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Original Article

Low C_t value as well as serum level of Alb, CK, ESR and CRP may be predictors in discriminating mild versus severe COVID-19

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Abstract: Coronavirus disease (COVID-19) caused by the 2019 novel coronavirus (SARS-CoV-2) still has no specific laboratory markers to assess severity. As a novel acute infectious disease, early recognition of severe cases (nearly 20%) is essential for early triage and corresponding treatment. This study aimed to summarize the potential practical predictors for clinicians to identify severe cases during hospitalization. We collected the clinical laboratory data as well as the demographic, epidemiological and clinical information from 58 COVID-19 patients (26 severe cases, 32 mild cases) in Xiangyang Central Hospital (Xiangyang, China) during their hospitalization. The correlation between laboratory parameters and disease severity, laboratory parameters dynamics and the outcome of severe COVID-19 patients were fully analyzed. Finally, we compared the characteristics between severe and mild cases and summarized several laboratory parameters. The median age, concomitant diseases, PT, FIB, DD, ISTH/CDSS score, UN, CK, ESR and CRP were significantly higher in the severe cases, while the LYM count, viral nucleic acid C_t value, and Alb were significantly lower. Logistic regression analysis and AUC of ROC showed that C_t, Alb, CK, ESR and CRP may be good predictors for the severity of COVID-19 cases and patient prognosis. Laboratory parameter dynamics indicated the repletion of LYM, Alb, D-D, UN, CK, ESR and CRP may be important for the recovery of severe cases. Low C_t value and other parameters may have the potential to discriminate mild and severe COVID-19 cases and could be used as prognostic markers to guide treatment.

Keywords: COVID-19, C_t value, Alb, CK, ESR, CRP

Introduction

Coronavirus disease (COVID-19) caused by SARS-CoV-2 [1] infection was first identified in Wuhan, China in January 2020 [2-4]. Currently the number of patients with COVID-19 has dramatically increased all around the world, and it has caused a great threat to human safety and mental health [5-7].

COVID-19 can be divided into mild and severe types (the latter accounting for nearly 20%) [8]. Severe COVID-19 patients may quickly progress to Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Failure (MOF), even death. Therefore, early diagnosis of severe forms of COVID-19 is of great importance for timely triage of patients and guiding clinical treatment. Analyzing the data between mild and severe COVID-19 cases to screen the potential indicators is urgent for us to improve prognosis and reduce mortality rate [9].

In this study, we provided a comprehensive analysis among patients with severe and mild COVID-19, our results indicated that several markers may be useful in the above mentioned purposes.

Material and methods

Study design

This retrospective cohort study enrolled 58 patients (26 severe cases, 32 mild cases) who were admitted to the Xiangyang Central Hospital (Xiangyang, China) from January 24 to February 15, 2020. We compared the demographic, epidemiological and clinical data along with laboratory results between the severe and

mild COVID-19 cases, and selected several laboratory parameters that may facilitate the assessment of disease severity. We further analyzed the association of those laboratory parameters with COVID-19 severity using logistic regression analysis and AUC of ROC. The recovery of severe COVID-19 patients was associated with dynamic of LYM, D-D, Alb, UN, CK, ESR and CRP. The treatment and outcome of severe COVID-19 patients were also explored to identify powerful indicators.

Patients

Altogether there were 58 confirmed COVID-19 patients by RT-PCR according to the "novel coronavirus pneumonia diagnosis and treatment plan (trial version 7)" [10] who were collected. Patients who had any of the following features at the time of admission, or thereafter were classified as severe cases: (1) respiratory distress (≥30 breaths per min); (2) oxygen saturation at rest ≤93%; (3) ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air ≤300 mm Hg; or (4) severe disease complications (e.g. respiratory failure, requirement of mechanical ventilation, septic shock, or non-respiratory organ failure). There were 32 (55%) individuals who were classified as mild cases and 26 (45%) who were diagnosed as severe cases. The inclusion and exclusion criteria included: 1. Confirmed COVID-19 upon admission were included; 2. Patients with comorbidities which might impair the immune function, such as autoimmune disease, hematological malignancies, recent chemotherapy, or blood transfusion were excluded.

Research methods

The demographic, epidemiological and clinical data of all patients were recorded, we also collected their laboratory results associated with COVID-19 and laboratory parameters dynamics. Treatment and outcome results of severe COVID-19 patients were also gathered. This protocol was approved by the ethics committee of Xiangyang Central Hospital, and all procedures were in accordance with the ethical standards specified by our institution (2020-006).

