Received: 24 March 2020 | Revised: 6 May 2020 | Accepted: 11 May 2020

DOI: 10.1111/tbed.13651

ORIGINAL ARTICLE

Transboundary and Emerging Diseases WILEY

A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection

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Funding information
This study was funded by the grants from the project of Thousand Youth Talents for DH; and from the National Natural Science Foundation of China (Nos. 31770983 and 81974249 to DH).

Abstract

An outbreak of pneumonia caused by a novel coronavirus (COVID-19) began in Wuhan, China in December 2019 and quickly spread throughout the country and world. An efficient and convenient method based on clinical characteristics was needed to evaluate the potential deterioration in patients. We aimed to develop a simple and practical risk scoring system to predict the severity of COVID-19 patients on admission. We retrospectively investigated the clinical information of confirmed COVID-19 patients from 10 February 2020 to 29 February 2020 in Wuhan Union Hospital. Predictors of severity were identified by univariate and multivariate logistic regression analysis. A total of 147 patients with confirmed SARS-CoV-2 infection were grouped into non-severe (94 patients) and severe (53 patients) groups. We found that an increased level of white blood cells (WBC), neutrophils, D-dimer, fibrinogen (FIB), IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), α-hydroxybutyrate dehydrogenase (HBDH), serum amyloid A (SAA) and a decreased level of lymphocytes were important risk factors associated with severity. Furthermore, three variables were used to formulate a clinical risk scoring system named COVID-19 index = 3 × D-dimer (μg/L) + 2 × lgESR (mm/hr) − 4 × lymphocyte ($\times 10^9$/L) + 8. The area under the receiver operating characteristic (ROC) curve was 0.843 (95% CI, 0.771–0.914). We propose an effective scoring system to predict the severity of COVID-19 patients. This simple prediction model may provide healthcare workers with a practical method and could positively impact decision-making with regard to deteriorating patients.

KEYWORDS

COVID-19, predict, risk factor, SARS-CoV-2, score model

1 | INTRODUCTION

In December 2019, an outbreak of pneumonia occurred in Wuhan, China, which was confirmed to be caused by a new coronavirus different from the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) (Jiang, Xia, Ying, & Lu, 2020; Tian, 2020). This virus is characterized by strong infectivity and a long incubation period after infection, and it was named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) on 11 February 2020.

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The pneumonia caused was named as COVID-19 by the World Health Organization (WHO). So far, SARS-CoV-2 has spread throughout the whole world, and there is no specific treatment for this pneumonia (Ahn et al., 2020; Cunningham, Goh, & Koh, 2020; Stebbing et al., 2020). Although the majority of infected patients showed mild symptoms, some can suddenly decline, leading to adverse outcomes. It is reported that the case fatality rate of COVID-19 is about 1.5% and could even be underestimated (Baud et al., 2020; Weiss & Murdoch, 2020). However, timely treatment for severe COVID-19 patients is associated with an improved survival rate. Thus, it is important for physicians to distinguish the patients who would probably suffer severe illness as soon as possible.

The early clinical manifestations of COVID-19 include fever, cough, sore throat and fatigue, and severe patients have symptoms such as dyspnoea, hypoxia and even respiratory failure (Chow et al., 2020; Xu et al., 2020). Infected patients present with varying degrees of lung imaging changes (Guan et al., 2020; Li and Xia, 2020; Pan et al., 2020). Laboratory tests found that patients had lymphopenia, liver and kidney damage, and severe lymphocyte subpopulation ratio abnormalities (Cai et al.., 2020; Chen, Wu, et al., 2020; Guan et al., 2020). Additionally, the appearance of cytokine storms and hypercoagulability may also contribute to death (Connors & Levy, 2020; Zhao, 2020). Clinical data demonstrated that older male patients are the high-risk population for severe outcomes, especially those with pre-existing diseases such as tumours (Guan et al., 2020; Wang, Yang, Li, Wen, & Zhang, 2020). Also, some young patients died from multiple organ injury, demonstrating the uncertainty of COVID-19 progression. Therefore, more factors need to be taken into account when assessing whether the patient is at risk for adverse outcomes.

