events (demonstrated by high D-dimer levels and APTT) in patients with COVID-19 could not be ignored. Further evidence is urgently needed regarding the coagulation pathways that related to the SARS-CoV-2 infection. It's notable that secondary infection was a common complication among patients in current cohort. The rate is similar to those in the previous report (5). One possible explanation is that the amount or time of antibiotics is excessive, which may lead to the imbalance of normal flora in human body and in turn secondary infection. Furthermore, invasive mechanical ventilation may increase the risk of secondary infection which deserved more clinical attention.

Strengths and limitations

This study analyzed a relatively large sample size to describe the characteristics and determinants of LOS and complications in a cohort of patients with COVID-19 at a designated hospital outside of Wuhan. The results from our study should be interpreted with caution because of potential bias and residual confounding due to its retrospective nature. Also, data were collected from case records and thus not systematic. Selection bias should also be considered when exploring factors that are related to clinical outcomes.

Conclusions

During the COVID-19 pandemic, the priority for clinical practices is to identify people with a high risk of progressing to poor clinical outcomes. We found that advanced age, higher levels of neutrophil counts, D-dimer and CRP were potential predictors for both longer LOS and elevated risk of adverse complications.

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Footnote

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Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional ethics board of Guangzhou Eighth People's Hospital approved the research and granted a waiver for informed consent from the patients in this study.

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Supplementary

Table S1 Laboratory findings of patients with COVID-19 during hospitalization

Characteristics	All patients (n=285)	Length of hospital stay			Complications		
		<18 days (n=131)	≥18 days (n=154)	P value	Yes (n=90)	No (n=195)	P value
At admission							
WBC, $\times10^9$/L	4.94 (3.99–6.31)	4.67 (3.90–6.00)	5.17 (4.11–6.53)	0.045	5.15 (3.90–6.53)	4.86 (4.00–6.24)	0.463
Neutrophil count, $\times10^9$/L	2.97 (2.14–4.00)	2.74 (2.05–3.60)	3.24 (2.19–4.40)	0.008	3.28 (2.08–4.66)	2.90 (2.15–3.89)	0.186
Monocytes, $\times10^9$/L	0.36 (0.29–0.58)	0.35 (0.28–0.44)	0.36 (0.29–0.48)	0.279	0.34 (0.27–0.41)	0.36 (0.30–0.47)	0.040
Haemoglobin, g/L	136 (123.5–146)	133.0 (121.0–145.0)	138.0 (125.0–146.0)	0.064	136.5 (125.5–145.5)	135.0 (123.0–146.0)	0.655
Lymphocyte count, $\times10^9$/L	1.37 (1.0–1.9)	1.45 (1.04–2.00)	1.35 (0.99–1.79)	0.089	1.29 (0.90–1.87)	1.43 (1.05–1.91)	0.067
Platelet count, $\times10^9$/L	186.5 (150.5–231.5)	193.0 (163.0–241.0)	176.0 (142.0–228.0)	0.021	175.5 (137.0–219.0)	188.0 (159.0–238.5)	0.033
APTT, s	39.15 (36.1–42.1)	38.1 (35.9–40.8)	39.9 (36.5–43.2)	0.003	39.6 (36.4–43.0)	39.0 (35.9–41.2)	0.141
D-dimer, mg/L	1090 (710–1570)	990 (640–1400)	1150 (740–1640)	0.014	1240 (780–1990)	1050 (660–1460)	0.006
Albumin, g/L	40.05 (36.65–42.45)	40.4 (37.4–42.9)	39.3 (36.0–42.2)	0.068	37.4 (34.7–40.5)	40.6 (37.7–43.2)	<0.001
ALT, U/L	20 (14–31.3)	17.70 (13.00–27.76)	21.60 (15.20–34.95)	0.024	22.65 (16.00–37.55)	19.60 (13.60–27.76)	0.014
AST, U/L	19.7 (16.4–27.6)	18.25 (15.10–24.00)	20.90 (17.30–29.00)	0.002	25.80 (18.40–33.30)	18.45 (15.85–23.15)	<0.001
Total bilirubin, mmol/L	9.58 (6.7–13.75)	10.22 (6.65–13.82)	9.26 (6.97–13.56)	0.908	10.14 (7.37–14.05)	9.39 (6.65–13.54)	0.364
Potassium, mmol/L	3.6 (3.3–3.89)	3.60 (3.34–3.80)	3.60 (3.30–3.90)	0.884	3.5 (3.2–3.9)	3.6 (3.4–3.8)	0.206
Sodium, mmol/L	140 (138–142)	141.0 (139.0–142.0)	139.0 (138.0–141.0)	<0.001	139.0 (136.3–141.0)	140.0 (139.0–142.0)	0.007
Creatinine, μmol/L	60.4 (49–76.6)	57.50 (46.80–74.60)	61.90 (51.55–77.45)	0.055	60365 (48.55–76.70)	60.40 (50.80–75.70)	0.576
CK, U/L	67 (44–104)	66.5 (45.0–92.0)	67.0 (44.0–117.0)	0.218	64.5 (44.0–128.0)	68.0 (45.0–101.1)	0.719
LDH, U/L	188 (152–235)	173.0 (144.0–223.0)	198.0 (157.0–249.0)	0.005	214.5 (158.0–292.0)	179.0 (149.0–224.0)	0.001
Procalcitonin, ng/mL	0.098 (0.0374–30)	0.10 (0.04–30.00)	0.09 (0.04–28.90)	0.446	0.13 (0.04–36.40)	0.07 (0.04–26.80)	0.129
CRP, mg/L	5 (5–45.5)	5.0 (5.0–17.0)	7.0 (5.0–57.0)	<0.001	17.0 (5.0–78.0)	5.0 (5.0–31.5)	<0.001
On serial assessment							
Nadir WBC, $\times10^9$/L	4.48 (3.52–5.42)	4.36 (3.48–5.44)	4.49 (3.57–5.35)	0.941	4.49 (3.36–5.60)	4.47 (3.67–5.34)	0.682
Nadir neutrophil count, $\times10^9$/L	2.36 (1.78–3.09)	2.36 (1.71–3.03)	2.33 (1.90–3.12)	0.407	2.52 (1.83–3.41)	2.33 (1.78–2.99)	0.180
Nadir lymphocyte count, $\times10^9$/L	1.27 (0.92–1.67)	1.37 (1.02–1.93)	1.14 (0.87–1.56)	<0.001	1.10 (0.81–1.58)	1.33 (0.99–1.72)	0.002
Peak neutrophil count, $\times10^9$/L	3.70 (2.90–5.05)	3.51 (2.89–4.46)	4.00 (3.06–5.64)	0.003	4.23 (3.12–6.55)	3.56 (2.82–4.60)	0.001
Peak monocytes, $\times10^9$/L	0.44 (0.37–0.55)	0.41 (0.35–0.49)	0.46 (0.38–0.57)	0.001	0.44 (0.38–0.56)	0.44 (0.36–0.54)	0.406
Peak D–dimer, 500 mg/L	1220 (820–1850)	1090 (720–1460)	1480 (1010–1990)	<0.001	1460 (910–2270)	1180 (780–1740)	0.025
Peak ALT, U/L	28.15 (17.30–44.00)	23.0 (16.0–39.0)	35.0 (21.7–56.3)	<0.001	38.70 (21.60–70.90)	25.55 (16.45–39.40)	<0.001
Peak AST, U/L	22.55 (17.90–32.25)	20.1 (16.6–27.4)	25.0 (19.1–37.8)	<0.001	29.45 (20.45–52.35)	20.90 (17.10–26.85)	<0.001
Peak creatinine, μmol/L	68.5 (56.6–82.1)	65.40 (52.45–79.70)	70.30 (58.45–82.35)	0.034	70.20 (55.60–81.90)	67.90 (57.50–82.70)	0.703
Peak CK, U/L	70.5 (49.0–106.0)	67.0 (47.0–93.0)	74.5 (51.5–120.5)	0.039	69.0 (47.0–129.0)	71.5 (51.0–103.5)	0.566
Peak LDH, U/L	210 (166–279)	188 (153–239)	223 (178–298)	<0.001	236.5 (185.0–324.0)	198.0 (158.0–241.0)	<0.001
Peak CRP, mg/L	5.00 (5.00–33.24)	5.00 (5.00–17.70)	20.49 (5.00–40.71)	<0.001	22.47 (5.00–50.01)	5.00 (5.00–25.15)	<0.001

