Neutrophil Percentage and Neutrophil-to-Monocyte Ratio as Independent Risk Factors in the Severity of COVID-19

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Abstract

Background

Inflammation plays an important role in progression of the various viral pneumonia containing COVID-19, severe inflammatory responses could lead to an imbalance of immune response. The purpose of this study was to explore the possibility of the white blood count, neutrophil percentage, neutrophil-to-monocyte ratio (NMR) and neutrophil-to-lymphocyte ratio (NLR) at admission to reflect the clinical severity in patients with COVID-19.

Methods

Clinical and laboratory data of adult COVID-19 patients in Changsha, China, were collected and analyzed on admission. A logistic regression model was adopted to analyze the association between the disease severity and related risk factors. The receiver operating characteristic (ROC) curve was utilized to analyze the abilities of potential risk factors in the prediction of COVID-19 severity.

Results

Compared with non-severe patients, the severe ones had significantly higher levels of neutrophil percentage (74.9% vs. 62.1%; P < 0.001), NLR (4.1 vs. 2.1; P < 0.001) and NMR (12.4 vs. 8.0; P < 0.001). A regression analysis showed that neutrophil percentage (OR,1.113; 95% CI, 1.020-1.213; P=0.016) and NMR (OR, 1.110; 95% CI, 1.002-1.230; P = 0.046) were significantly associated with severity of COVID-19 patients. ROC curve showed that the area under the curves of neutrophil percentage, NMR and the combination of them were 0.842 (95% confidence interval (CI), 0.782-0.902), 0.790 (95% CI, 0.710-0.871) and 0.851 (95% CI, 0.790-0.911), respectively.

Conclusions

Neutrophil percentage and NMR may act as independent risk factors in the severity of COVID-19.

Background

To our knowledge, coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], which broke out firstly in December 2019, Wuhan, China[2, 3] and spread rapidly around the world. SARS-CoV-2 is the seventh member of coronaviruses family and can be transmitted from person to person [4, 5]. As of July 31, 2020, nearly 88122 people were diagnosed and 4668 people died from COVID-19 in China[6], and more than seventeen million cases as well as 680000 deaths have been identified across the world [7].

Generally speaking, the manifestations of COVID-19 are typically mild or moderate, but it can also contribute to severe illness especially progress rapidly to dyspnea, acute respiratory failure or even death[8]. There is mounting evidence that inflammation plays an important role in progression of the

various viral pneumonia containing COVID-19[9, 10]. Severe inflammatory responses could lead to an imbalance of immune response. Therefore, if early identifications and interventions can be taken in time through recognizing the warning signals of severe COVID-19, it is possible to boost cure rate, reduce mortality and shorten length of hospital stay. White blood cell count, neutrophil percentage, neutrophil-to-monocyte ratio (NMR) and neutrophil-to-lymphocyte ratio (NLR) are good biomarkers for inflammation and immune status in vivo, which are also simple, reproducible and cost-effective[11–18]. Given this situation, we wondered if these parameters at admission could help reflect the clinical severity in patients with COVID-19.

Methods

Study Design and Participants

This case series was subjected to approval by the institutional ethics board of the Second Xiangya Hospital of Central South University (No. 2020001). Laboratory-confirmed adult COVID-19 patients using real-time polymerase chain reaction admitted to the Public Health Treatment Center of Changsha, China, by March 14th 2020, were retrospectively collected and enrolled using the following inclusion criteria: 1) ≥ 18 years old; 2) Without disease history of blood system. Additional informed consent was obtained from all patients for which identifying information is included in this article.

Data Collection

Two members of our team carefully collected and reviewed the medical records of patients individually. The detailed information on demographic data, underlying comorbidities, medical history, symptoms, blood test parameters, and chest computed tomography (CT) scans on admission were recorded. The date of disease onset was defined as the day when the symptoms was noticed. We used one of the following criteria to determine severe cases of COVID-19: 1) respiratory rate ≥ 30/min; 2) oxygen saturation ≤ 93%; 3) PaO2/FiO2 ≤ 300 mmHg; 4) lung lesions progressed > 50% within 24–48 hours; 5) mechanical ventilation was implemented; 6) shock; 7) intensive care unit admission.

