Original article

Risk factors for disease progression in patients with mild to moderate coronavirus disease 2019—a multi-centre observational study

Y. Cen [1, 2, †], X. Chen [3, 4, †], Y. Shen [5, †], X.-H. Zhang [2, 6, †], Y. Lei [2, 3], C. Xu [7], W.-R. Jiang [4, 8], H.-T. Xu [4, 9], Y. Chen [2, 10], J. Zhu [10], L.-L. Zhang [10, **], Y.-H. Liu [4, 10, *]

[1)] *Department of Orthopedics, Daping Hospital, Army Medical University, Chongqing, China*
[2)] *Department of Infectious Disease, Huoshenshan Hospital, Wuhan, China*
[3)] *Department of Anaesthesiology, Daping Hospital, Army Medical University, Chongqing, China*
[4)] *Department of Critical Care Medicine, Huoshenshan Hospital, Wuhan, China*
[5)] *Department of Respiratory Disease, Daping Hospital, Army Medical University, Chongqing, China*
[6)] *Department of General Surgery, Daping Hospital, Army Medical University, Chongqing, China*
[7)] *Department of Oncology, General Hospital of the Central Theatre Command of the People's Liberation Army, Wuhan, China*
[8)] *Department of Respiratory Disease, Xijing Hospital, Fourth Military Medical University, Xi'an, China*
[9)] *Department of Anaesthesiology, Changzheng Hospital, Second Military Medical University, Shanghai, China*
[10)] *Department of Neurology and Centre for Clinical Neuroscience, Daping Hospital, Army Medical University, Chongqing, China*

A R T I C L E   I N F O

A B S T R A C T

Objectives: Since December 2019, the novel coronavirus disease 2019 (COVID-19) that emerged in Wuhan city has spread rapidly around the world. The risk for poor outcome dramatically increases once a patient progresses to the severe or critical stage. The present study aims to investigate the risk factors for disease progression in individuals with mild to moderate COVID-19.
Methods: We conducted a cohort study that included 1007 individuals with mild to moderate COVID-19 from three hospitals in Wuhan. Clinical characteristics and baseline laboratory findings were collected. Patients were followed up for 28 days for observation of disease progression. The end point was the progression to a more severe disease stage.
Results: During a follow up of 28 days, 720 patients (71.50%) had recovered or were symptomatically stable, 222 patients (22.05%) had progressed to severe disease, 22 patients (2.18%) had progressed to the critically ill stage and 43 patients (4.27%) had died. Multivariate Cox proportional hazards models identified that increased age (hazard ratio (HR) 2.56, 95% CI 1.97−3.33), male sex (HR 1.79, 95% CI 1.41 −2.28), presence of hypertension (HR 1.44, 95% CI 1.11−1.88), diabetes (HR 1.82, 95% CI 1.35−2.44), chronic obstructive pulmonary disease (HR 2.01, 95% CI 1.38−2.93) and coronary artery disease (HR 1.83, 95% CI 1.26−2.66) were risk factors for disease progression. History of smoking was protective against disease progression (HR 0.56, 95% CI 0.34−0.91). Elevated procalcitonin (HR 1.72, 95% CI 1.02−2.90), urea nitrogen (HR 1.72, 95% CI 1.21−2.43), α-hydroxybutyrate dehydrogenase (HR 3.02, 95% CI 1.26−7.21) and D-dimer (HR 2.01, 95% CI 1.12−3.58) at baseline were also associated with risk for disease progression.
Conclusions: This study identified a panel of risk factors for disease progression in individuals with mild to moderate COVID-19. **Y. Cen, Clin Microbiol Infect 2020;26:1242**

Introduction

As of 10 May 2020, 4 118 326 confirmed cases of coronavirus disease 2019 (COVID-19) have been reported globally, with 280 718 deaths. The clinical spectrum of COVID-19 pneumonia ranges from mild to critically ill patients [1]. According to a recent report, the proportions of of patients being admitted to intensive care units

* Corresponding author. Y.-H. Liu, Changjiang Branch Road 10, Yu Zhong district, Chongqing, China.
** Corresponding author. L.-L. Zhang, Changjiang Branch Road 10, Yu Zhong district, Chongqing, China.
E-mail addresses: zll19731220@126.com (L.-L. Zhang), liuyuhui07-8909@163.com (Y.-H. Liu).
† Y. Cen, X. Chen, Y. Shen and X.-H. Zhang contributed equally to this work.

(ICU), requiring invasive ventilation and dying were 5.00%, 2.18% and 1.36%, respectively [2]. The risk for poor outcome dramatically increases once patients advance to the severe or critical stage [3]. The identification of those COVID-19 patients at risk for disease progression is necessary for early assessment and timely intervention to improve prognosis.

People with co-morbidities are at risk for COVID-19 pneumonia Furthermore, blood biomarkers differ significantly among COVID-19 patients with different disease severities [2]. A recent study indicated that the dynamic change of circulating leucocyte percentage is predictive for the outcome of individuals with COVID-19 [4]. However, strategies for monitoring the risk of disease progression are limited. Therefore, we conducted a follow-up study to investigate the association of clinical characteristics and laboratory findings with the prognosis of COVID-19.