Previous studies have shown that the clinical symptoms and some laboratory parameters of patients may predict the prognosis of patients with pneumonia (Chen, Liang, et al., 2020; Zhang et al., 2020). At present, there are no relevant studies showing early reference indications and systems related to COVID-19 outcomes. Patients with severe COVID-19 show some differences at admission. Therefore, we analysed and screened the risk factors for the adverse outcome from the baseline features, clinical symptoms, laboratory parameters and other aspects of the patients and developed a scoring system for predicting the outcome of the patients based on multiple regression, to predict the severity of the patients at the initial stage on admission and guide the treatment.

2 | METHODS

2.1 | Case inclusion and classification

We conducted a retrospective study of 147 patients treated in Wuhan Union Hospital from 10 February 2020 to 29 February 2020. All the patients included were confirmed COVID-19 patients with a positive throat swab test for SARS-CoV-2 nucleic acid and ground-glass CT changes in the lung. Each patient received active treatment and laboratory testing of multiple parameters during hospitalization, and all medical records could be traced. Patients were divided into non-severe and severe groups as described below according to the Guidelines of the Diagnosis and Treatment of New Coronavirus Pneumonia (version 7) published by the National Health Commission of China. Briefly, non-severe patients met at least one of the criteria together with confirmed SARS-CoV-2 infection: (a) Epidemiologic history, (b) Fever or other respiratory symptoms, (b) Typical CT image abnormities of viral pneumonia. Severe patients additionally had to fulfil at least one of the following criteria: (a) Shortness of breath, RR ≥ 30 times/min, (b) Oxygen saturation (Resting state) ≤93%, or (c) PaO_2/FiO_2 ≤ 300 mmHg. This research was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (No. 2020[58]).

2.2 | Data collection

Demographic characteristics (age, gender, height and weight), basic information (pre-existing disease, time from onset to admission), symptoms and signs were extracted from medical records on admission. Computed tomographic (CT) scans and the laboratory examination results of patients on the first day of admission—including blood routine, biochemical, inflammation and immune-related indicators—were collected for later analysis.

2.3 | Statistical analysis

All statistical comparisons were performed between non-severe and severe cases. For continuous variables, Mann–Whitney U test analysis was performed; and for categorical variables, Pearson's chi-square test or Fisher's exact test was applied as appropriate. Univariate logistic regression analysis was performed to screen the risk factors, and multivariate logistic regression analysis was used to assess the impact of different risk factors on the patient's condition and a scoring system was developed. The predictive value of the scoring system was evaluated by the ROC curve, and the cut-off value that can predict the severity of disease was subsequently determined. All analyses were performed using SPSS 20.0 software. $p < .05$ was considered a significant difference.

3 | RESULTS

3.1 | Clinical and laboratory characteristics

A total of 147 patients with confirmed SARS-CoV-2 infection were grouped into 94 non-severe patients and 53 severe patients. Of the 94 non-severe patients, there were 34 males and 60 females with a median age of 40. For the 53 severe patients, there were 29 males and 24 females, with a median age of 60. When taking

into account age and gender, severe cases were significantly older with a greater proportion of males, which is consistent with other reports that older men are a susceptible group and more likely to have severe symptoms (Guan et al., 2020). In terms of comorbidity, severe patients suffered from more pre-existing diseases. No difference was observed in BMI between the severe and non-severe groups. The clinical characteristics of the patients are shown in Table 1, from which we found that the most frequent symptoms were fever, cough, fatigue, and the frequency of all symptoms that appeared at admission was not significantly different between the two groups. In addition, the time from symptom onset to admission was longer in the severe group compared with the non-severe group.