Statistical Analysis

Because all continuous variables in our study were non–normally distributed, we used median with range and the Mann-Whitney test to depict and analyze them. The χ^2 test or Fisher exact test was utilized to compare differences for categorical variables. Univariate analyses were carried out using a logistic regression model to analyze the association between the disease severity of COVID-19 and related factors. Multivariate linear regression was used to analyze the correlation between multiple variables (gender, age, neutrophil percentage, NMR, NLR, chest CT with ground glass change, hypertension, cardiovascular disease) and the severity of COVID-19. Areas under the curve (AUCs) with 95% confidence intervals (CIs) were computed to assess the severity of COVID-19 using potential predictors; AUC > 0.70 was considered clinically relevant. All analyses were performed using IBM SPSS, version 26.

Results

Baseline characteristics of the participants were summarized in Table 1. A total of 220 adult patients with laboratory-confirmed COVID-19 without histories of blood system were included in our study; 40 patients (18.2%) progressed to severe cases. Males were more likely to have severe COVID-19 (65.0% vs. 35.0%, P = 0.042). Compared to non-severe patients, the severe ones were older (57 years vs. 41 years, P < 0.001). The virus shedding time (21 days vs. 15 days, P = 0.001) and the duration of hospitalization (21 days vs. 17 days, P = 0.002) were both significantly longer in severe patients than non-severe cases. With regard to comorbidities, hypertension (35.0% vs. 13.3%; P = 0.001) and cardiovascular disease (12.5% vs 2.8%; P = 0.020) were more common in severe cases. They also showed higher ratios of several symptoms than non-severe cases, including fever (90.0% vs. 62.8%; P < 0.001), fatigue (70.0% vs. 38.9%; P < 0.001), anorexia (65.0% vs. 47.2%; P = 0.042), chills (25.0% vs. 9.4%; P = 0.014), myalgia (20.0% vs. 8.3%; P = 0.043), dyspnea (90.0% vs. 21.1%; P = 0.001), expectoration (62.5% vs. 42.8%; P = 0.024), and hemoptysis (10.0% vs. 2.2%; P = 0.038). In addition, chest CT with ground glass change was more common in severe cases (75.0% vs. 43.3%; P < 0.001).

Neutrophil percentage (74.9% vs. 62.1%; P < 0.001), NLR (4.1 vs. 2.1; P < 0.001) and NMR (12.4 vs. 8.0; P < 0.001) were significantly increased in severe COVID-19, whereas the white blood cell count did not show any statistically significant difference (P = 0.521). (Table 2)

In the univariate analysis, the severity was associated with gender (odds ratio [OR], 0.482; 95% CI, 0.236–0.982; P = 0.045), age (OR, 1.046; 95% CI, 1.021–1.071; P < 0.001), hypertension (OR, 0.286; 95% CI, 0.131–0.623; P = 0.002), cardiovascular disease(OR, 0.200; 95% CI, 0.055–0.728; P = 0.015), neutrophil percentage (OR, 1.168; 95% CI, 1.110–1.228; P < 0.001), NLR (OR, 1.773; 95% CI, 1.424–2.207; P < 0.001), NMR (OR, 1.253; 95% CI, 1.151–1.363; P < 0.001) (Table 3). However, in multivariate analysis, only neutrophil percentage (OR,1.113; 95% CI, 1.020–1.213; P = 0.016) and NMR (OR, 1.110; 95% CI, 1.002–1.230; P = 0.046) were found to be independent risk factors for the severe COVID-19. (Table 4)

Receiver operating characteristics (ROC) analysis showed that neutrophil percentage, NMR and the combination of them were able to predict the severity of COVID-19 (P < 0.001 for all). The AUC of neutrophil percentage, NMR and the combination were 0.842 (95% CI, 0.782–0.902), 0.790 (95% CI, 0.710–0.871), and 0.851 (95% CI, 0.790–0.911), respectively. The optimum cutoffs were 49.7%, 45.3%, and 53.6%, respectively. The sensitivities were 92.5%, 57.5% and 72.5%, respectively, and the specificity was 57.3%, 87.8%, and 81.2% respectively. (Table 5)

Table 1
Comparison of general data between the patients in non-severe group and severe group