Methods

Study design and participants

This follow-up study included three cohorts of inpatients from Huoshenshan Hospital, General Hospital of the Central Theatre Command of the People's Liberation Army, and mobile cabin hospitals in Wuhan, China. As of 10 February 2020, inpatients who were diagnosed with COVID-19 according to WHO interim guidance [5] were screened. Patients diagnosed with severe or critical COVID-19 at admission were excluded. A total of 1007 individuals with mild or moderate COVID-19 at admission were consecutively recruited in the present study. Cases of COVID-19 were defined as having positive results to high-throughput sequencing or real-time RT-PCR for nasal and pharyngeal swab specimens. Only laboratory-confirmed cases were included in the present study.

Patients recruited to the present study were followed up for 28 days after admission. The end point was conversion from mild or moderate stage to severe or critical stage, or death. The study was approved by the institutional board of each participating site. The participants' written consents were waived in light of reducing exposure possibility and the urgent need to collect clinical data. However, verbal consent from each patient or its legal relatives was obtained.

Clinical assessment

All cases were diagnosed and classified according to Interim Guidelines for COVID-19 of China (6th edition) provided by the National Health Commission of China. Clinical manifestations consist of four categories, mild, moderate, severe and critical. Mild cases were defined as: (a) mild symptoms and (b) no abnormity on chest CT. Moderate cases were defined as: (a) mild symptoms and (b) abnormalities on chest CT. Severe cases were defined as either: (a) respiratory rate >30 breaths/min, or (ii) oxygen saturation ≤93%, or (iii) Pao_2/Fio_2 ratio ≤300 mmHg. Critical cases were defined as including one criterion as follows: shock, respiratory failure requiring mechanical ventilation, organ failure requiring admission to ICU. The recruited patients received standard medication following the Interim Guidelines for COVID-19 of China (6th edition). Notably, as all participants recruited were at the mild to moderate stage at baseline, specific medications, such as mechanical ventilation, high-flow oxygen therapy, glucocorticoid therapy and immunoglobulin therapy, were given at the time of disease progression. However, anti-viral therapy was given at admission. Currently, no anti-viral drug has shown definite efficacy for COVID-19. Therefore, selection of anti-viral drug was based on clinician experience and previous studies [6]. Four classical anti-viral drugs, arbidol, kaletra, oseltamivir and ribavirin, were used. The Chinese

drug *Lianhua Qingwen* capsules, which were suggested to be potentially effective in the treatment of COVID-19 [7] were also used. Anti-bacterial therapy was given once disease was combined with bacterial infection.

Data sources

The baseline characteristics, clinical symptoms, chronic co-morbidities and laboratory findings were extracted from the electronic medical records. Chest CT was conducted before or after admission. Laboratory assessments included blood count, blood chemistry, liver and renal function, D-dimer, C-reactive protein, procalcitonin, lactate dehydrogenase and α-hydroxybutyrate dehydrogenase (α-HBDH). Methods for laboratory confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been described by others [8]. SARS-CoV-2 RNA was detected by local Centers for Disease Control and Prevention, local health institutions and Huoshenshan Hospital and General Hospital of the Central Theatre Command of the People's Liberation Army.

All medical records of the participants were copied and sent to the data processing centre of Daping Hospital, Army Military Medical University. A team of experienced respiratory clinicians abstracted and reviewed the data. Data were entered into a computerized database and cross-checked. The mobile cabin hospitals serve as alternative hospitals to treat individuals with mild COVID-19. Patients admitted to these hospitals were transferred from other medical centres once SARS-CoV-2 infection was confirmed by RT-PCR. Laboratory assessments were not available in mobile cabin hospitals. Therefore, in the analysis of laboratory findings, we did not include patients from mobile cabin hospitals.

Statistical analysis

Continuous variables were expressed as medians (interquartile ranges). Categorical variables were summarized as the counts and percentages in each category. Wilcoxon rank-sum tests were applied to continuous variables, chi-square tests and Fisher's exact tests were used for categorical variables as appropriate. Disease progression was defined as the progression from mild or moderate stage to a more severe disease stage. Comparisons between groups of time-to-event data were made using the Cox proportional hazards model. We first fitted univariate models with a single candidate variable one at a time. The statistically significant risk factors were included in the final multivariate Cox proportional hazards model. The first model included increased age, male sex, smoking history and co-morbidities as candidate risk factors. The second model included increased age, male sex and blood biomarkers that were differential between groups as candidate risk factors. Disease progression and mechanical ventilation were set as dependent variable. The sub-distribution hazards ratio (HR) along with the 95% CI were reported. All analyses were conducted with R software version 3.6.2 (R Foundation for Statistical Computing).