Laboratory examinations were performed to dynamically monitor the course of patients' conditions. For each parameter, the values on admission were chosen to compare differences between the two groups. As shown in Table 2, severe patients exhibited higher levels of white blood cells (WBC) (4, IQR [3.17–5.50] versus 4.89, IQR [3.82–7.11]), neutrophils (2.32, IQR [1.75–3.51] versus 3.46, IQR [2.42–5.40]), D-dimer (0.37, IQR [0.22–0.80] versus 0.91, IQR [0.55–1.60]), fibrinogen (FIB) (4.16, IQR [3.42–5.04] versus 5.44, IQR [4.34–6.79]), IL-6 (8.54, IQR [3.52–17.29] versus 21.85, IQR [11.77–38.68]), C-reactive protein (CRP) (10.95, IQR [3.73–26.08] versus 43.10, IQR [17.70–74.80]), erythrocyte sedimentation rate (ESR) (18.50, IQR [7.00–33.00] versus 47.50, IQR [29.50–72.50]), alanine aminotransferase (ALT) (22.00, IQR [16.00–36.50] versus 31, IQR [19.00–47.50]), aspartate aminotransferase (AST) (24.00, IQR [20.00–31.00] versus 33.00, IQR [23.75–45.00]), α-hydroxybutyrate dehydrogenase (HBDH) (157.00, IQR [135.80–213.80] versus 233.00, IQR [176.00–323.25]) and serum amyloid A (SAA) (71.25, IQR [19.08–342.93] versus 658.50, IQR [282.05–730.25]), as well as lower lymphocyte counts (1.19, IQR [0.93–1.50] versus 0.72, IQR [0.58–0.96]).

3.2 | Risk factors for severity

Univariate regression analysis was performed to identify the factors statistically associated with severity of COVID-19. Our results showed that increased level of WBC (OR, 1.325; 95% CI, 1.121–1.566; p = .001), neutrophils (OR, 1.416; 95% CI, 1.189–1.685; p < .001), D-dimer (OR, 2.848; 95% CI, 1.602–5.064; p < .001), FIB (OR, 1.669; 95% CI, 1.296–2.148; p < .001), CRP (OR, 1.023; 95% CI, 1.011–1.035; p < .001), ESR (OR, 1.029; 95% CI, 1.014–1.044; p < .001), SAA (OR, 1.004; 95% CI, 1.002–1.006; p < .001), HBDH (OR, 1.011; 95% CI, 1.005–1.017; p < .001) and decreased lymphocytes (OR, 0.062; 95% CI, 0.019–0.200; p < .001) were independent risk factors for disease progression (Table 3). Furthermore, the independent risk factors were analysed by multivariate regression analyses with the method of stepwise forward selection. The results indicated that the following three variables were most predictive for the deterioration of COVID-19 patients and retained in the final scoring model: lymphocytes (OR, 0.412; 95% CI, 0.280–0.615; p < .001), D-dimer

TABLE 1 Clinical characteristics of patients infected with SARS-CoV-2

	No. (%)			
	Total (n = 147)	Non-severe (n = 94)	Severe (n = 53)	p Value[a]
Age, median (IQR), years	48 (36–62)	40 (32–56)	60 (49–64)	.085
Sex				
Male	63 (42.9)	34 (36.2)	29 (54.7)	.029
Female	84 (57.1)	60 (63.8)	24 (45.3)	
BMI, median (IQR)	24.1 (21.6–25.6)	24.2 (21.6–25.6)	22.9 (21.7–25.6)	.940
Comorbidities	71 (48.3)	37 (39.4)	34 (64.2)	.004
Signs and symptoms				
Fever	124 (84.4)	77 (81.9)	47 (88.7)	.278
Cough	84 (57.1)	52 (55.3)	32 (60.4)	.552
Chest congestion	40 (27.2)	28 (29.8)	12 (22.6)	.350
Fatigue	46 (31.3)	29 (30.9)	17 (32.1)	.878
Myalgia	41 (27.9)	24 (25.5)	17 (32.1)	.396
Diarrhea	16 (10.9)	13 (13.8)	3 (5.7)	.127
Dyspnoea	21 (14.3)	13 (13.8)	8 (15.1)	.833
Pharyngalgia	17 (11.6)	12 (12.8)	5 (9.4)	.544
Onset of symptom to, median (IQR), days				
Hospital admission	7 (5–10)	7 (6–10)	9 (4–10)	.036

[a]P values indicate differences between non-severe and severe patients. p < .05 was considered statistically significant.