Statistical analysis

Statistical analysis SPSS 24.0 software was used for statistical analysis. The data of continuous variables was expressed as mean ± standard deviation (mean ± SD) and the comparison between two groups was conducted by independent sample *t* test. The categorical variables were expressed as constituent ratio or case (%) and the comparison between groups was performed by χ^2 test. Area under curves (AUC) of receiver operating characteristic (ROC) was calculated to evaluate the prediction effect of different index. A logistic regression model was performed to evaluate the association between laboratory parameters and severe COVID-19 cases, OR (odd ratio) and 95% CI (95% confidence interval) were presented. A *P* value of less than 0.05 was considered statistically significant (P<0.05). GraphPad prism 6.0 was used to describe the comparison between both groups at different time points (**P*<0.05, ***P*<0.01, ****P*<0.001).

Results

Comparison of the demographic, epidemiological, and clinical information between mild and severe COVID-19 cases

Among the 58 COVID-19 patients (30 male and 28 female), the median age of the severe cases (56, rang 25 to 81) was higher than that of mild cases (41, rang 11 to 70), (*P*<0.001). There was no significant difference in the number of COVID-19 patients with SARS-CoV-2 contact history between the mild (16 cases, 50%) and severe (10 cases, 38.5%) groups.

The number of patients with concomitant diseases (including hypertension, diabetes, coronary heart disease, chronic cough) in the severe group (12 cases, 46.2%) was higher than that of the mild group (6 cases, 18.8%), (*P* = 0.044).

The time interval from disease onset to admission was 5.172 ± 0.8 days in the mild group and 5.521 ± 0.7282 days in the severe group (no statistical difference).

The common clinical symptoms of COVID-19 were fever, cough, and other discomfort such as sore throat, muscle aches, diarrhea, fatigue and runny nose [11]. These indicators did not differ significantly between the mild and severe groups.

Chest CT scan after admission showed that there were different degrees of infectious lesions including multiple small patchy shadows, interstitial changes or ground glass shadows

Table 1. Demographic, epidemiological and clinical characteristics of two groups

	Mild (32)	Severe (26)	*P* value
Age			
Mean	41	56***	<0.001
Range	11~70	25~81	
≤39	13 (41%)	4 (15.4%)	
40-49	4 (12.5%)	4 (15.4%)	
50-59	11 (34.3%)	8 (30.8%)	
60-69	2 (6.3%)	4 (15.4%)	
≥70	2 (6.3%)	6 (23.1%)	
Sex			0.771
Female	16 (50%)	12 (46.2%)	
Male	16 (50%)	14 (53.8%)	
Exposure	16 (50%)	10 (38.5%)	0.380
Chronic disease	6 (18.8%)	12 (46.2%)*	0.044
Time from illness onset to hospital admission (days)	5.172 ± 0.8	5.521 ± 0.7282	0.505
Signs and symptoms at admission			
Fever	20 (62.5%)	23 (88.4%)	0.055
Cough	15 (46.9%)	8 (30.8%)	0.212
Muscle ache	2 (6.3%)	1 (3.8%)	0.681
Sore throat	3 (9.4%)	1 (3.8%)	0.760
More than one sign or symptom	20 (62.5%)	19 (73.1%)	0.393
No sign or symptom	2 (6.3%)	0 (0%)	0.119
diarrhea	0 (0%)	3 (11.5%)	0.168
Rhinorrhoea	1 (3.1%)	4 (15.4%)	0.236
CT Founding			
Multiple mottling and ground-glass opacity	28 (87.5%)	26 (100%)	0.178
Unilateral pneumonia	3 (9.4%)	0 (0%)	0.314
Bilateral pneumonia	25 (78.1%)	26 (100%)	0.053

vs Mild *P <0.05, ***P <0.001.

scattered among bilateral lung tissue in the severe group. However, in mild COVID-19 cases, 4 had no obvious infection lesions on CT scan, and 3 cases had only unilateral infection lung lesions (**Table 1**).

Comparison of the laboratory test between mild and severe COVID-19 cases

The white blood cell (WBC), neutrophil (NE), hemoglobin (Hb) and platelet (PLT) in the peripheral blood of the severe group were higher than those of the mild group, but with no statistical difference. While early stage median LYM of the severe group was significantly lower than that of mild group ($P = 0.017$).