Results

Demographics and baseline biomarkers

This study consecutively recruited 1007 individuals with mild to moderate COVID-19 in three designated medical centres in Wuhan, China. Among these patients, 720 (71.50%) recovered or became symptomatically stable (stable group), 222 (22.05%) progressed to severe disease (severe group), 22 (2.18%) progressed to become critically ill but remained alive (critical group), 43 (4.27%) had progressed to the critically ill stage but had died (deceased group) during a 28-day follow up. The severe group, critical group and

deceased group were collectively classified as the progression group.

The demographic and baseline clinical characteristics are shown in Table 1. The median ages of the stable, severe, critical and deceased groups were 69 (63–75), 68 (62–74), 67 (63–72) and 72 (67–78) years, respectively (p < 0.001). There were 319 (44.3%), 131 (59.0%), 12 (54.5%) and 31 (72.1%) men in the stable, severe, critical and deceased groups, respectively (p < 0.001). There was no significant difference in the onset of symptoms between the stable and progression groups. The frequencies of co-existing disorders, including hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary artery disease, chronic kidney disease and cerebral vascular disease were higher in the progression group than in the stable group. Moreover, the progression group had a slightly lower proportion of smokers than the stable group, although no significance was achieved (p 0.080). The progression group had a significantly higher proportion of patients who received invasive ventilation (p < 0.001), non-invasive

Table 1
Clinical characteristics of patients with COVID-19

Variables	All patients (n = 1007)	Stable (n = 720)	Progression			p value (stable versus progression)
			Severe (n = 222)	Critical (n = 22)	Deceased (n = 43)	
Age (years), median (IQR)	61 (49–68)	69 (63–75)	68 (62–74)	67 (63–72)	72 (67–78)	<0.001
0–15	5 (0.5)	5 (0.7)	0	0	0	/
15–49	256 (25.4)	238 (33.1)	17 (7.7)	0	1 (2.3)	<0.001
50–64	362 (36.0)	286 (39.7)	61 (27.5)	7 (31.8)	8 (18.6)	<0.001
≥65	384 (38.1)	191 (26.5)	144 (64.9)	15 (68.2)	34 (79.1)	<0.001
Male, n (%)	493 (49.0)	319 (44.3)	131 (59.0)	12 (54.5)	31 (72.1)	<0.001
Symptoms onset, n (%)						
Fever	753 (74.8)	546 (75.8)	161 (72.5)	11 (50.0)	35 (81.4)	0.221
Cough	653 (64.8)	470 (65.3)	150 (67.6)	14 (63.6)	19 (44.2)	0.649
Fatigue	396 (39.3)	272 (37.8)	93 (41.9)	9 (40.1)	22 (51.2)	0.111
Shortness of breath	363 (36.0)	245 (34.0)	92 (41.4)	7 (31.8)	19 (44.2)	0.034
Anorexia	46 (4.6)	28 (3.9)	15 (6.8)	2 (9.1)	1 (2.3)	0.102
Diarrhoea	46 (4.6)	32 (4.4)	12 (5.4)	0	2 (4.7)	0.766
Sputum production	30 (3.0)	20 (2.8)	10 (4.5)	0	0	0.552
Sore throat	25 (2.5)	21 (2.9)	4 (1.8)	0	0	0.161
Mylgia or arthralgia	24 (2.4)	15 (2.1)	9 (4.1)	0	0	0.323
Headache	14 (1.4)	12 (1.7)	2 (0.9)	0	1 (2.3)	0.235
Nausea or vomiting	13 (1.3)	9 (1.3)	3 (1.4)	0	1 (2.3)	0.855
Dizziness	11 (1.1)	6 (0.7)	4 (1.8)	1 (4.5)	0	0.210
Coexisting disorder, n (%)						
Any	364 (36.1)	195 (27.1)	128 (57.7)	15 (68.2)	26 (60.5)	<0.001
Hypertension	270 (26.8)	145 (20.1)	93 (41.9)	12 (54.5)	20 (46.5)	<0.001
Diabetes	119 (11.8)	51 (7.1)	54 (24.3)	2 (9.1)	12 (27.9)	<0.001
COPD	46 (4.6)	14 (1.9)	25 (11.3)	3 (13.6)	4 (9.3)	<0.001
Coronary heart disease	65 (6.5)	31 (4.3)	20 (9.0)	4 (18.2)	10 (23.3)	<0.001
Chronic renal disease	14 (1.4)	6 (0.8)	6 (2.7)	0	2 (4.7)	0.017
Cerebrovascular disease	25 (2.5)	11 (1.5)	9 (4.1)	2 (9.1)	3 (7.0)	0.002
Hepatitis B infection	9 (0.9)	8 (1.1)	1 (0.5)	0	0	0.430
Smoking history, n (%)	88 (8.7)	70 (9.7)	16 (7.2)	1 (4.5)	1 (2.3)	0.080
Treatment						
Invasive ventilation						
n (%)	51 (5.1)	0	1 (0.5)	7 (31.8)	43 (100.0)	<0.001
Duration (days)	7.0 (4.0–13.0)	NA	3.0 (3.0–3.0)	6.0 (6.0–7.0)	8.0 (4.0–13.0)	NA
Non-invasive ventilation						
n (%)	54 (5.4)	0	0	11 (50.0)	43 (100.0)	<0.001
Duration (days)	3.0 (2.0–4.0)	NA	NA	4.0 (3.0–5.0)	2.0 (2.0–3.0)	NA
High-flow oxygen therapy						
n (%)	189 (18.8)	0	136 (61.3)	21 (95.5)	32 (74.4)	<0.001
Duration (days)	7.0 (4.0–10.0)	NA	8.0 (6.0–10.0)	6.0 (3.5–9.0)	3.0 (2.0–3.0)	NA
Glucocorticoid therapy						
n (%)	241 (23.9)	72 (10.0)	120 (54.1)	19 (86.4)	30 (69.8)	<0.001
Duration (days)	3.0 (3.0–5.0)	4.5 (3.0–6.0)	3.0 (3.0–4.0)	5.0 (5.0–7.0)	4.0 (2.5–4.0)	<0.001
Immunoglobulin therapy						
n (%)	71 (7.1)	5 (0.7)	18 (8.1)	15 (68.2)	33 (76.7)	<0.001
Duration (days)	3.0 (3.0–5.0)	3.0 (3.0–5.0)	4.5 (3.0–5.0)	3.0 (3.0–3.0)	4.0 (3.0–5.0)	0.317
Anti-viral therapy						
n (%)	795 (78.9)	527 (73.2)	213 (95.9)	22 (100.0)	33 (76.7)	<0.001
Duration (days)	9.0 (7.0–12.0)	8.0 (7.0–11.0)	11.0 (9.0–12.0)	11.0 (8.0–11.3)	6.0 (3.0–9.0)	<0.001
Anti-viral drug						
Lianhua Qingwen	651 (64.6)	462 (64.2)	156 (70.3)	13 (59.1)	20 (46.5)	0.613
Arbidol	499 (49.6)	357 (49.6)	114 (51.4)	14 (63.6)	14 (32.6)	0.976
Kaletra	72 (7.1)	46 (6.4)	22 (9.9)	0	4 (9.3)	0.138
Oseltamivir	7 (0.7)	5 (0.7)	0	0	2 (4.7)	1.000
Ribavirin	13 (1.3)	10 (1.4)	0	0	3 (7.0)	0.899
Anti-bacterial therapy						
n (%)	288 (28.6)	80 (11.1)	154 (69.4)	22 (100.0)	32 (74.4)	<0.001
Duration (days)	5.0 (3.0–6.0)	3.0 (3.0–5.0)	5.0 (4.0–5.0)	6.0 (6.0–7.0)	6.0 (5.0–7.0)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range. Data are median (IQR), n (%), where n is the total number of patients with available data. p values comparing groups are from χ^2 test, Fisher's exact test, or Mann–Whitney U test.