	Severe (n = 40)	Non-severe (n = 180)	P Value
Sex	26/40	84/180	0.042
Male	14/40	96/180	
Female			
Age, years	57 (45,66)	41 (34,54)	0.000
Comorbidity			
Hypertension, %	14 (35.0)	24 (13.3)	0.001
Cardiovascular disease, %	5 (12.5)	5 (2.8)	0.020
Diabetes, %	3 (1.7)	13 (32.5)	1.000
Cerebrovascular disease, %	1 (0.6)	2 (5.0)	0.454
Digestive system disease, %	2 (1.1)	16 (40.0)	0.539
Respiratory system disease, %	3 (1.7)	7 (17.5)	0.394
Endocrine system disease, %	2(1.1)	5 (12.5)	0.614
No signs and symptoms, %	0 (0.0)	17 (9.4)	0.047
Symptoms			
Fever, %	36 (90.0)	113 (62.8)	< 0.001
Fatigue, %	28 (70.0)	70 (38.9)	< 0.001
Cough, %	27 (67.5)	167 (92.8)	0.132
Anorexia, %	26 (65.0)	85 (47.2)	0.042
Chills, %	10 (25.0)	17 (9.4)	0.014
Myalgia, %	8 (20.0)	15 (8.3)	0.043
Dyspnea, %	36 (90.0)	38 (21.1)	0.001
Expectoration, %	25 (62.5)	77 (42.8)	0.024
Pharyngalgia, %	3 (7.5)	31 (17.2)	0.124
Diarrhea, %	6 (15.0)	44 (24.4)	0.197

Abbreviation: CT, computed tomography; NLR, neutrophil/ lymphocyte ratio; NMR, neutrophil/ monocyte ratio.

	Severe (n = 40)	Non-severe (n = 180)	P Value
Hemoptysis, %	4 (10.0)	4 (2.2)	0.038
Dizziness, %	5 (12.5)	20 (11.1)	0.785
Headache, %	9 (22.5)	21 (11.7)	0.071
Vomiting, %	6 (15.0)	18 (10.0)	0.400
Abdominal pain, %	2 (5.0)	7 (9)	0.669
Nausea, %	4 (10.0)	25 (13.9)	0.511
Chest CT positive rate, %	40 (100.0)	169 (93.9)	0.222
Chest CT with ground glass change, %	30 (75.0)	78 (43.3)	< 0.001
Virus shedding time, days	21(16, 32)	17(13, 24)	0.002
Duration of hospitalization, days	21(14, 32)	15(11, 23)	0.001
Abbreviation: CT, computed tomography; NLR, neutrophil/ lymphocyte ratio; NMR, neutrophil/ monocyte ratio.			

P values indicate differences between severe and non-severe COVID-19 patients. $P < 0.05$ was considered statistically significant. Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher exact test.

Table 2
Blood test parameters of patients with COVID-19 on admission.

	Normal Range	Severe (n = 40)	Non-severe (n = 180)	P Value
White blood cell count, $\times 10^9$/L	3.5–9.5	4.8(3.3–6.5)	4.5(3.6–5.6)	0.521
Neutrophil percentage, %	40–75	74.9(68.0-83.1)	62.1(55.6–68.4)	< 0.001
NLR	/	4.1(3.0–7.0)	2.1(1.6-3.0)	< 0.001
NMR	/	12.4(8.9–22.5)	8.0(6.1–10.0)	< 0.001
Abbreviation: NLR, neutrophil/ lymphocyte ratio; NMR, neutrophil/ monocyte ratio.				
P values indicate differences between non-severe COVID-19 patients and severe COVID-19 patients. $P < 0.05$ was considered statistically significant. Continuous variables were described as median with range and analyzed by Mann-Whitney test.				

Table 3
Univariate analysis of factors related to the severity of COVID-19 patients

Variables	Odds Ratio (95% CI)	P Value
Gender	0.482 (0.236–0.982)	0.045
Age	1.046 (1.021–1.071)	< 0.001
White blood cell count	1.108 (0.903–1.360)	0.325
Neutrophil percentage	1.168 (1.110–1.228)	< 0.001
NLR	1.773 (1.424–2.207)	< 0.001
NMR	1.253 (1.151–1.363)	< 0.001
Hypertension	0.286 (0.131–0.623)	0.002
Cardiovascular disease	0.200 (0.055–0.728)	0.015
Chest CT with ground glass change	0.255 (0.118–0.553)	0.001
Univariate analysis was carried out using a logistic regression model.		
Abbreviation: CI, confidence interval; NLR, neutrophil/ lymphocyte ratio; NMR, neutrophil/ monocyte ratio.		
P < 0.05 was considered statistically significant.		