WBC, white blood cell count; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

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Table S2 Clinical outcomes and adverse complications during hospitalization

Variables	No. (%)	Time from admission to clinical outcomes or adverse complications, days
Clinical outcomes		
Discharge	280 (98.25)	18 (13–24)
ICU admission	20 (7.02)	0 (0–4.5)
Death	1 (0.35)	33
Adverse complications		
Any complication	90 (31.58)	13 (8–21)
Electrolyte disturbances	43 (15.09)	5 (1–8)
Liver damage	34 (11.93)	8 (3–13)
Secondary infection	15 (5.26)	5 (2–8)
Acute kidney injury	11 (3.86)	7 (2–10)
Respiratory failure	9 (3.16)	7 (5–10)
Myocardial damage	9 (3.16)	5 (1–13)
Arrhythmia / Atrial fibrillation	9 (3.16)	8 (5–10)
MODS	4 (1.40)	11 (3–26)
ARDS	3 (1.05)	17 (16–34)
VAP	3 (1.05)	34 (31–37)
Shock	3 (1.05)	17 (12–19)
Gastrointestinal hemorrhage	3 (1.05)	1 (1–10)
Acute kidney failure	2 (0.70)	16.5 (15–18)
Depression	2 (0.70)	12.5 (0–25)
DIC	1 (0.35)	26 (26–26)
Pulmonary embolism	1 (0.35)	18 (18–18)
Heart failure	1 (0.35)	12 (12–12)

Data are presented as the median (interquartile range) or n (%). MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; VAP, ventilator associated pneumonia; DIC, disseminated intravascular coagulation.

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Table S3 Symptoms during hospitalization

Symptoms	No. (%)
Fever	221 (77.5)
Dry cough	218 (76.5)
Expectoration	130 (45.6)
Anorexia	118 (41.4)
Dyspnea	99 (34.7)
Fatigue	79 (27.7)
Chills	73 (25.6)
Nausea	72 (25.3)
Myalgia	39 (13.7)
Headache	38 (13.3)
Pharyngalgia	38 (13.3)
Vomiting	38 (13.3)
Dizziness	36 (12.6)
Diarrhea	35 (12.3)
Abdominal pain	18 (6.3)

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