ventilation (p < 0.001), high-flow oxygen therapy (p < 0.001), immunoglobulin therapy (p < 0.001), anti-viral therapy (p < 0.001) and anti-bacterial therapy (p < 0.001). There was no significant difference in the selection of anti-viral drugs (Lianhua Qingwen capsules: p 0.613; Arbidol: p 0.976; Kaletra: p 0.138; Oseltamivir: p 1.000; Ribavirin: p 0.899) between the groups.

Furthermore, patients in the progression group had significantly different baseline profiles of laboratory findings in comparison with the stable group. Specifically, lymphopenia, leucocytosis, decreased platelet count or haemoglobin, increased C-reactive protein, pro-calcitonin, aspartate aminotransferase, creatine, urea nitrogen, lactate dehydrogenase, α-HBDH and D-dimer were more frequent in the progression group in comparison with those in the stable group (Table 2).

Factors affecting the disease progression

Disease progression was defined as progression to the severe or critical disease stage, or death. It was found that age over 65 (HR 2.56, 95% CI 1.97−3.33), male sex (HR 1.79, 95% CI 1.41−2.28), presence of hypertension (HR 1.44, 95% CI 1.11−1.88), diabetes mellitus (HR 1.82, 95% CI 1.35−2.44), COPD (HR 2.01, 95% CI 1.38−2.93) and coronary artery disease (HR 1.83, 95% CI 1.26−2.66) were independent risk factors for disease progression. Interestingly, history of smoking was found to be a protective factor against disease progression (HR 0.56, 95% CI 0.34−0.91). Anti-viral therapy had no significant impact on the outcome of the disease, although the duration of anti-viral therapy seemed to be positively associated with disease progression (HR 3.19, 95% CI 2.33−4.38) (Table 3). Similarly, age over 65 (HR 16.62, 95% CI 7.94−34.81), male sex (HR 2.55, 95% CI 1.44−4.50), presence of COPD (HR 3.20, 95% CI 1.47−6.98) and coronary artery disease (HR 2.36, 95% CI 1.21−4.61) were independent risk factors for mechanical ventilation. Anti-viral therapy had no significant impact on the mechanical ventilation.

