Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Clinical Microbiology and Infection 26 (2020) 1400–1405

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Predictors of progression from moderate to severe coronavirus disease 2019: a retrospective cohort

B. Cheng [1, †], J. Hu [2, †], X. Zuo [3, †], J. Chen [3, †], X. Li [4], Y. Chen [5], G. Yang [3, **], X. Shi [2, ***], A. Deng [1, *]

[1)] *Department of Pharmacy, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[2)] *Department of Respiratory and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[3)] *Information Centre, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[4)] *Department of Research, Wuhan Hospital of Traditional Chinese and Western Medicine, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[5)] *Tongji School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*

ARTICLE INFO

Article history:
Received 24 June 2020
Received in revised form
26 June 2020
Accepted 28 June 2020
Available online 2 July 2020

Editor: L. Leibovici

Keywords:
Coronavirus disease 2019
Moderate
Neutrophil–lymphocyte ratio
Predict
Prognosis

ABSTRACT

Objective: Most cases of coronavirus disease 2019 (COVID-19) are identified as moderate, which is defined as having a fever or dry cough and lung imaging with ground-glass opacities. The risk factors and predictors of prognosis in such cohorts remain uncertain.
Methods: All adults with COVID-19 of moderate severity diagnosed using quantitative RT-PCR and hospitalized at the Central Hospital of Wuhan, China, from 1 January to 20 March 2020 were enrolled in this retrospective study. The main outcomes were progression from moderate to severe or critical condition or death.
Results: Among the 456 enrolled patients with moderate COVID-19, 251/456 (55.0%) had poor prognosis. Multivariate logistic regression analysis identified higher neutrophil count: lymphocyte count ratio (NLR) on admission (OR 1.032, 95% CI 1.042–1.230, p 0.004) and higher C-reactive protein (CRP) on admission (OR 3.017, 95% CI 1.941–4.690, $p < 0.001$) were associated with increased OR of poor prognosis. The area under the receiver operating characteristic curve (AUC) for NLR and CRP in predicting progression to critical condition was 0.77 (95% CI 0.694–0.846, $p < 0.001$) and 0.84 (95% CI 0.780–0.905, $p < 0.001$), with a cut-off value of 2.79 and 25.95 mg/L, respectively. The AUC of NLR and CRP in predicting death was 0.81 (95% CI 0.732–0.878, $p < 0.001$) and 0.89 (95% CI 0.825–0.946, $p < 0.001$), with a cut-off value of 3.19 and 33.4 mg/L, respectively.
Conclusions: Higher levels of NLR and CRP at admission were associated with poor prognosis of individuals with moderate COVID-19. NLR and CRP were good predictors of progression to critical condition and death. **B. Cheng, Clin Microbiol Infect 2020;26:1400**
© 2020 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Introduction

As of 19 April 2020, there had been 2 241 359 confirmed cases of coronavirus disease 2019 (COVID-19) worldwide, including 152 551 deaths reported by WHO [1]. The outbreak of COVID-19 has become an international public health emergency [2,3].

The prognosis of individuals with COVID-19 of different severities at admission is significantly different. Most patients with mild or moderate disease who receive basic medical care at Fangcang shelter hospitals, which are large-scale, temporary hospitals rapidly built since 5 February in China, have a better prognosis [4]. Relative

* Corresponding authors: A. Deng, Department of Pharmacy, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430021, Hubei, China.
** Corresponding authors: G. Yang, Information Centre, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430021, Hubei, China.
*** Corresponding authors: X. Shi, Department of Respiratory and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430014, Hubei, China.
E-mail addresses: 564027263@qq.com (G. Yang), sandyshi125@163.com (X. Shi), dapsci@126.com (A. Deng).
† B. Cheng, J. Hu, X. Zuo and J. Chen contributed equally to this work.

https://doi.org/10.1016/j.cmi.2020.06.033
1198-743X/© 2020 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

to the moderate cases, patients with severe or critical disease have a higher probability of being admitted to intensive care units, have longer stays [5,6] and are more likely to die [7,8].

