Diagnostic Value of Hematological and Biochemical Parameters Combinations for Predicting Coronavirus Disease 2019 (COVID-19) in Suspected Patients

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ABSTRACT

Background: The severe epidemiologic situation of COVID-19 due to the limited capacity of healthcare systems makes it necessary to improve the hospital management and early identification and stratification of patients. The aim of the study was to explore hematological and biochemical parameters at admission to the hospital as novel early predictors for diagnosis with coronavirus disease 2019 (COVID-19) among all suspected patients.

Methods: This was a retrospective, multicenter, observational study. The clinical data of all suspected patients were analyzed. The suspected patients with negative RT-PCR results were included as the control group, and compared with confirmed patients. Receiver- operating characteristic (ROC) curves and logistic regression analyses were used to evaluate the hematological indexes.

Results: In total, 326 confirmed COVID-19 patients and 116 control patients were included. The predictive ability of combinations of the hematological and biochemical parameters was significantly superior to that of a single parameter. The area under the ROC curve (AUC) of the aspartate aminotransferase (AST) to neutrophil ratio index (ANRI) and the AST to monocyte ratio index (AMRI) were 0.791 and 0.812, respectively. In the multivariate analysis, an ANRI $\geq$ 6.03(OR: 3.26, 95% CI: 1.02-10.40, P=0.046) and an AMRI $\geq$ 36.32(OR: 3.64. 95% CI: 1.24-10.68, P=0.02) at admission were independent risk factors related to the occurrence of COVID-19.

Conclusions: We found two novel predictors with promising predictive capacities for COVID-19 among all suspected patients: ANRI and AMRI. Our findings need to be confirmed in further studies.

Keywords: COVID-19; Suspected cases; ANRI; AMRI; Predictive parameters. **[Am J Med Sci 2021;362(4):387–395.]**

INTRODUCTION

Currently, the world is experiencing a pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). The rapid worldwide spread of SARS-CoV-2 has resulted in over 11 million infected people and 540,000 deaths so far.[1] The severe epidemiologic situation due to the limited capacity of healthcare systems makes it necessary to improve the hospital management and early identification and stratification of patients.

Nucleic acid testing remains the gold standard method for confirming SARS-CoV-2 infection. The demand for real-time reverse transcription-polymerase chain reaction (RT-PCR) tests is dramatically increasing. Meanwhile, limitations, such as the high rates of false-negatives, shortages of PCR kits, requirement of expensive equipment and trained clinicians, and possible delays of diagnosis due to the time-consuming process, are becoming apparent.[2,3] These limitations make RT-PCR unsuitable for large-scale screening, especially in areas with limited medical resources. Given that the early identification of COVID-19 patients among suspected individuals is crucial for the stratification of patients, prevention of virus transmission and early administration of treatment, there is an urgent need for easy-to-obtain, effective alternative approaches to RT-PCR.

Serum biomarkers are often considered routine and cost-effective indexes in clinical practice. A few previous studies have found some hematological and biochemical

indexes used for the differentiation of COVID-19 patients from patients without COVID-19. For example, confirmed COVID-19 patients often have lower procalcitonin, urea and creatinine levels than SARS-CoV-2-negative patients.[4] However, it has been reported that SARS-CoV-2 infection can cause systemic inflammation and multiorgan dysfunction in patients. Respiratory failure, heart failure, liver injury, kidney injury and sepsis are all possible complications of the disease.[5] Thus, a single biomarker might not necessarily reflect the complexity of COVID-19. As a result, combinations of serum parameters have also been tested. For instance, the neutrophil-lymphocyte ratio (NLR), which can be calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, was found to be associated with the occurrence and severity of COVID-19.[6]

However, these studies also had some limitations, including relatively small sample sizes, confounding factors, insufficient clinical utility, etc. Early warning markers used for identifying COVID-19 remain poorly defined and challenging to investigate. The current study was conducted to explore the various potential hematological and biochemical parameters, especially combinations of parameters, used for predicting the probability of diagnosis at an early stage among all suspected COVID-19 patients.

MATERIALS AND METHODS

Study design

This was a retrospective, multicenter, observational study on patients admitted to twenty-six COVID-19 designated hospitals in Sichuan Province, China, between January 21 and February 13, 2020. Among these hospitals, Chengdu Public Health Clinical Medical Center reported the highest number of cases. Meanwhile, the detailed clinical data of all suspected patients admitted to Chengdu Public Health Clinical Medical Center and Sichuan University West China Hospital in the same period were also collected.