Table 3
Cox regression analysis of association between clinical characteristics and disease progression in patients with COVID-19

Variables	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, ≥65 years	4.308 (3.364−5.516)	2.563 (1.973−3.330)
Sex, male	1.722 (1.359−2.182)	1.793 (1.410−2.280)
Smoking history, versus no	0.511 (0.317−0.823)	0.559 (0.344−0.909)
Coexisting disorder, versus none		
Hypertension	2.540 (2.011−3.209)	1.442 (1.109−1.876)
Diabetes	2.920 (2.224−3.835)	1.816 (1.351−2.442)
Chronic obstructive lung disease	3.582 (2.478−5.178)	2.010 (1.380−2.926)
Coronary artery disease	2.459 (1.719−3.520)	1.828 (1.256−2.660)
Chronic renal disease	3.057 (1.513−6.174)	
Cerebrovascular disease	2.410 (1.408−4.124)	
Hepatitis B infection	0.333 (0.047−2.377)	
Anti-viral drug	4.292 (2.695−6.837)	
Duration of anti-viral therapy	4.689 (3.463−6.349)	3.192 (2.329-4.375)

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio.

However, the duration of anti-viral therapy seemed to be negatively associated with mechanical ventilation (HR 0.79, 95% CI 0.73−0.85) (see Supplementary material, Table S1).

Procalcitonin >0.5 ng/mL (HR 1.72, 95% CI 1.02−2.90, p 0.044), urea nitrogen >7.1 mmol/L (HR 1.72, 95% CI 1.21−2.43, p 0.002), α-HBDH over 200 U/L (HR 3.02, 95% CI 1.26−7.21, p 0.013) and D-dimer over 0.5 mg/L (HR 2.01, 95% CI 1.12−3.58, p < 0.001) at baseline were independent risk factors affecting the disease progression. However, there was no significant association between other laboratory findings at baseline and odds of disease progression (Table 4). White-cell count >10 × 10⁹/L (HR 3.05, 95% CI 1.63−5.70, p < 0.001), platelet count <150 × 10⁹/L (HR 2.30, 95% CI 1.25−4.21, p 0.007), urea nitrogen >7.1 mmol/L (HR 2.54, 95% CI 1.38−4.70, p 0.003) and α-HBDH ≥200 U/L (HR 12.33, 95% CI

Table 2
Laboratory findings of patients with COVID-19

Variables	All patients (n = 674)	Stable (n = 409)	Progression			p value (stable versus progression)
			Severe (n = 200)	Critical (n = 22)	Deceased (n = 43)	
WBCs (10⁹/L)	6.1 (4.6−7.9)	7.0 (5.4−9.5)	6.8 (5.1−9.1)	9.6 (7.3−12.7)	8.4 (6.1−12.3)	<0.001
>10, n (%)	76/668 (11.4)	23/405 (5.7)	28/200 (14.0)	8/22 (36.4)	17/41 (41.5)	
<4, n (%)	91/668 (13.6)	66/405 (16.3)	20/200 (10.0)	1/22 (4.5)	4/41 (9.8)	
Lymphocyte (10⁹/L)	1.2 (0.8−1.6)	1.4 (1.1−1.8)	0.9 (0.6−1.3)	0.7 (0.5−1.1)	0.5 (0.3−0.8)	<0.001
<1.5, n (%)	455/668 (68.1)	234/405 (57.9)	162/200 (81.0)	22/22 (100.0)	37/41 (90.2)	<0.001
Platelet (10⁹/L)	237 (178−303)	216 (165−284)	225 (165−289)	175 (111−289)	145 (86−226)	<0.001
<150, n (%)	107/668 (16.0)	41/405 (10.1)	36/200 (18.0)	9/22 (40.9)	21/41 (51.2)	<0.001
Haemoglobin (g/dl)	123 (112−135)	124 (114−136)	122 (110−135)	128 (111−134)	122 (109−133)	0.006
C-reactive protein (mg/L)	8 (2.0−52.1)	44.89 (7.4−93.5)	25.5 (5.6−77.1)	72.1 (25.0−127.4)	104.3 (42.6−159.6)	<0.001
≥10, n (%)	291/638 (45.6)	108/378 (28.6)	129/197 (65.5)	20/22 (90.9)	34/41 (82.9)	<0.001
Procalcitonin (ng/ml)	0.05 (0.03−0.11)	0.08 (0.04−0.18)	0.07 (0.04−0.13)	0.14 (0.08−0.34)	0.18 (0.02−0.77)	<0.001
≥0.5, n (%)	24/406 (5.9)	1/178 (0.6)	6/165 (3.6)	4/22 (18.2)	13/41 (31.7)	<0.001
ALT (U/L)	27 (17.6−44.9)	29.8 (18.2−57.1)	29.6 (18.1−54.1)	33.8 (20.8−68.6)	30.2 (16.9−68.8)	0.032
>40, n (%)	207/645 (32.1)	113/387 (29.2)	70/195 (35.9)	10/22 (45.5)	14/41 (34.1)	0.054
AST (U/L)	23 (16.8−33.7)	27.7 (19.3−42.5)	26 (19−41)	31.5 (21.8−40.5)	31.0 (21.5-47.5)	<0.001
>40, n (%)	103/595 (17.3)	39/355 (11.0)	44/177 (24.9)	6/22 (27.3)	14/41 (34.1)	<0.001
Creatinine (μmol/L)	64.6 (54.5−75.2)	66.9 (55.8−79.9)	64.5 (55.2−77.2)	65.5 (54.2−75.5)	75.5 (58.4−94.4)	0.014
>133, n (%)	18/655 (2.7)	6/394 (1.5)	6/198 (30.3)	0/22 (0.0)	6/41 (14.6)	0.018
Urea nitrogen (mmol/L)	4.64 (3.7−6.1)	5.61 (4.1−8.1)	5.1 (4.0−7.2)	5.8 (5.0−9.4)	8.4 (4.9−11.1)	<0.001
>7.1, n (%)	117/655 (17.9)	31/394 (7.9)	54/198 (27.3)	9/22 (40.9)	23/41 (56.1)	<0.001
LDH (U/L)	220.2 (171.9−296.9)	289.5 (222.1−422.6)	262 (210−332)	446 (269−529)	482 (354−720)	<0.001
>240, n (%)	255/618 (41.3)	84/363 (23.1)	113/192 (58.9)	20/22 (90.9)	38/41 (92.7)	<0.001
α-HBDH (U/L)	179.81 (140.1−245.6)	244.8 (179.9−346)	220.6 (162.9−290.6)	363 (248−453)	421 (289−608)	<0.001
>200, n (%)	253/619 (40.9)	79/364 (21.7)	115/192 (59.9)	21/22 (95.5)	38/41 (92.7)	<0.001
D-dimer (mg/L)	0.8 (0.4−2.2)	0.5 (0.2−1.1)	1.3 (0.6−2.9)	3.9 (1.8−14.2)	5.2 (0.9−7.7)	<0.001
≥0.5, n (%)	300/443 (67.7)	122/236 (51.7)	126/153 (82.3)	21/21 (100.0)	31/33 (93.9)	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; α-HBDH, α-hydroxybutyrate dehydrogenase; IQR, interquartile range; LDH, lactate dehydrogenase; PCT, procalcitonin; WBC, white blood cells. Data are median (IQR), n (%), where n is the total number of patients with available data. p values comparing groups are from χ² test, Fisher's exact test, or Mann−Whitney U test.