TABLE 2 Laboratory features of patients infected with SARS-CoV-2 on admission

Laboratory examination	Median (IQR)			*p* value[a]
	Total (*n* = 147)	Non-severe (*n* = 94)	Severe (*n* = 53)	
White blood cells (×10^9/L)	4.37 (3.32–6.12)	4.00 (3.17–5.50)	4.89 (3.82–7.11)	.002
Lymphocytes (×10^9/L)	1.00 (0.73–1.30)	1.19 (0.93–1.50)	0.72 (0.58–0.96)	<.001
Neutrophils (×10^9/L)	2.50 (1.62–4.19)	2.32 (1.75–3.51)	3.46 (2.42–5.40)	<.001
D-dimer (μg/L)	0.55 (0.25–1.14)	0.37 (0.22–0.80)	0.91 (0.55–1.60)	<.001
FIB (g/L)	4.57 (3.70–5.86)	4.16 (3.42–5.04)	5.44 (4.34–6.79)	<.001
INR	1.01 (0.97–1.06)	1.00 (0.97–1.06)	1.02 (0.98–1.09)	.057
IL–6 (pg/ml)	12.81 (5.05–28.15)	8.54 (3.52–17.29)	21.85 (11.77–38.68)	<.001
IL–10 (pg/ml)	4.49 (3.67–6.15)	4.51(3.48–6.23)	4.50 (3.91–5.45)	.703
TNF-a (pg/ml)	2.12 (1.87–2.33)	2.18 (1.93–2.35)	2.07 (1.81–2.22)	.182
C-reactive protein (mg/L)	17.10 (6.57–49.70)	10.95 (3.73–26.08)	43.10 (17.70–74.80)	<.001
ESR(mm/hr)	25.00 (10.00–58.25)	18.50 (7.00–33.00)	47.50 (29.50–72.50)	<.001
Alanine aminotransferase (U/L)	24.00 (17.00–41.75)	22.00 (16.00–36.50)	31.00 (19.00–47.50)	.027
Aspartate aminotransferase (U/L)	26.00 (20.25–36.00)	24.00 (20.00–31.00)	33.00 (23.75–45.00)	.001
Serum creatinine (μmol/L)	65.90 (55.60–77.50)	66.90 (56.00–77.30)	65.60 (53.90–77.88)	.902
Blood urea nitrogen (mmol/L)	3.84 (2.82–4.55)	3.84 (2.80–4.63)	3.88 (3.22–4.54)	.562
Serum Amyloid A (mg/dL)	159.10 (26.40–643.20)	71.25 (19.08–342.93)	658.50 (282.05–730.25)	<.001
HBDH (U/L)	181.00 (142.50–240.00)	157.00 (135.80–214.80)	233.00 (176.00–323.25)	<.001

Abbreviation: FIB, fibrinogen; ESR, erythrocyte sedimentation rate; HBDH, α-hydroxybutyrate dehydrogenase; INR, international normalized ratio.
[a]*p* values indicate differences between non-severe and severe patients. $p < .05$ was considered statistically significant.