Identification of which individuals with initially mild or moderate disease will deteriorate into having severe or critical illness is useful, as it would allow for earlier treatment to prevent worsening outcomes and save medical resources for other patients. In this study, we focus on the clinical features and outcomes of patients with moderate COVID-19 treated at a single institution and explore the factors and indicators associated with their prognosis.

Methods

Study design and participants

All adult patients with moderate cases of COVID-19 hospitalized at the Central Hospital of Wuhan from 1 January to 20 March 2020, were enrolled in this retrospective cohort study. This is a tertiary hospital located in the central area of Wuhan, China, and is one of the designated hospitals for treating COVID-19 patients. The data cut-off for this study was 31 March 2020. The flowchart of confirmed patients enrolled in this study is shown in the Supplementary material (Fig. S1). All patients were diagnosed with COVID-19 based on positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quantitative RT-PCR using throat swab samples, in accordance with the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* recommended by the National Health Commission of China (version 7.0) [9]. This study was approved by the Central Hospital of Wuhan Hospital Ethics Committee (No. 2020-75). Written informed consent was waived by the ethics commission of the designated hospital for emerging infectious diseases.

Data collection

Epidemiological, demographic, clinical, laboratory, treatment and outcome data (progression to severe/critical/death) were reviewed and extracted by experienced clinicians from electronic medical records using a standardized data collection form and independently reviewed by two researchers.

Definitions

Fever was defined as an axillary temperature of at least 37.3°C. Disease severity grading (mild, moderate, severe, or critical) of COVID-19 was defined according to the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*. Mild grade was defined as few symptoms (low fever, fatigue) and without lung CT findings. Moderate grade was defined as fever, respiratory symptoms (dry cough, chest distress and shortness of breath after activities) and lung CT findings (i.e. ground-glass opacity, multiple small patchy shadows and pulmonary consolidation). Severe grade was defined as respiratory frequency $\geq$30 breaths/min, blood oxygen saturation $\leq$93%, oxygenation index <300 mmHg and/or lung infiltrates >50% within 24–48 hours. Critical grade was defined as respiratory failure, septic shock and/or multiple organ dysfunction or failure. Poor prognosis refers to progression from moderate to severe grade, critical grade or death.

Statistical analysis

Categorical variables are reported as number (%). Normally distributed continuous data were reported as mean ± standard deviation (SD) and non-normally distributed continuous data were reported as median (interquartile range (IQR)). Categorical data were compared using the χ^2 test or Fisher exact test. Independent *t* tests were used to compare normally distributed continuous data, and the Mann–Whitney *U*-test or Exact Mann–Whitney rank sum test was used to compare non-normally distributed continuous data. To adjust for the risk factors associated with illness progression in-hospital, univariable and multivariable logistic regression models were used. Considering the total number of prognoses ($n = 251$) in our study and to avoid overfitting of the model, 12 variables were chosen for multivariable logistic analysis on the basis of univariable logistic analysis results and clinical significance. Multivariable Cox proportional hazards regression analyses were used to further adjust the risk factors associated with survival. Considering the total number of deaths ($n = 46$) in our study and to avoid overfitting of the model, four variables were chosen for Cox regression analysis on the basis of multivariable logistic analysis results and clinical significance. Receiver operating characteristic (ROC) curves were used to evaluate the potential predictive value of risk factors on prognoses in-hospital. The Hosmer–Lemeshow test was used to calibrate the ROC curves. The Net Reclassification Index (NRI) was used to determine which indicators of ROC curves analysis were better at predicting outcomes, in line with previously published methods [10]. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 19.0) (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 8.0) (GraphPad, San Diego, CA, USA) software.

Results

Demographics, laboratory, treatment and prognosis characteristics

A total of 456 (100%) moderate cases were recruited in this study (Table 1), of which 44.96% (205/456) did not progress and 55.04% (251/456) had poor prognosis in-hospital. Briefly, 33.99% (155/456) of individuals worsened to a severe condition, 10.96% (50/456) of individuals worsened to become critical cases and 9.8% (46/456) of individuals died (Table 2). Basic information characteristics are shown in Table 1. The mean patient age was 54.97 years (range 18–99 years), and more than half of patients were female (245/456, 53.73%). Compared with individuals with no progression, individuals with poor prognoses were significantly older and more likely to have co-morbidities.