Table 4
Cox regression analysis of association between baseline laboratory findings and disease progression in patients with COVID-19

Variables	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, ≥65 years	2.836 (2.182—3.685)	1.615 (1.143—2.282)
Sex, male	1.475 (1.152—1.887)	
Laboratory findings		
White-cell count >10 × 10^9/L	2.846 (2.103—3.851)	
Lymphocyte count <1.5 × 10^9/L	3.048 (2.191—4.241)	
Platelet count <150 × 10^9/L	2.175 (1.691—2.797)	
Haemoglobin <110 g/L	3.906 (2.99—5.102)	
C-reactive protein ≥10 mg/L	2.991 (1.934—4.626)	
Procalcitonin ≥0.5 ng/mL	1.294 (1.004—1.667)	1.715 (1.015—2.899)
Alanine aminotransferase >40 U/L	2.137 (1.604—2.846)	
Aspartate aminotransferase >40 U/L	2.249 (1.259—4.016)	
Creatinine, ≥133μmol/L	3.401 (2.622—4.411)	
Urea nitrogen, >7.1mmol/L	4.124 (3.171—5.362)	1.716 (1.211—2.431)
Lactate dehydrogenase ≥250U/L	4.528 (3.473—5.903)	
α-HBDH ≥200U/L	4.008 (2.705—5.940)	3.017 (1.263—7.211)
D-dimer ≥0.5mg/L	2.846 (2.103—3.851)	2.007 (1.124—3.584)

Abbreviations: COVID-19, coronavirus disease 2019; α-HBDH, α-hydroxybutyrate dehydrogenase; HR, hazard ratios; LDH, lactate dehydrogenase.

2.91—52.34, p 0.001) at baseline were independent risk factors for mechanical ventilation (see Supplementary material, Table 2).

Discussion

This study aimed to determine the association of clinical characteristics and laboratory findings with short-term outcome of individuals with mild to moderate COVID-19 from three medical centres in Wuhan. We found that several chronic co-morbidities and baseline blood biomarkers were independently associated with risk for disease progression during a 28-day follow up.