TABLE 3 Univariate logistic regression analysis of variables associated with severity of COVID-19

Variable	OR	95% CI	*p* Value[a]
White blood cells (×10^9/L)	1.325	1.121–1.566	.001
Lymphocytes (×10^9/L)	0.062	0.019–0.200	<.001
Neutrophils (×10^9/L)	1.416	1.189–1.685	<.001
D-dimer (μg/L)	2.848	1.602–5.064	<.001
FIB (g/L)	1.669	1.296–2.148	<.001
C-reactive protein (mg/L)	1.023	1.011–1.035	<.001
ESR(mm/hr)	1.029	1.014–1.044	<.001
Serum Amyloid A (mg/dl)	1.004	1.002–1.006	<.001
HBDH (U/L)	1.011	1.005–1.017	<.001

Abbreviation: FIB, fibrinogen; ESR, Erythrocyte sedimentation rate; HBDH, α-hydroxybutyrate dehydrogenase; INR, international normalized ratio.
[a]*p* values indicate differences between non-severe and severe patients. $p < .05$ was considered statistically significant.

(OR, 2.013; 95% CI, 1.079–3.757; $p = .028$) and ESR (OR, 1.025; 95% CI, 1.007–1.043; $p = .006$; Table 4).

3.3 | Establishment of prediction score system

To predict the possibility of deterioration of the disease on admission, a simple and efficient clinical scoring model, the COVID-19 index, was established based on laboratory parameters. The formula consisted of key risk factors including the lymphocytes counts, the serum level of D-dimer and ESR. Based on the β value presented in Table 4, the contributions of the risk factors were identified. The formula was constructed from the multivariate logistical regression model and presented as COVID-19 index = 3 × D-dimer (μg/L) + 2 × lgESR (mm/hr) − 4 × lymphocyte (×10^9/L) + 8.

3.4 | Validation of score system

To assess the performance of the predictive scoring system, we performed an ROC analysis. The area under the receiver operating characteristic curve was 0.843 (95% CI, 0.771–0.914, $P < 0.001$; Figure 1). It can be seen that our model was positively correlated with the degree of the disease and had a very good predictive value.

The severity of COVID-19 patients in different ranges of the COVID-19 index is shown in Figure 2. Most (70.4%) of patients with scores > 11 were severe, while patients with scores ≤ 7 rarely develop to severe cases. When the patients' admission scores were higher than 9, the proportion of severe patients was 61.5%, which was significantly different when compared to those with scores < 7. Our findings might suggest that the optimal cut-off value of COVID-19 index was 9, and the sensitivity, specificity and Youden index were 0.8, 0.79 and 0.59, respectively. This means that SARS-CoV-2-infected patients with a COVID-19 index higher than 9 were much more likely to progress to severe illness.

TABLE 4 Multivariate logistic regression analysis of variables associated with severity of COVID-19

Risk factor	β	OR	95% CI	p Value[a]
Lymphocytes ($\times 10^9$/L)	−2.372	0.412	0.280–0.615	<.001
D-dimer (μg/L)	0.700	2.013	1.079–3.757	.028
ESR(mm/hr)	0.025	1.025	1.007–1.043	.006

Abbreviation: ESR, erythrocyte sedimentation rate.

[a]p values indicate differences between non-severe and severe patients. $p < .05$ was considered statistically significant.