The coagulation parameters including Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), Fibrinogen (FIB) and D-dimer (DD) between both groups were compared. The PT ($P = 0.046$), FIB ($P = 0.001$) and DD ($P = 0.005$) increased significantly in the severe group compared to the mild group. We used the ISTH/CDSS Disseminated Intravascular Coagulation (DIC) to assess coagulation disorders, and found that the ISTH ($P<0.001$) and CDSS ($P = 0.004$) of the severe group were significantly higher than those of the mild group.

The ORF1ab and N gene cycle threshold (C_t) values of SARS-CoV-2 samples collected from patients' lower respiratory tract were detected. The C_t value (inversely proportional to virus titer) of the severe group was significantly lower than that of the mild group (ORF1ab, $P<0.001$; N, $P = 0.004$).

The biochemical indices related to liver, kidney and heart function, such as albumin (Alb), urea nitrogen (UN) and creatine kinase (CK), were

Table 2. Laboratory test of two groups

Items	Mild (32)	Severe (26)	*P* value
Blood routine			
WBC (10^9/L)	4.265 (3.755, 5.718)	4.77 (3.75, 9.1)	0.159
NE (10^9/L)	2.635 (2.07, 3.670)	2.99 (1.596, 4.8)	0.558
LYM (10^9/L)	1.225 (0.885, 1.74)	1.030 (0.7025, 1.303)*	0.017
PLT (10^9/L)	155.5 (143.8, 155.5)	178 (109, 178)	0.345
Hemoglobin (g/L)	140.5 (128.3, 149.5)	134 (119.8, 140.3)	0.082
Coagulation function			
APTT	26.45 (23.75, 29.48)	25.2 (21.3, 30.78)	0.518
PT	10.85 (10.4, 11.4)	11.35 (10.78, 12.38)*	0.046
FIB	3.515 (2.465, 4.058)	4.59 (3.498, 5.308)**	0.001
D-D	0.23 (0.16, 0.2975)	0.81 (0.315, 3.025)**	0.005
ISTH	1.031 ± 0.2176	2.346 ± 0.2414***	<0.001
CDSS	1.250 ± 0.1100	2.231 ± 0.2561**	0.004
C_t value			
ORF1ab	30.61 ± 0.6805	26.62 ± 0.8037***	<0.001
N	29.76 ± 0.7695	26.23 ± 0.8666**	0.004
Blood biochemistry			
Alb (g/L)	42.4 (39.78, 44.73)	39.2 (35.13, 42.03)***	<0.001
Ala (U/L)	17 (12.25, 22)	19.5 (11.75, 31.25)	0.274
Asa (U/L)	21 (18.25, 29.5)	27.5 (20.75, 38)	0.052
UN	4.1 (2.8, 4.8)	4.7 (3.9, 6)*	0.032
Serum creatinine	60.2 (47.2, 71)	64.55 (52.93, 75)	0.249
CK	9.5 (6, 13)	15 (11.5, 20.75)**	0.009
Infection-related biomarkers			
ESR	9.5 (6, 13)	38 (33.5, 45)***	<0.001
CRP	8.89 (5, 24.7)	21.8 (6.42, 51.6)*	0.034
Fungus	0	0	-
Bacteria	0	1 (3.8%)	0.202
Virus	0	2 (7.7%)	0.069

vs Mild *P <0.05, **P <0.01, ***P <0.001.

compared between both groups. Alb (P<0.001) was significantly decreased, while UN (P = 0.032) and CK (P = 0.009) were significantly increased in the severe group compared to the mild group.

The infection and tissue injury indices including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were compared between both groups. ESR (P<0.001) and CRP (P = 0.034) were significantly increased in the severe group compared to the mild group. There were 3 cases with mycoplasma and virus co-infection in the severe group (**Table 2**).

Logistic regression analysis of severe COVID-19 related laboratory parameters

As the laboratory parameters with significant difference were found between the mild and severe groups (**Table 2**), and knowing that D-D may be of great importance for judging thrombotic disease and hyper-coagulable state, we analyzed the association of laboratory parameters with COVID-19 severity by logistic regression analysis.

Logistic regression analysis showed that ORF1ab C_t, Alb, CK, ESR and CRP may be risk factors of severe COVID-19 and thus potential indicators to discriminate mild and severe COVID-19 cases (P<0.05) (**Table 3**).