This study was conducted in accordance with the amended Declaration of Helsinki and approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (No. 2020-272). The requirement for written informed consent was waived because of the urgent need to collect clinical data and the retrospective observational design. All data were anonymously recorded to ensure patient confidentiality. Two doctors independently reviewed the medical records of all patients. Any disagreement was resolved with the third doctor and through team discussion until a consensus was reached.

Participants and data collection

All patients enrolled in this study were diagnosed with confirmed or suspected COVID-19 according to the World Health Organization interim guidance.[7] A confirmed case was defined as a positive result for SARS-CoV-2 nucleic acid by fluorescence RT-PCR, and the suspected patients who had definitive RT-PCR negative results were included in the control group. The specific inclusion criteria for the control group are as follows: (1) patients with at least two RT-PCR tests on samples taken at least 24 hours apart; (2) patients with negative results on all RT-PCR tests; and (3) patients without a clinical diagnosis of COVID-19 during the follow-up period, which lasted 14 days or longer.

The following exclusion criteria were used: (1) was under 18 years old; (2) was pregnant; (3) had died within 24 hours after admission or had missing baseline data; (4) received blood transfusion during hospitalization; or (5) had chronic hematological diseases, malignancy, chronic liver disease or chronic kidney diseases.

Demographic characteristics, comorbidities, basic vital signs, symptoms and signs, chest computed tomography (CT) scan images and laboratory examination data were retrospectively collected from the electronic medical records. All these baseline data were recorded at admission or within 24 hours after admission to the hospitals. If the performance of a single parameter was not satisfactory, a combination of parameters was introduced and evaluated. Two doctors performed the data collection independently.

Statistical analysis

The data were analyzed by using IBM SPSS Statistical version 23.0 (SPSS, Chicago, IL, USA). Data were expressed as the mean $\pm$ standard deviation or median (interquartile range [IQR]) for continuous variables, as well as counts and percentages for categorical variables. The differences between the two groups were tested using two-tailed independent Student's t-tests for normally distributed continuous variables, the Mann-Whitney U-test for nonnormally distributed continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. The data were tested by the Kolmogorov-Smirnov normality test and Bartlett's test for the homogeneity of variance.

To assess the accuracy of the hematological parameters as predictors of COVID-19, a receiver-operating characteristic (ROC) curve analysis was conducted and the area under the ROC curve (AUC) was reported. The optimal cut-off value of the parameters was based on Youden's index of the ROC curve, corresponding to the maximum joint sensitivity and specificity. A Pearson or Spearman correlation analysis was carried out to test the correlation of the hematological parameters. The odds ratio (OR) and confidence interval (CI) were used to evaluate the risk factors. Univariate and multivariate logistic regression analyses were conducted to identify the independent risk factors. P<0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

A total of 593 patients who had suspected COVID-19 and met the inclusion criteria were retrospectively enrolled in the study. Ultimately, 151 patients were excluded according to the exclusion criteria, and 442 patients were analyzed (Fig. 1). Our study consisted of 249 male patients and 193 female patients, who had a median age of 41 years old (IQR 30-53 years old). The most common comorbidities were hypertension (n=64, 14.5%) and diabetes (n= 35, 7.9%). The most common symptoms were fever (n=301, 68.1%) and dry cough (n=186, 42.1%).

In total, 326 (73.8%) patients were confirmed to have COVID-19. The median age of the confirmed patients was higher than that of the control group (43 vs 34 years old, P<0.01). There were some other significant differences between confirmed cases and control cases in terms of history of alcohol use (P=0.01), epidemiological exposure history(P<0.01), hypertension (P<0.01), diabetes (P=0.04), heart rate (P<0.01), rhinorrhea(P=0.02), dry cough (P<0.01), weakness/fatigue (P=0.01), and bilateral pneumonia (P<0.01). Additionally, significant differences in some laboratory examinations were also demonstrated.

Compared with the control group, confirmed patients had lower white blood cell counts (5.37 vs 7.34 $\times 10^9$/L, P<0.01), neutrophil counts (3.53 vs 5.3 $\times 10^9$/L, P<0.01), lymphocyte counts (1.08 vs 1.38 $\times 10^9$/L, P<0.01), platelet counts (167 vs 194 $\times 10^9$/L, P<0.01), eosinophil counts (0.01 vs 0.06 $\times 10^9$/L, P<0.01), monocyte counts (0.38 vs 0.53 $\times 10^9$/L, P<0.01), creatinine levels (66.5 vs 75 μmol/L, P=0.012) and NLR(3.25 vs 4.01, P=0.02) but higher aspartate aminotransferase (AST) levels (27 vs 19 U/L, P<0.01) and glucose levels (6.11 vs 5.39 mmol/L, P<0.01). The detailed baseline characteristics of the patients are shown in Table 1.