The laboratory data of all moderate cases on admission are shown in Table 1. Numerous variables were significantly associated with outcome, and individuals with poor prognoses generally had lower lymphocyte counts and higher levels of C-reactive protein (CRP) and procalcitonin, and higher neutrophil/lymphocyte ratio (NLR).

Treatment and outcome data are presented in Table 2. As indicated, antiviral treatment (i.e. ribavirin, arbidol and lopinavir/ritonavir) was the most common treatment method for moderate cases (437/456, 95.83%), followed by antibiotic treatment (i.e. cephalosporins and quinolones; 369/456, 80.92%) and glucocorticoid treatment (226/456, 49.56%). Glucocorticoid treatment and intravenous immunoglobulin were more commonly used for individuals with poor prognoses than for those that did not progress. The median time from illness onset to admission was 7 days (IQR 4.25–14 days) in all moderate patients and did not differ significantly between the two groups ($p > 0.05$).

Risk factors associated with poor prognosis

Table 3 summarizes the results of univariable and multivariable logistic analyses of risk factors associated with progression from moderate to severe or critical condition or death. After adjusting for age, gender, co-morbidities, neutrophil count, lymphocyte count,

Table 1
Demographic, clinical, laboratory findings of patients with moderate coronavirus disease 2019 on admission

	Total (n = 456)	No progression (n = 205)	Poor prognoses (n = 251)	p value
Demographics and clinical characteristics				
Age (years)	54.97 ± 18.59	48.95 ± 18.17	59.89 ± 17.48	<0.001
≤45	159 (34.88%)	97 (47.32%)	62 (24.70%)	
45–65	137 (30.04%)	56 (27.32%)	81 (32.27%)	
≥65	160 (35.08%)	52 (25.36%)	108 (43.03%)	
Sex				<0.001
Male	211 (46.27%)	71 (34.63%)	140 (55.77%)	
Female	245 (53.73%)	134 (65.37%)	111 (44.23%)	
Systolic pressure (mmHg)	126.08 ± 23.86	126.75 ± 22.75	125.54 ± 24.77	0.592
Diastolic pressure (mmHg)	76.09 ± 15.39	77.38 ± 13.93	75.03 ± 16.44	0.104
Co-morbidities				
Hypertension	150 (32.89%)	48 (23.41%)	102 (40.63%)	<0.001
Diabetes	70 (15.35%)	20 (9.76%)	50 (19.92%)	0.003
Chronic kidney disease	19 (4.16%)	2 (0.97%)	17 (6.77%)	0.002
Cardiovascular disease	52 (11.40%)	15 (7.32%)	37 (14.74%)	0.013
Neural system diseases	33 (7.23%)	6 (2.92%)	27 (10.75%)	0.001
Pulmonary disease	18 (3.94%)	4 (1.95%)	14 (5.57%)	0.048
Cancer	12 (2.63%)	2 (0.97%)	10 (3.98%)	0.046
Signs and symptoms				
Fever	297 (65.13%)	136 (66.34%)	161 (64.14%)	0.624
Cough	241 (52.85%)	111 (54.14%)	130 (51.79%)	0.616
Sputum production	66 (14.47%)	28 (13.65%)	38 (15.13%)	0.655
Shortness of breath	102 (22.23%)	46 (22.24%)	56 (22.31%)	0.974
Myalgia or fatigue	153 (33.55%)	69 (33.65%)	85 (33.86%)	0.963