Area under curves (AUC) of receiver operating characteristic (ROC) of laboratory parameters between both groups

We further analyzed the association of ORF1ab C_t, Alb, CK, ESR and CRP with COVID-19 severity by AUC of ROC.

Table 3. Logistic regression analysis of laboratory parameters associated with severe COVID-19

Laboratory parameters	OR (95% CI)	*P* value
WBC	1.246 (0.975, 1.591)	0.079
NE	1.001 (0.962, 1.041)	0.967
LYM	0.939 (0.837, 1.053)	0.28
PLT	1.002 (0.993, 1.012)	0.665
Hb	0.979 (0.945, 1.014)	0.238
D-D	70.982 (0.907, 5554.924)	0.055
ORF1ab C_t	0.78 (0.661, 0.911)	0.002
Alb	0.736 (0.598, 0.906)	0.004
Ala	1.023 (0.98, 1.069)	0.298
UN	1.523 (0.991, 2.341)	0.055
Serum creatinine	1.03 (0.993, 1.068)	0.111
CK	1.173 (1.031, 1.334)	0.015
ESR	1.192 (1.08, 1.316)	0.001
CRP	1.048 (1.013, 1.085)	0.007

The AUC of ORF1ab C_t was 0.7536 (**Figure 1**). The AUC of Alb reflecting liver function and CK reflecting heart function were 0.7615 and 0.7283, separately. The AUC of ESR and CRP reflecting infection and tissue injury were 0.9576 and 0.6652, respectively (**Figure 1**).

These results further confirmed that ORF1ab C_t, Alb, CK, ESR and CRP were closely related with COVID-19 severity.

The LYM, D-D, Alb, UN, CK, ESR, CRP dynamics in the severe group during hospitalization

The LYM, D-D, Alb, UN, CK, ESR and CRP level dynamics of the severe COVID-19 cases during hospitalization were analyzed. We noticed that LYM and Alb were increased, while D-D, UN, CK, ESR and CRP were decreased to normal level with timely treatment in severe COVID-19 cases (**Figure 2**).

The treatment and outcome of severe COVID-19 cases

All 26 severe cases received anti-viral and anti-infection treatment and different forms of respiratory support therapy (**Table 3**). There were 22 cases were supported with Traditional Chinese Medicine (TCM) treatment. Another 12 cases received intravenous immunoglobulin therapy while 20 cases were infused with glucocorticoid treatment. A total of 6 patients needed anticoagulation therapy and 2 cases were given plasma therapy from convalescent patients.

The average hospital stay of severe patients was 36.14 days. During hospitalization, 8 patients developed respiratory failure, 3 patients developed ARDS, 2 patients with coronary heart disease developed heart failure, 1 patient developed sepsis, 20 patients developed coagulopathy, 6 patients received intensive care unit (ICU) treatment, and 2 patients died. The average time of nucleic acids turning negative was 9.5 days after patients received antiviral treatment in hospital (**Table 4**).

Discussion

Altogether, 58 patients (26 severe cases, 32 mild cases) who were admitted to Xiangyang Central Hospital (Xiangyang, China) from January 24 to February 15, 2020, were included in this study. We compared the characteristics between severe and mild cases and summarized several laboratory parameters which may facilitate the assessment of disease severity.

The basic demographic and epidemiological data and initial clinical symptoms (**Table 1**) did not differ significantly between both groups, except that patients in the severe group were significantly older and the ratio of patients with chronic diseases was also higher in the severe group.

Then, we further confirmed the risk factors such as old age and underling comorbidities may modulate the course of COVID-19. Therefore, we should pay more attention to aged patients with COVID-19 and their underlying diseases in clinical treatment.