Predictive significance of hematological parameters

The diagnostic value of neutrophil count, lymphocyte count, platelet count, monocyte count, creatinine, aspartate aminotransferase and NLR were evaluated at first. The AUC for COVID-19 occurrence only varied from 0.574 to 0.730 among these hematological parameters (Table 2).

Thus, we decided to evaluate combinations of hematological and biochemical parameters. The ANRI (AST to neutrophil ratio index) was calculated by dividing the AST count by the neutrophil count. Similarly, ALRI, APRI, AMRI and ACRI represent the AST to lymphocyte ratio index, AST to platelet ratio index, AST to monocyte ratio index and AST to creatinine ratio index, respectively.

As shown in Table 1, confirmed patients had higher ANRI, ALRI, APRI, AMRI and ACRI values. The AUCs of these five indexes varied from 0.718 to 0.812, which were all significantly superior to those of the single parameters (Fig. 2). Among the indexes, the AMRI (AUC: 0.812; 95% CI: 0.751-0.873) and ANRI (AUC: 0.791; 95% CI: 0.728-0.854) had the highest AUCs. Optimal cut-off values of 6.03 (sensitivity: 0.70; specificity: 0.82) for ANRI, and 36.32 (sensitivity: 0.853; specificity: 0.661) for AMRI were established to predict COVID (Table 2).

The correlations between these indexes were also evaluated. The results showed that the indexes were significantly positively correlated with each other (Table 3). Finally, the factors with a P value less than 0.05 in Table 1 were added to the logistic regression model analysis. The univariate logistic regression analysis indicated that the ANRI, ALRI, APRI, AMRI and ACRI at admission were all risk factors for diagnosis with COVID-19 in suspected
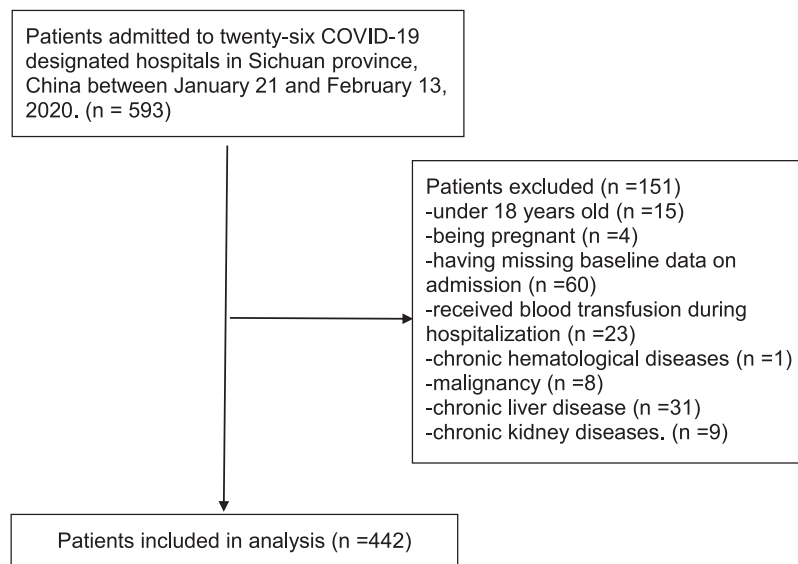

FIGURE 1. Study population.

TABLE 1. Comparisons of the clinical characteristics between patients with confirmed COVID-19 and the control group.