Once a patient advances to severe disease, the risk for poor outcome increases dramatically [3]. Therefore, identification of patients with risk for progressing to severe disease is essential for timely intervention to improve prognosis. In the present study, we used Cox proportional hazards models to assess the association between clinical characteristics, baseline blood biomarkers and short-term outcome of the disease. Age above 65 years and male sex were found to be significant risk factors for disease progression, which is consistent with previous findings [2,9]. T-cell and B-cell function is attenuated with aging, and the excess production of pro-inflammatory cytokines could induce a deficiency in controlling viral replication and prolonged pro-inflammatory responses [10], so leading to poor outcome. SARS-CoV-2 employs angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry [11]. The high expression of ACE2 in testes may underlie the phenomenon that men have an increased risk for severe disease [12]. Interestingly, although the frequencies of smoking history were not significantly different between the stable and progression groups, smoking history seemed to be protective against disease progression. This phenomenon could be explained by a previous finding that long-term nicotine administration reduces oxidative damage in several tissues [13], which is commonly seen in viral infectious disease [14]. Nicotine also dose-dependently reduces the severity of virus-induced inflammation through inhibiting the production of pro-inflammatory cytokines [15], so may be protective against the cytokine storm during SARS-CoV-2 infection. However, findings about the association between smoking history and disease progression of COVID-19 are not consistent [16—18]. Further clinical and mechanistic studies are needed to address a more convincing conclusion upon this issue. In the present study, we found no association between anti-viral therapy and disease progression of COVID-19. The efficacy of anti-viral treatment was inconsistent in previous studies [7,19]. The duration of anti-viral therapy was found to be positively associated with disease progression but negatively associated with mechanical ventilation. This might be attributed to the fact that the progression group had a significantly longer duration of anti-viral therapy. However, the deceased group had a significantly shorter duration of anti-viral therapy and most cases receiving mechanical ventilation were allocated in this group.

It was reported in a recent epidemic study of COVID-19 in China that patients with co-existing disorders accounted for 23.2% in non-severe cases and for 37.6% in severe cases [2]. Earlier observational studies that summarized the characteristics of patients with COVID-19 had similar findings [1,8], indicating that the presence of co-morbidities is associated with the severity of the disease. The proportion of patients with co-existing disorders was relatively higher in our study (36.1%) in comparison with previous ones, which might be attributed to the sampling bias between different studies. Previous studies focused on the cross-sectional association between co-existing conditions and disease severity. However, studies investigating the association between the presence of co-morbidities and risk for disease progression of COVID-19 are limited.

Previous studies of severe acute respiratory syndrome (SARS) in different regions worldwide reported that an increased burden of co-morbidities was associated with poor outcome of the disease [20,21]. In the present study, we found that the risk factors for disease progression of COVID-19 included the presence of hypertension, diabetes mellitus, COPD and coronary artery disease. Although ACE2 is the key receptor for cellular entry of SARS-CoV, it in return acts in protecting against subsequent pulmonary injury by this virus [22]. SARS-CoV infection causes robust down-regulation of ACE2 expression, subsequently increasing the permeability of the pulmonary vascular system [23], so exacerbating pulmonary injury. The down-regulated expression of ACE2 in hypertension [24,25] might explain the phenomenon that individuals with hypertension were more vulnerable to disease progression of COVID-19 once infected by SARS-CoV-2. Similar to our findings, diabetes mellitus has also been identified as a prognostic factor in patients with community-acquired pneumonia [26] and SARS [27]. These findings might be explained by the impaired immune functions of individuals with diabetes mellitus [28]. Furthermore, ACE2 expression is also decreased in people with diabetes [29]. The association between COPD and COVID-19 could be attributed to the coexistence of chronic and acute lung injuries, which may each exacerbate the pathogenesis of the other [30,31]. Collectively, these findings along with ours point to a consensus that the co-existing chronic diseases may contribute to the poor prognosis of individuals infected by human coronavirus including SARS-CoV-2.

Another significant finding of the present study is that several laboratory markers at baseline may have potential predictive effects on the short-term prognosis of COVID-19. Elevated procalcitonin, urea nitrogen, α-HBDH and D-dimer were independently associated with risk for progression of COVID-19 during follow up. Moreover, elevated white blood cell count, urea nitrogen, α-HBDH and decreased platelet count were associated with risk for mechanical ventilation, which reflects critical disease. These findings point to a possibility that the presence of systemic inflammation, impairment of renal or cardiac function, hypercoagulability or hyperfibrinolysis may be associated with the prognosis. However, although lymphopenia was observed to be more frequent in patients in the progression group, the Cox proportional hazards model did not indicate a significant association between lymphopenia and risk for disease progression, which is not consistent with a recent study [4].

Our study has some limitations. First, because of the different diagnostic paradigm among hospitals, not all laboratory tests were performed in all patients. Besides, a follow up of 28 days may not cover all disease stages and so is likely to miss important end-point events in a longer time. Third, patients in the mobile cabin hospitals were not included in the analysis of association between laboratory findings and disease progression, which might limit the confidence of the present findings. However, the present study documented several warning signs for disease progression in individuals with mild to moderate COVID-19. Individuals with such warning signs should be intensively monitored for possible adverse events.

Acknowledgement

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.041.

Transparency declaration

The authors declared no conflicts of interest.