Table 4
Multivariate analysis of factors related to the severity of COVID-19 patients

	B	SE	Wald	P	OR	95% CI
Gender	0.796	0.462	2.963	0.085	2.216	0.896–5.483
Age	0.022	0.017	1.683	0.195	1.022	0.989–1.056
Neutrophil percentage	0.107	0.044	5.843	0.016	1.113	1.020–1.213
NMR	0.105	0.052	3.997	0.046	1.110	1.002–1.230
NLR	-0.050	0.117	0.187	0.666	0.951	0.756–1.195
Chest CT with ground glass change	-0.703	0.480	2.145	0.143	0.495	0.193–1.268
Hypertension	0.065	0.590	0.012	0.912	1.068	0.336–3.392
Cardiovascular disease	-0.958	0.914	1.100	0.294	0.384	0.064-2.300
Multivariate analysis was carried out using a logistic regression model.						
Abbreviation: CI, confidence interval; NMR, neutrophil/ monocyte ratio; NLR, neutrophil/ lymphocyte ratio;						
P < 0.05 was considered statistically significant.						

Table 5
Comparison of three predictors for predicting the severity of COVID-19

virables	AUC	SE	95%CI	Cutoff	Sensitivity	Specificity	P
Neutrophil percentage	0.842	0.031	0.782–0.902	49.72%	92.5%	57.2%	< 0.001
NMR	0.790	0.041	0.710–0.871	45.29%	57.5%	87.8%	< 0.001
Neutrophil percentage combined NMR[a]	0.851	0.031	0.790–0.911	53.61%	72.5%	81.8%	< 0.001
Abbreviations: AUC: Area under curve; SE: Standard error; CI: Confidential interval; NMR, Neutrophil/ monocyte ratio; a: Combination of Neutrophil percentage and NMR was used to establish the logistic regression model to obtain the prediction probability.							
P < 0.05 was considered statistically significant.							

Abbreviations: ROC, receiver operating characteristics; NMR, neutrophil/ monocyte ratio.

ROCs of neutrophil percentage, NMR and combination of them for the predictors of severity of COVID-19 patients.

Discussion

To date, although the relationship between blood test parameters and COVID-19 has been repeatedly addressed, but the role of neutrophil percentage, NMR in the severity of COVID-19 has not been elaborated yet. The important finding of the study was that neutrophil percentage and NMR might act as independent risk factors in the severity of COVID-19.

Previous studies have shown that SARS-CoV-2 could contribute to hyperinflammatory response which was the main reason of the severity and death of COVID-19 patients[15, 19]. Traditional systemic inflammatory is triggered by white blood cell which comprises of neutrophils, lymphocytes, monocytes, and immature cells[20]. Neutrophils are the most abundant leukocytes in blood circulation which are the first line of host defense against pathogens [21, 22]. It was reported that humans produced 1 billion neutrophils per day per kilogram of body weigh whereas increased to 10 billion when infected [21]. In vivo, the release of danger signals recruit the neutrophils to the site of tissue necrosis [23], then activated neutrophils through releasing preformed mediators, recognizing foreign nucleic acids, extruding neutrophil extracellular traps (NETs), presenting antigens to memory CD4 T cells, producing a variety of cytokines to regulate innate and adaptive immune responses, and to some degree, neutrophils could also lead to tissue necrosis[24–28]. Neutrophils were confirmed having influence on not only infectious and autoimmune diseases but hematopoiesis, angiogenesis and cancer growth [25, 28]. The effect of neutrophils in viral infections remains ill defined, research has showed that neutrophils were the predominant cells in virus-induced lung infection and could control the replication and transmission of virus[29, 30]. In addition, neutrophils played important role in COVID-19 [17].

Neutrophil percentage usually act as the index of inflammation and increases in infected diseases [16]. In our study, univariate regression analysis showed that neutrophil percentage was the independent risk factor in the severity of COVID-19 and the AUC was 0.842 which suggested the good predictive value in the severity of COVID-19. The optimal threshold at 49.7% for neutrophil percentage signified a possibility of clinical symptoms changing from non-severity to severity with high sensitivity of 92.5 percent. Zhang et al. found higher neutrophil percentage has been reported to be related with the severity of COVID-19[31], consistent with our study, although further research hasn’t been explored.

The source of monocytes is bone marrow which drives from progenitor cells. Monocytes have the ability of phagocytic activity and can differentiate into antigen-presenting cells which contribute to the participation of innate and adaptive immune responses[32]. After migrating from blood to inflammatory sites, response is different whether monocytes differentiate into macrophages or myeloid dendritic cells[33, 34]. Activated monocytes release inflammatory cytokines to fight for infection, and the overexpression of cytokines is closely related with mortality, nevertheless, immunological paralysis characterized by monocyte deactivation can also explain for the poor clinical outcomes of sepsis[35, 36]. Recent study suggested that bronchoalveolar fluid were enriched in CCL2 and CCL7 in patients with severe COVID-19,which were the recruitment of CC-chemokine receptor 2-positive monocytes[37]. Single-cell RNA sequencing analysis also showed that mononuclear phagocyte comprising of depletion of tissue-resident alveolar macrophages and monocyte-derived macrophages was higher in severe COVID-19 than that of mild or healthy controls [38].