Variables	Overall (n = 442)	RT-PCR test positive (confirmed cases) (n=326)	RT-PCR test negative (control cases) (n=116)	P value
Demographic characteristics				
Sex (male)	249 (56.3)	178 (54.6)	71 (61.2)	0.218
Age, years	41 (30-53)	43 (32-55)	34 (26-49)	<0.01
History of alcohol use	76 (17.2)	65 (19.9)	11 (9.5)	0.01
Smoking history	64 (14.5)	47 (14.4)	17 (14.7)	0.95
Epidemiological exposure history	251 (56.8)	234 (71.8)	17 (14.7)	<0.01
Close contact with animals	4 (0.9)	3 (0.9)	1 (0.9)	1.00
Comorbidities				
COPD	12 (2.7)	12 (3.7)	0 (0)	0.08
Asthma	5 (1.1)	4 (1.2)	1 (0.9)	1.00
Hypertension	64 (14.5)	56 (17.2)	8 (6.9)	<0.01
Cardiovascular disease	15 (3.4)	11 (3.4)	4 (3.4)	1.00
Diabetes mellitus	35 (7.9)	31 (9.5)	4 (3.4)	0.04
Cerebrovascular disease	5 (1.1)	4 (1.2)	1 (0.9)	1.00
Vital signs on admission				
Temperature (°C)	37 (36.6-37.7)	37 (36.5-37.8)	37.05 (36.6-37.58)	0.8
Respiratory rate (breaths/min)	20 (20-21)	20 (20-21)	20 (20-21)	0.6
Heart rate (beats/min)	92 (82-104)	88 (80.5-98)	104 (91-113.8)	<0.01
Systolic pressure (mmHg)	125 (116-138)	126 (116-139)	123.5 (114-133)	0.07
Diastolic pressure (mmHg)	81 (73-89)	80 (73-88.5)	81 (74.8-90)	0.46
Symptoms and Signs				
Fever	301 (68.1)	220 (67.5)	81 (69.8)	0.64
Headache	47 (10.6)	36 (11)	11 (9.5)	0.64
Rhinorrhea	26 (5.9)	14 (4.3)	12 (10.3)	0.02
Shortness of breath/dyspnea	37 (8.4)	26 (8)	11 (9.5)	0.62
Wheeze	33 (7.5)	24 (7.4)	9 (7.8)	0.89
Dry cough	186 (42.1)	157 (48.2)	29 (25)	<0.01
Hemoptysis	2 (0.5)	2 (0.6)	0 (0)	1.00
Diarrhea	21 (4.8)	17 (5.2)	4 (3.4)	0.44
Rash	0 (0)	0 (0)	0 (0)	1.00
Earache/ear pain	1 (0.2)	1 (0.3)	0 (0)	1.00
Enlargement of lymph nodes	2 (0.5)	0 (0)	2 (1.7)	0.07
Weakness/Fatigue	91 (20.6)	77 (23.6)	14 (12.1)	0.01
Muscle ache/Myalgia	45 (10.2)	33 (10.1)	12 (10.3)	0.95
Stuffy nose	14 (3.2)	11 (3.4)	3 (2.6)	0.91
Sore throat	70 (15.8)	56 (17.2)	14 (12.1)	0.20
Chest pain	32 (7.2)	27 (8.3)	5 (4.3)	0.16
Productive cough	160 (36.2)	124 (38)	36 (31)	0.18
Stomachache	8 (1.8)	6 (1.8)	2 (1.7)	1.00
Nausea/Vomiting	17 (3.8)	16 (4.9)	1 (0.9)	0.10
Arthralgia	7 (1.6)	4 (1.2)	3 (2.6)	0.57
Skin ulcer	1 (0.2)	1 (0.3)	0 (0)	1.00
Unconsciousness	1 (0.2)	1 (0.3)	0 (0)	1.00
Chest CT scan images				
Abnormal chest image	418 (94.6)	309 (94.8)	109 (94)	0.74
Bilateral pneumonia	235 (53.2)	221 (67.8)	54 (46.6)	<0.01
Ground-glass opacities	316 (71.5)	235 (72.1)	81 (69.8)	0.64
Presence with consolidation	60 (13.6)	41 (12.6)	19 (16.4)	0.30
Laboratory parameters				
White blood cell count, $\times 10^9$/L	6.02 (4.51-7.69)	5.37 (4.11-7.04)	7.34 (6.11-8.97)	<0.01
Neutrophil count, $\times 10^9$/L	3.98 (2.79-5.51)	3.53 (2.59-4.89)	5.3 (4.09-6.68)	<0.01
Lymphocyte count, $\times 10^9$/L	1.16 (0.79-1.52)	1.08 (0.75-1.42)	1.38 (1.03-1.75)	<0.01
Platelet count, $\times 10^9$/L	175 (140-224)	167 (135.8-213.3)	194 (158.5-238)	<0.01
Eosinophil count, $\times 10^9$/L	0.016 (0.001-0.057)	0.01 (0.00-0.03)	0.06 (0.02-0.11)	<0.01
Monocyte count, $\times 10^9$/L	0.42 (0.28-0.62)	0.38 (0.26-0.54)	0.53 (0.4-0.76)	<0.01
Alanine aminotransferase, U/L	24 (15-38)	24.4 (15.8-39)	23 (13-37)	0.123
Aspartate aminotransferase, U/L	25 (19-36)	27 (20.75-39)	19 (15-26)	<0.01

(continued)

TABLE 1. (*continued*)