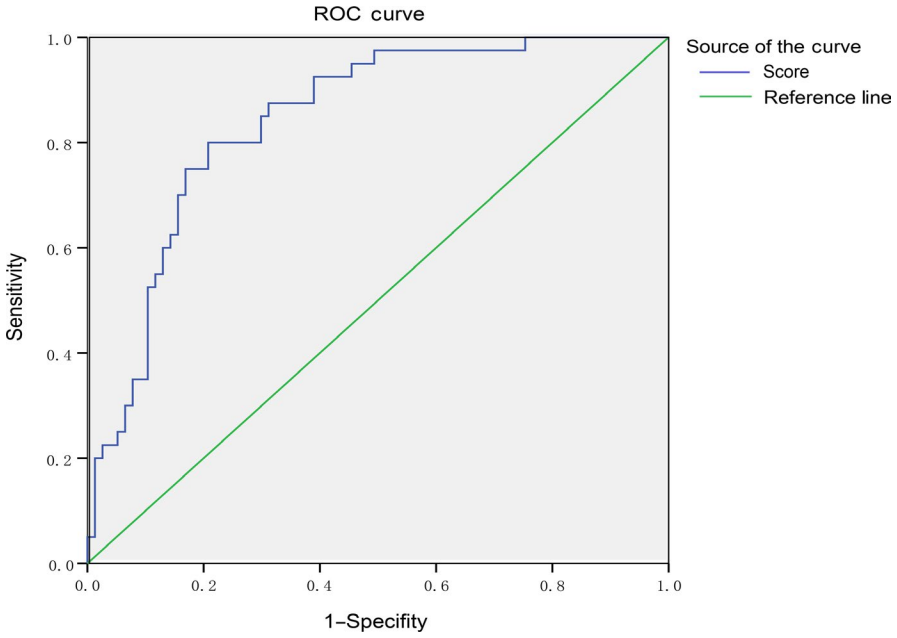

FIGURE 1 ROC curve for COVID-19 index in patients infected with SARS-CoV-2. ROC, receiver operating characteristic [Colour figure can be viewed at wileyonlinelibrary.com]

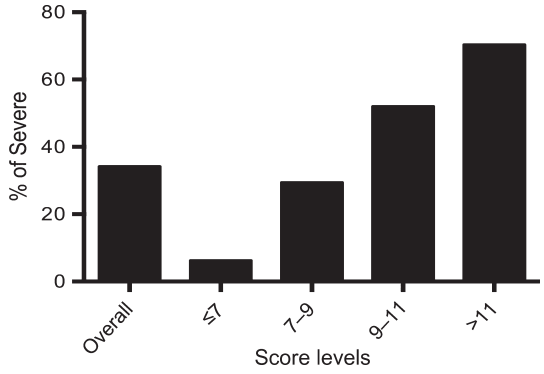

FIGURE 2 The rate of severe patient increases as the COVID-19 index increases

4 | DISCUSSION

The purpose of this study was to establish a scoring system to predict the patient's progression in advance. After identifying the three key risk factors of lymphocytes, D-dimer and ESR, we developed a scoring system based on their contribution to patient severity. Our study provides a simple and effective method for predicting the severity of a patient's condition.

COVID-19 is a disease caused by SARS-CoV-2 infection, which is a novel virus that belongs to the beta coronavirus and is highly pathogenic. Since the first COVID-19 patient was confirmed, it has spread throughout the China quickly. At present, COVID-19 has become a pandemic. To 20 April 2020, the cumulative number of confirmed diagnoses has exceeded 2,300,000 and 160,120 people have died in 213 countries, areas or territories (WHO, 2020). Infection with SARS-CoV-2 usually present as flu-like symptoms, such as fever, cough and shortness of breath. However, a considerable number of patients undergo rapid deterioration and die suddenly. Therefore, being able to timely and effectively predict the progression of disease is important for clinicians to implement beneficial interventions, which would promote the efficient use of healthcare resources and save more lives.

It has been reported that age and pre-existing diseases are considered to be the risk factors for severe COVID-19 patients. In addition, several studies have shown that chest CT scans and many laboratory test parameters, including the levels of various enzymes, coagulation factors, inflammatory markers and absolute counts of immune cells in peripheral blood of patients with COVID-19 were related to the severity of the disease (Hoffmann et al., 2020; Li, Wu, et al., 2020; Zhang, 2020). Importantly, the clinical acquisition of these indicators is quick and easy. Therefore, in this study, we tried

to identify key risk factors from these laboratory test parameters to establish a predictive model.