These peripheral blood inflammatory cells are often studied together, NLR and NMR are easily calculated and serve as systemic inflammation biomarkers [11, 39]. NLR has been studied in the severity and prognosis of COVID-19 [12–14, 18, 40], in our study, NLR was also higher in severe COVID-19. According to Fang[11], segmented NMR can act as an immune dysfunction score to predict the 28-day mortality of patients with sepsis. In present study, levels of NMR were significantly higher in severe COVID-19 than non-severe patients, which implied that NMR might be a potential serum marker for severity of COVID-19. In addition, the logistic regression analysis showed that NMR was correlated with the severity of disease and ROC analysis also suggested that NMR was a valuable predictor.

A combination of different texts can improve the sensitivity of single test, we combined NMR with neutrophil percentage and proved a sensitivity of 72.5 percent, a specificity of 81.8 percent and AUC 0.851 in recognizing the severity of COVID-19.

This study has several limitations. First, the enrolled number of patients is small which may limit the conclusions of the study. For example, several parameters at admission are related to severity of the disease in univariate regression analysis, while only neutrophil percentage and NMR make sense in the multivariate analysis. In the future research, these indicators also need closer attention. Second, disease is a process of deterioration, the indexes at admission can’t reflect the changes in diseases.

Conclusions

In summary, this retrospective cohort study revealed that the neutrophil percentage and NMR are independent risk factors for the severity of COVID-19. Further researches are needed to enlarge the sample size and assess dynamically to confirm these results.

List of abbreviations

COVID-19: coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

NMR: neutrophil-to-monocyte ratio

NLR: neutrophil-to-lymphocyte ratio

CT: computed tomography

AUCs: Areas under the curve

CIs: confidence intervals

OR: odds ratio

ROC: Receiver operating characteristics

NETs: neutrophil extracellular traps

Declarations

Competing interests

The authors declare that they have no competing interests.

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Author contributions

FP and SL are joint first authors. YZ and SW contributed to the study design, implementation, manuscript discussion and critical revision. FP, SL, CW, and BY collected and interpreted the data. All authors read and approved the final manuscript.

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Figures

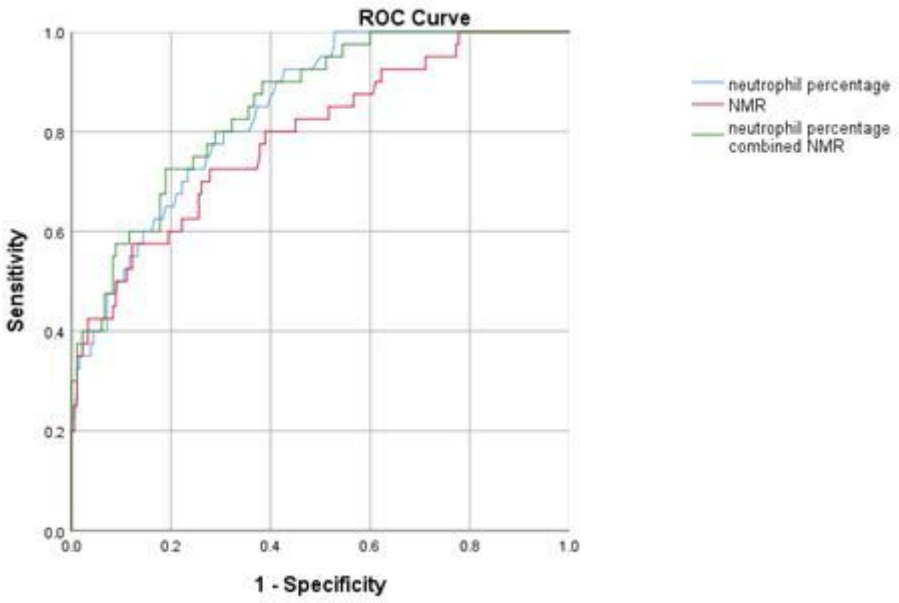

Figure 1

ROC curves of three methods for predicting the severity of COVID-19 Abbreviations: ROC, receiver operating characteristics; NMR, neutrophil/ monocyte ratio. ROCs of neutrophil percentage, NMR and combination of them for the predictors of severity of COVID-19 patients.