Many studies showed that LYM was decreased in most cases of COVID-19 [12-18]. We further discovered the LYM of severe COVID-19 patients was significantly lower than in mild COVID-19, as expected. Huang et al reported that PT (12.2 s *vs* 10.7 s, $P = 0.012$) and DD (2.4 mg/L *vs* 0.5 mg/L, $P = 0.0042$) were significantly increased in severe COVID-19 patients compared to mild cases [14]. Chen et al reported that DD exceeded the upper limit in 36% patients among 99 COVID-19 [15]. Tang et

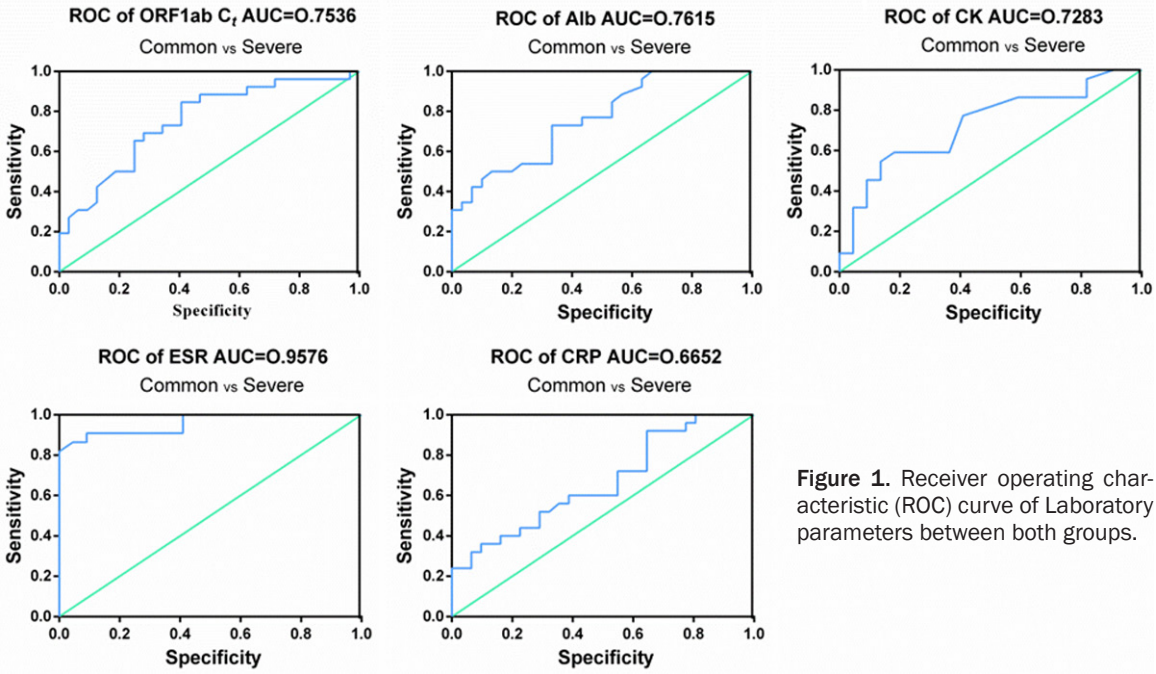

Figure 1. Receiver operating characteristic (ROC) curve of Laboratory parameters between both groups.

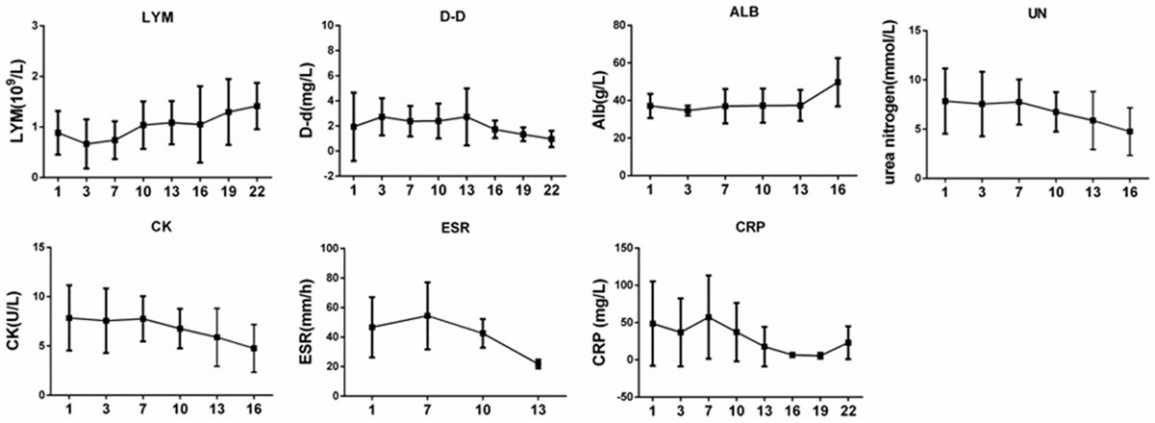

Figure 2. Laboratory parameters dynamics in the severe group.

al reported that DD was evidently higher, PT and APTT were obviously longer in deceased patients compared to the results in survival patients among 183 COVID-19 cases [19]. Wang et al reported that the DD level was increased in dead patients upon admission among 138 COVID-19 cases [16]. Some studies suggested that increased DD level may act as an independent risk factor for the development of ARDS and death of COVID-19 [20]. Severe COVID-19 increased the risk of pulmonary embolism in those patients, and preventive anticoagulant drugs or physical therapy can be given if necessary [21].