Diarrhoea	28 (6.14%)	10 (4.87%)	18 (7.17%)	0.310
Nausea and vomiting	18 (3.94%)	7 (3.41%)	11 (4.38%)	0.598
Respiratory rate (breaths/min)	20 (18–20)	20 (18–20)	20 (18–21)	0.448
Oxygen saturation (%)	98 (96–99)	98 (97–99)	96 (97–99)	0.493
Leucocytes count (× 10^9/L)	5.14 (3.95–6.75)	5.24 (4.03–6.25)	5.02 (3.90–6.92)	0.019
<4	117 (25.65%)	46 (22.43%)	71 (28.28%)	
4–10	315 (69.07%)	149 (72.68%)	166 (66.13%)	
>10	24 (5.28%)	10 (4.89%)	14 (5.59%)	
Neutrophil count (× 10^9/L)	3.20 (2.35–4.75)	3.03 (2.23–4.25)	3.29 (2.38–5.18)	0.006
Lymphocyte count (× 10^9/L)	1.19 (0.85–1.61)	1.47 (1.05–1.86)	1.02 (0.70–1.42)	<0.001
NLR	2.59 (1.66–4.55)	2.00 (1.42–3.25)	3.37 (2.06–5.66)	<0.001
Haemoglobin (g/L)	126.50 ± 19.58	125.38 ± 21.78	125.09 ± 20.99	0.886
Platelet count (× 10^9/L)	189 (147–246)	216 (167–255)	174 (130–231)	<0.001
Albumin (g/L)	38.89 ± 6.23	40.16 ± 5.88	37.86 ± 6.33	<0.001
APTT (seconds)	28.00 (24.00–21.70)	26.94 (24.44–30.45)	29.50 (25.50–33.90)	0.001
Prothrombin time (seconds)	11.21 ± 2.74	10.85 ± 2.81	11.50 ± 2.56	0.011
INR	0.98 (0.93–1.05)	0.98 (0.92–1.04)	1.0 (0.94–1.06)	0.008
D-dimer (μg/L)	0.52 (0.21–1.31)	0.4 (0.36–1.04)	0.66 (0.3–1.66)	<0.001
<1.0	314	153	161	
≥1.0	142	52	90	
Total bilirubin (mmol/L)	9.40 (7.1–12.97)	9.3 (7.2–12.55)	9.5 (7.0–13.50)	0.900
Alanine aminotransferase (U/L)	18.55 (12.5–30.37)	17.50 (11.5–29.65)	19.3 (13.4–31.90)	0.539
Aspartate aminotransferase (U/L)	20.80 (15.7–29.60)	18.50 (14.95–23.10)	24.00 (17.00–36.60)	0.006
Creatinine (μmol/L)	66.60 (51.4–79.8)	61.00 (50.90–73.60)	70.0 (53.20–85.80)	<0.001
<133	436 (95.61%)	200 (97.56%)	236 (94.02%)	
≥133	20 (4.39%)	5 (2.44%)	15 (5.98%)	
Potassium (mmol/L)	3.3 (3.10–4.00)	3.72 (3.50–4.30)	3.90 (3.40–4.60)	0.021
Creatine kinase (U/L)	63.5 (32.32–111.50)	52.50 (42.00–100.75)	74.5 (40.00–139.90)	0.002
Lactate dehydrogenase (U/L)	166 (132–213)	148 (110–180)	191 (150–237)	<0.001
Procalcitonin (ng/mL)	0.05 (0.04–0.08)	0.04 (0.03–0.06)	0.07 (0.17–0.60)	<0.001
<0.5	438 (96.05%)	204 (99.51%)	234 (93.22%)	
≥0.5	18 (3.95%)	1 (0.49%)	17 (6.79%)	
C-reactive protein (mg/L)	0.61 (0.10–3.12)	0.28 (0.06–1.05)	2.02 (0.24–4.98)	<0.001
<6.0	226 (49.56%)	141 (68.78%)	85 (33.86%)	
≥6.0	230 (50.44%)	64 (31.22%)	166 (66.14%)	
Erythrocyte sedimentation rate (mm/h)	31.00 (14.00–54.75)	17.00 (10.0–41.25)	38.00 (13.00–58.5)	<0.001
Interleukin-6 (pg/mL)	3.83 (1.67–10.41)	2.43 (1.5–4.99)	5.94 (2.47–24.07)	<0.001

Data are n (%). Normal distributed data are mean ± SD and non-normal distributed data are median (IQR). p values were calculated by Mann–Whitney U-test, χ^2 test, or Fisher's exact.
Abbreviations: APTT, activated partial thromboplastin time; INR, international normalized ratio; NLR, neutrophil count/lymphocyte count ratio.