Author contributions

LYH, ZLL and ZJ contributed to the study design and writing of the report. CY, CX and ZXH contributed to the data collection and writing of the report. SY conducted the data analysis and revision of the manuscript. LY, XC, JWR and XHT contributed to the data collection. CY contributed to the revision of the manuscript. All authors had full access to study data for interpretation and drafting of the report.

References

[1] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020. epub ahead of print.

[2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for, clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. epub ahead of print.

[3] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020. epub ahead of print.

[4] Li Tan QW, Zhang D, Ding J, Huang Q, Tang Y-Q, Wang Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. medRxiv 2020. https://doi.org/10.1101/2020.03.01.20029074.

[5] WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Available at: https://www.who.int/publications-detail/clinical-management-ofsevere-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected; 2020.

[6] Totura AL, Bavari S. Broad-spectrum coronavirus antiviral drug discovery. Expert Opin Drug Discov 2019;14:397—412.

[7] Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, et al. Efficacy and safety of lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine 2020:153242. epub ahead of print.

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020. epub ahead of print.

[9] Yanli Liu WS, Li J, Chen L, Wang Y, Zhang L, Yu L. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv 2020. https://doi.org/10.1101/2020.02.17.20024166.

[10] Smits SL, de Lang A, van den Brand JM, Leijten LM, van IJcken WF, Eijkemans MJ, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog 2010;6:e1000756.

[11] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020. epub ahead of print.

[12] Aditi Shastri JW, Agrawal S, Chaterjee N, Pradhan K, Goldfinger M, Kornblum N, et al. Delayed clearance of SARS-CoV2 in male compared to female patients: high ACE2 expression in testes suggests possible existence of gender-specific viral reservoirs. medRxiv 2020. epub ahead of print.

[13] Ozdemir-Kumral ZN, Ozbeyli D, Ozdemir AF, Karaaslan BM, Kaytaz K, Kara MF, et al. Protective effect of nicotine on sepsis-induced oxidative multiorgan damage: role of neutrophils. Nicotine Tob Res 2017;19:859—64.

[14] Zhou F, Wang Y, Liu Y, Liu X, Gu L, Zhang X, et al. Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-China Network. Eur Respir J 2019;54.

[15] Li-Sha G, Jing-Lin Z, Guang-Yi C, Li L, De-Pu Z, Yue-Chun L. Dose-dependent protective effect of nicotine in a murine model of viral myocarditis induced by coxsackievirus B3. Sci Rep 2015;5:15895.

[16] Patanavanich GS. Smoking is associated with COVID-19 progression: a meta-analysis. MedRxiv 2020. epub ahead of print.

[17] Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med 2020;75:107—8.

[18] Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of Covid-19: a systemic review and meta-analysis. J Med Virol 2020. epub ahead of print.

[19] Xu P, Huang J, Fan Z, Huang W, Qi M, Lin X, et al. Arbidol/IFN-α2b therapy for patients with corona virus disease 2019: a retrospective multicenter cohort study. Microbe Infect 2020. epub ahead of print.

[20] Leong HN, Earnest A, Lim HH, Chin CF, Tan C, Puhaindran ME, et al. SARS in Singapore—predictors of disease severity. Ann Acad Med Singapore 2006;35:326—31.

[21] Trombetta H, Faggion HZ, Leotte J, Nogueira MB, Vidal LR, Raboni SM. Human coronavirus and severe acute respiratory infection in Southern Brazil. Pathog Glob Health 2016;110:113—8.

[22] Kuba K, Imai Y, Penninger JM. Angiotensin-converting enzyme 2 in lung diseases. Curr Opin Pharmacol 2006;6:271—6.

[23] Dijkman R, Jebbink MF, Deijs M, Milewska A, Pyrc K, Buelow E, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol 2012;93:1924—9.

[24] Yang Z, Yu X, Cheng L, Miao LY, Li HX, Han LH, et al. Effects of enalapril on the expression of cardiac angiotensin-converting enzyme and angiotensin-converting enzyme 2 in spontaneously hypertensive rats. Arch Cardiovasc Dis 2013;106:196—201.

[25] Yuan YM, Luo L, Guo Z, Yang M, Ye RS, Luo C. Activation of renin-angiotensin-aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats. J Renin Angiotensin Aldosterone Syst 2015;16:249—53.

[26] Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax 2013;68:1057—65.

[27] Chan JW, Ng CK, Chan YH, Mok TY, Lee S, Chu SY, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax 2003;58:686—9.

[28] Mincu I, Cheta D. Diabetes mellitus and immunity. Med Interne 1983;21:257—66.

[29] Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int J Pept 2012;2012:256294.

[30] Kurai D, Saraya T, Ishii H, Takizawa H. Virus-induced exacerbations in asthma and COPD. Front Microbiol 2013;4:293.

[31] Seys LJM, Widagdo W, Verhamme FM, Kleinjan A, Janssens W, Joos GF, et al. DPP4, the Middle East respiratory syndrome coronavirus receptor, is upregulated in lungs of smokers and chronic obstructive pulmonary disease patients. Clin Infect Dis 2018;66:45—53.