In this study, we found PT, FIB, DD and ISTH/CDSS DIC scores of severe cases were significantly increased compared to those of mild cases, suggesting the coagulation function of severe COVID-19 may be hypercoagulable and prone to deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebral infarction.

SARS-CoV-2 Viral nucleic acid titers from patients' lower respiratory tract samples, were highly correlated with ARDS indicator PaO_2/FiO_2 and Murray score related to lung injury [22]. We noted the C_t value in severe cases was

Table 4. The treatment and outcome of severe group

Treatment	
Antiviral therapy	26 (100%)
Antibiotic therapy	26 (100%)
Traditional Chinese medicine treatment	22 (84.6%)
Oxygen therapy	26 (100%)
Intravenous immunoglobulin therapy	12 (46.2%)
Anticoagulation Therapy	6 (23.1%)
Plasma convalescent patients of therapy	2 (7.7%)
Glucocorticoids	20 (76.9%)
Outcomes	
Time from illness onset to death or discharge	36.14 (10-67)
Respiratory failure	8 (31%)
ARDS	3 (11.5%)
Heart failure	2 (7.7%)
SPESIS	1 (3.8%)
Coagulopathy	20 (77%)
ICU admission	6 (23%)
Death	2 (7.7%)
Time of SARS-CoV-2 RNA positive	9.5 (6-20)

significantly lower at the time of admission, suggesting that patients with severe COVID-19 tended to have a high viral load and bear high risk of ARDS and lung injury.

SARS-CoV-2 infects individuals by the binding of virus surface spike glycoprotein (S protein) with Angiotensin-Converting Enzyme 2 (ACE2) on epithelial cells of different organs, leading to organ dysfunction [23, 24]. Patients with severe COVID-19 appeared to have more frequent signs of liver, kidney and heart dysfunction than those with mild disease. The decrease in Alb and increase in UN and CK were observed among severe COVID-19 in our study, indicating that serum levels of CK, Alb and UN can discriminate between mild and sever COVID-19 cases.

CRP, an indicator of bacterial and viral infection and inflammation [25], was increased in COVID-19 [15], especially in those severe cases [26]. ESR generally started to rise in 2-3 days after acute inflammation, so ESR was often used in combination with CRP clinically. ESR was also increased in most COVID-19 cases [15, 27]. In this study, CRP and ESR were significantly increased in severe patients, and 3 cases had mycoplasma co-infection. When COVID-19 patients were complicated with infection, their situations worsened quickly, though we still have no evidence that inflammatory indicators have a direct/indirect relationship with the death caused by COVID-19. Physicians should pay close attention to patients with elevated CRP and ESR levels which imply that they may be complicated with other infections.

Together, we summarized several laboratory parameters including LYM, D-D, C_t, Alb, UN, CK, ESR and CRP which may facilitate the assessment of disease severity. The logistic regression analysis and AUC of ROC further confirmed our analysis, and may have the potential of predicting COVID-19 severity. LYM and Alb were increased, and D-D, UN, CK, ESR and CRP were decreased in patients with effective treatment in severe cases during hospitalization, indicating restoration of those parameters may be of great importance for recovery.

Lung protection strategy should be implemented throughout the whole treatment process [28]. All 26 severe cases received different forms of respiratory support treatment. Besides, the Traditional Chinese Medicine (TCM) treatment, rehabilitation treatment, immunotherapy together with strictly controlled glucocorticoids were also timely used, only 2 aged patients with multiple concurrent diseases died in this study.

In summary, clinicians should pay close attention to older patients with underlying comorbidities. Low C_t value as well as serum level of Alb, CK, ESR and CRP may be used in risk stratification to predict severe and fatal COVID-19.

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Disclosure of conflict of interest

None.

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