NLR, CRP and procalcitonin, we found that older age (>45 years) (odds ratio (OR) 1.885, 95% CI 1.094–3.249, p = 0.022), male gender (OR 2.314, 95% CI 1.385–3.287, p < 0.001), higher NLR on admission (OR 1.032, 95% CI 1.042–1.230, p = 0.004) and higher CRP on admission (OR 3.017, 95% CI 1.941–4.690, p < 0.001) were associated with increased OR of poor prognoses. Furthermore, we calculated the OR for the different prognoses in more detail (see Supplementary material, Table S1). Briefly, older age, male gender, NLR and CRP levels at admission >6.0 mg/L were associated with increased OR of severe progression. Male gender, NLR, CRP >6.0 mg/

Table 2
Treatments and outcomes of patients with moderate coronavirus disease 2019

	Total (n = 456)	No progression (n = 205)	Poor prognoses (n = 251)	p value
Treatment				
Antiviral[a]	437 (95.83%)	193 (94.14%)	244 (97.21%)	0.103
Antibiotic[b]	369 (80.92%)	173 (84.39%)	196 (78.08%)	0.088
Glucocorticoids	226 (49.56%)	70 (34.14%)	156 (62.15%)	<0.001
Intravenous immunoglobulin	145 (31.79%)	54 (26.31%)	91 (36.25%)	0.024
Outcomes				
Time from illness onset to admission, days	7 (4.25–14)	8 (4–14)	7 (5–11)	0.135
Severe progression	—	—	155 (61.75%)	
Critical progression	—	—	50 (19.92%)	
Death progression	—	—	46 (18.33%)	

Data are n (%). Normal distributed data are mean ± SD and non-normal distributed data are median (IQR).
[a] Antiviral treatments included ribavirin, arbidol and lopinavir/ritonavir.
[b] Antibiotic treatments included cephalosporins and quinolones.

l on admission were associated with increased OR of progression to critical condition. Older age, male gender, NLR, procalcitonin >0.5 ng/mL and CRP >6.0 mg/L on admission were associated with increased OR of death. These results are consistent with our Cox regression analysis (see Supplementary material, Table S2).

Risk factors predicting the prognosis of individuals with moderate COVID-19

To explore risk factors that can predict the prognosis of individuals with moderate COVID-19, we used ROC curve analysis.