Through univariate logistic regression, we found that WBC, lymphocytes, neutrophils, D-dimer, FIB, CRP, ESR, SAA and HBDH were independent risk factors for severe patient outcome. Recent studies revealed that most COVID-19 patients presented with lymphocytopenia, elevated levels of D-dimer, CRP as well as IL-6, and some cases had increased AST, ALT, FIB and SAA (Fan et al., 2020; Guan et al., 2020; Huang et al., 2020). Laboratory abnormalities are more obvious in severe patients, suggesting that patient severity may be associated with the multiple organ damage, cytokine storms and hypercoagulability. Furthermore, multiple regression analysis revealed that lymphocytes, D-dimer and ESR were the key risk factors for patient severity, which may be related to the more severe inflammation, hypercoagulable state and poorer body condition. Hence, we used these three variables to assemble a score formula named COVID-19 index. Although many variables are related to the patient's disease trend, a scoring system that incorporates multiple variables is more predictive. In addition, as a newly discovered coronavirus, COVID-19 caused by SARA-CoV-2 has not been thoroughly studied, and there is no accepted clinical grading and treatment system. Therefore, the disease prediction scoring system established in this study fills this gap and has relevance. For newly admitted inpatients with SARS-CoV-2 infection, the risk of the disease can be evaluated and the treatment can be guided by quickly improving the corresponding examination, reducing the probability of the patient developing serious illness, and increasing the timeliness of treatment for severe patients.

Currently, predicted risk factors associated with a severe outcome have been identified in some studies. Chen's group proposed a nomogram to predict the prognosis of patients with COVID-19, including age, dyspnoea, coronary heart disease, cerebrovascular disease, elevated procalcitonin (PCT) and aspartate aminotransferase (AST) (Chen, Liang, et al., 2020). Similarly, Gong et al also generated a nomogram for early identification of severe COVID-19 composed of 7 features, including age, direct bilirubin (DBIL), red blood cell distribution width-coefficient variation (RDW_CV), blood urea nitrogen (BUN), CRP, lactate dehydrogenase (LDH) and albumin (Gong et al.., 2020). Ji et al constructed a score model named CALL (comorbidity, age, lymphocyte and LDH) to predict the likelihood of disease progression (Ji et al., 2020). In addition, Li and his group revealed that older age, hypertension, high LDH and D-dimer level were risk factors for severe cases (Li, Xu, et al., 2020). Compared with these investigations, our study establish a simple scoring formula to early identify patients who will progress to severe COVID-19. Although the model includes only 3 parameters, it is able to efficiently distinguish patients at higher risk to progress to severe cases. As far as we know, it is the first predictive formula relevant to severity of COVID-19 patients.

As a simple and practical method for predicting the progression of COVID-19, this model provides a valuable approach for clinicians to stratify patients and then implement prompt and efficient therapy as soon as possible. ROC curve analysis showed that our scoring formula was capable of discriminating between severe and non-severe patients. For a given specificity, our severity score always presents a better sensitivity than chance. Although this predictive scoring system is reasonable and can be used conveniently and quickly by clinicians, it still has certain shortcomings. In making the scoring system, the inclusion of a larger sample can improve accuracy; moreover, we also need to conduct prospective studies to verify the predictive value of the system.

ACKNOWLEDGEMENT

The authors sincerely thank every research object and Prof. Xin Zheng for offering convenience in data collection and assistance in draft review in this study.

CONFLICT OF INTERESTS

We declare no competing interests.

AUTHOR CONTRIBUTIONS

D.H., H.F. and S.L. designed the study. Y.D., H.Z., M.L., Z.Z., W.G., T.Y. and Y.G. researched data. Y.D. and M.L. contributed to the data analysis. W.G., M.L., Y.D., K.D., Q.W., H.Z. and Z.Z. contributed to the discussion. Y.D., and H.Z. wrote manuscript. X.Z., L.Z., H.F., S.L. and D.H. reviewed/edited the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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How to cite this article: Dong Y, Zhou H, Li M, et al. A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection. *Transbound Emerg Dis*. 2020;67:2823–2829. https://doi.org/10.1111/tbed.13651