Table 3
Risk factors associated with any in-hospital disease progression

	Univariable regression		Multivariable regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Demographics and clinical characteristics				
Age (years)				
≤45	1 (ref)			
45–65	2.263 (1.149–3.608)	0.001	1.885 (1.094–3.249)	0.022
≥65	3.249 (2.053–5.144)	<0.001	2.247 (1.242–4.064)	0.007
Male (versus female)	2.380 (1.627–3.483)	<0.001	2.134 (1.385–3.287)	0.001
Hypertension	0.447 (0.296–0.673)	<0.001	0.929 (0.557–1.550)	0.778
Diabetes	0.435 (0.249–0.758)	0.003	0.749 (0.392–1.432)	0.382
Chronic kidney disease	0.136 (0.031–0.594)	0.008	0.415 (0.078–2.206)	0.302
Cardiovascular disease	0.457 (0.243–0.859)	0.015	1.204 (0.554–2.619)	0.639
Neural system diseases	0.250 (0.101–0.618)	0.003	0.462 (0.160–1.336)	0.154
Pulmonary disease	0.337 (0.109–1.040)	0.058		
Cancer	0.237 (0.051–1.096)	0.065		
Laboratory findings				
Leucocytes count (× 10^9/L)				
<4	1.012 (0.452–2.691)	0.830		
4–10	0.796 (0.343–1.845)	0.595		
>10	1 (ref)			
Neutrophil count (× 10^9/L)	1.169 (1.071–1.276)	<0.001	1.097 (0.996–1.208)	0.062
Lymphocyte count (× 10^9/L)	0.443 (0.316–0.620)	<0.001	0.789 (0.581–1.072)	0.129
NLR	1.251 (1.148–1.362)	<0.001	1.132 (1.042–1.230)	0.004
Platelet count (× 10^9/L)	0.997 (0.994–0.999)	0.002		
Albumin (g/L)	0.931 (0.897–0.966)	<0.001		
APTT (seconds)	1.031 (1.008–1.055)	0.008		
Prothrombin time (seconds)	1.095 (1.018–1.178)	0.015		
INR	2.840 (1.241–6.50)	0.013		
D-dimer (μg/L)				
<1.0	1 (ref)			
≥1.0	1.298 (0.280–6.027)	0.739		
Aspartate aminotransferase (U/L)	1.033 (1.018–1.048)	<0.001		
Creatinine (μmol/L)				
<133				
≥133	9.330 (0.624–139.57)	0.106		
Potassium (mmol/L)	1.240 (1.128–1.363)	<0.001		
Creatine kinase (U/L)	1.005 (1.003–1.008)	<0.001		
Lactate dehydrogenase (U/L)	1.008 (1.005–1.010)	<0.001		
Procalcitonin (ng/mL)				
<0.5	1 (ref)		1 (ref)	
≥0.5	14.291 (1.955–112.339)	0.009	4.003 (0.442–36.272)	0.217
C-reactive protein (mg/L)				
<6.0	1 (ref)		1 (ref)	
≥6.0	4.303 (2.900–6.383)	<0.001	3.017 (1.941–4.690)	<0.001
Erythrocyte sedimentation rate (mm/h)	1.013 (1.005–1.021)	0.002		
Interleukin-6 (pg/mL)	1.035 (1.011–1.059)	0.004		

Abbreviations: APTT, activated partial thromboplastin time; INR, international normalized ratio; NLR, neutrophil count/lymphocyte count ratio.

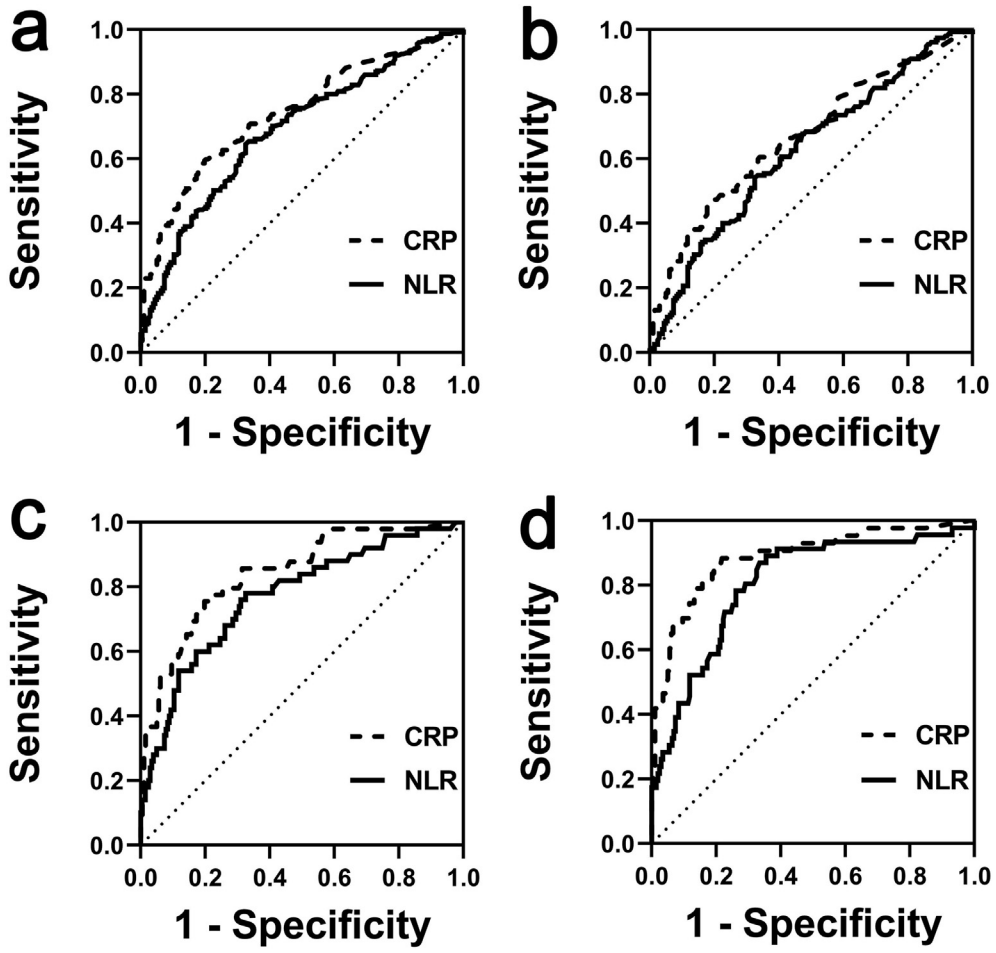

Fig. 1. Receiver operating characteristics (ROC) curves of neutrophil: lymphocyte ratio (NLR) and C-reactive protein (CRP) in patients with moderate coronavirus disease 2019 (COVID-19). (a) ROC curve of NLR and CRP in predicting total poor prognoses; (b) ROC curve of NLR and CRP in predicting severe progression; (c) ROC curve of NLR and CRP in predicting critical progression; (d) ROC curve of NLR and CRP in predicting death. Total poor prognoses, moderate cases progress to severe, critical cases or death.

The ROC curve of NLR and CRP in predicting the total poor prognoses and severe progression is shown in Figs. 1a,b. The areas under the curve (AUC) of NLR and CRP in predicting critical progression were 0.77 (95% CI 0.694–0.846, $p < 0.001$) and 0.84 (95% CI 0.780–0.905, $p < 0.001$), with cut-off values of 2.79 and 25.95 mg/L, respectively (Fig. 1c). Additionally, the AUC of NLR and CRP in predicting death outcome were 0.81 (95% CI 0.732–0.878, $p < 0.001$) and 0.89 (95% CI 0.825–0.946, $p < 0.001$), with cut-off values of 3.19 and 33.4 mg/L, respectively (Fig. 1d). Other exact results of the ROC curve analysis, including sensitivity, specificity, Youden Index, Hosmer–Lemeshow test and NRI, are shown in Table 4.

Discussion

In this retrospective study, the major symptoms of moderate COVID-19 were fever and cough and these symptoms did not differ between the two outcome groups (Table 1). Therefore, predicting prognosis based on symptoms was not possible. Using comparative and multivariable analyses of basic patient characteristics, we found that co-morbidities in moderate cases are not a risk factor for poor prognosis, which is consistent with recent studies [11]. However, older age, male gender, NLR and CRP levels on admission were significantly associated with poor prognoses in individuals with moderate COVID-19.

In our study, the AUC of both NLR and CRP in predicting progression to critical condition and death was >0.75 (Table 4), which suggests that NLR and CRP may act as predictors of progression. Compared with NLR, the NRI of CRP was >0 in predicting progression to critical condition and death, indicating that CRP is a better predictor, which is consistent with the AUC results. Additionally, although the AUC of procalcitonin in predicting death was also >0.75, the p value of the ROC curve of the Hosmer–Lemeshow test for procalcitonin was <0.001 (Table 4), which suggests poor calibration of the ROC curve. Hence, the difference between the predicted value and the true value cannot be explained by chance. Hence, these results indicate that procalcitonin is not a good predictor of death in individuals with moderate COVID-19 in our study.

Additionally, multivariable logistic analysis revealed that treatments using antibiotics, intravenous immunoglobulin and glucocorticoids were not associated with prognosis (see Supplementary material, Table S3), suggesting that these medications did not improve prognosis when given to individuals with moderate COVID-19. As most COVID-19 cases are mild or moderate and medical resources are limited, these findings are clinically significant for taking appropriate treatment options and using medical resources in a cost-effective way. However, randomized controlled trials are required to confirm the impact of drug treatment on individuals with moderate COVID-19.

There are several limitations of the study. First, this is a single centre, retrospective study. Second, most individuals with

Table 4
The parameter results of ROC curve analysis

	AUC (95% CI)	p value[a]	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Youden index	Cut-off value	p value[b]	NRI
Prediction for total prognoses								
NLR	0.69 (0.637–0.734)	<0.001	64.54 (0.583–0.706)	67.49 (0.606–0.739)	0.32	2.59	0.035	—
CRP	0.74 (0.695–0.786)	<0.001	61.48 (0.552–0.674)	78.17 (0.719–0.834)	0.39	10.85 mg/L	0.009	—
Prediction for severe progression								
NLR	0.62 (0.565–0.681)	<0.001	54.19 (0.463–0.618)	67.49 (0.608–0.736)	0.22	2.60	0.343	—
CRP	0.67 (0.609–0.725)	<0.001	45.39 (0.377–0.533)	81.73 (0.757–0.865)	0.28	14.15 mg/L	0.646	—
Prediction for critical progression								
NLR	0.77 (0.694–0.846)	<0.001	76.00 (0.618–0.869)	68.97 (0.621–0.753)	0.45	2.79	0.635	ref
CRP	0.84 (0.780–0.905)	<0.001	78.00 (0.645–0.872)	67.49 (0.608–0.735)	0.45	25.95 mg/L	0.134	15.52
Prediction for in-hospital death								
NLR	0.81 (0.732–0.878)	<0.001	78.26 (0.637–0.891)	73.89 (0.673–0.798)	0.52	3.16	0.059	ref
CRP	0.89 (0.825–0.946)	<0.001	67.44 (0.525–0.7951)	0.929 (0.884–0.957)	0.60	33.40 mg/L	0.121	31.75
PCT	0.89 (0.835–0.962)	<0.001	73.81 (0.589–0.847)	93.62 (0.892–0.963)	0.67	0.85 ng/mL	<0.001	—

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil count/lymphocyte count ratio; NRI, net reclassification index.
[a] p value for ROC curve.
[b] p value for Hosmer–Lemeshow test.

moderate COVID-19 that were enrolled in this study were older and had multiple co-morbidities, so were more likely to have adverse outcomes. Hence, the rate of disease progression in our study may not reflect the true rate.

In conclusion, age, gender, NLR and CRP levels at admission are associated with poor prognoses of patients with moderate COVID-19. NLR and CRP levels on admission tend to be good predictors of critical progression and death.

Contributors

BC contributed to writing and editing; JH contributed to writing and checking data; XZ contributed to formal analysis and software; JC contributed to data curation and resources; XL contributed to methodology; YC contributed to formal analysis; GY contributed to conceptualization and supervision; XS contributed to conceptualization and checking data; and AD contributed to supervision and editing. All authors contributed to the review and revision of the manuscript and have read and approved the final version.

Funding

This work was supported by the Natural Science Foundation of Hubei Province of China (2019CFA426).

Transparency declaration

The authors declare that they have no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.06.033.

References

[1] World Health Organization. Coronavirus disease (COVID-19) outbreak situation. Available from: https://who.sprinklr.com/; 2020.
[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020. epub ahead of print.
[3] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199–207.
[4] Chen S, Zhang Z, Yang J, Wang J, Zhai X, Barnighausen T, et al. Fangcang shelter hospitals: a novel concept for responding to public health emergencies. Lancet 2020. epub ahead of print.
[5] Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 2020. epub ahead of print.
[6] 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;395:497–506.
[7] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. epub ahead of print.
[8] Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 2020. epub ahead of print.
[9] National health Commission of the People's Republic of China. Diagnosis and treatment protocol for novel coronavirus pneumonia recommended. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml. [Accessed 5 March 2020].
[10] Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. JAMA 2017;318:1377–84.
[11] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. epub ahead of print.