Variables	Overall (n = 442)	RT-PCR test positive (confirmed cases) (n=326)	RT-PCR test negative (control cases) (n=116)	P value
Total bilirubin, μ mol/L	9.85 (6.88-15.00)	9.6 (6.5-14.6)	10.2 (8.3-16.2)	0.08
Direct bilirubin, μ mol/L	3.48 (2.5-4.9)	3.44 (2.5-4.88)	3.7 (2.5-4.9)	0.558
Blood urea nitrogen, mmol/L	4 (3.2-5.1)	3.9 (3.2-4.91)	4.2 (3.3-5.5)	0.276
Creatinine, μ mol/L	68 (54-82)	66.5 (53-79)	75 (61-88)	0.012
Creatine kinase, U/L	69 (50-119)	70 (50.5-128)	67 (46.3-95.8)	0.243
Albumin, g/L	43.1 (39.2-46)	43.3 (39.6-46.08)	41.7 (37.3-45.5)	0.211
Glucose, mmol/L	5.97 (5.16-7.28)	6.11 (5.29-7.35)	5.39 (4.98-6.16)	<0.01
C-reactive protein, mg/L	18.42 (4.46-42.69)	15.8 (6.26-35.19)	22.36 (2.72-58.33)	0.22
APTT, s	31.1 (27.9-34.7)	31.2 (27.9-35)	30.1 (27.9-31.4)	0.167
PT, s	12.2 (11.5-13.1)	12.3 (11.5-13.2)	11.8 (11.1-12.5)	0.054
Fibrinogen, g/L	3.77 (2.69-4.65)	3.77 (2.69-4.59)	4.56 (2.66-5.09)	0.577
INR	1.03 (0.96-1.10)	1.03 (0.96-1.11)	0.99 (0.93-1.05)	0.059
D-dimer, mg/L	0.37 (0.17-1.26)	0.38 (0.18-1.45)	0.32 (0.12-0.82)	0.259
Procalcitonin, μ g/L	0.059 (0.031-0.12)	0.05 (0.32-0.12)	0.06 (0.03-0.15)	0.18
NLR	3.55 (2.32,5.30)	3.25 (2.19,5.07)	4.01 (2.49,5.67)	0.02
ANRI	7.30 (4.33-11.67)	8.53 (5.08-12.94)	4.17 (2.56-5.86)	<0.01
ALRI	23.67 (14.73-38.14)	26.67 (16.36-44.97)	13.24 (9.26-21.11)	<0.01
APRI	0.14 (0.10-0.25)	0.16 (0.11-0.27)	0.09 (0.07-0.15)	<0.01
AMRI	60 (36.07-110.53)	70 (45.3-131.61)	32.32 (23-48.09)	<0.01
ACRI	0.39 (0.28-0.55)	0.41 (0.32-0.57)	0.27 (0.2-0.42)	<0.01

Data are shown as the medians with interquartile ranges (IQRs) for continuous variables or as numbers with percentages for categorical variables.
n, numbers; COPD, chronic obstructive pulmonary disease; CT, computed tomography; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; ANRI, aspartate aminotransferase (AST) to neutrophil ratio index; ALRI, aspartate aminotransferase (AST) to lymphocyte ratio index; APRI, aspartate aminotransferase (AST) to platelet ratio index; AMRI, aspartate aminotransferase (AST) to monocyte ratio index; ACRI, aspartate aminotransferase (AST) to creatinine ratio index.

patients. However, in the multivariate logistic regression analysis, only ANRI ≥ 6.03 (OR: 3.26, 95%: 1.02-10.40, P=0.046) and AMRI ≥ 36.32(OR: 3.64. 95%: 1.24-10.68, P=0.02) were independent risk factors related to COVID-19 when adjusted by age, history of alcohol use, epidemiological exposure history, hypertension, diabetes, heart rate, rhinorrhea, dry cough, weakness/fatigue and bilateral pneumonia (Table 4).

DISCUSSION

To our knowledge, this is the first report that the ANRI and AMRI could be used to predict the possibility of the occurrence of COVID-19 among all suspected patients at admission to the hospital. We found that ANRI ≥ 6.03 and AMRI ≥ 36.32 were both independent risk factors with promising predictive ability for diagnosis with COVID-19.

TABLE 2. ROC analysis of laboratory indexes for predicting the diagnosis of COVID-19 among suspected patients.

Variables	AUC	95% CI	P value	Optimal cut-off value	Sensitivity	Specificity
AST	0.730	0.657-0.804	<0.01			
Neutrophil	0.703	0.632-0.773	<0.01			
Lymphocyte	0.703	0.630-0.777	<0.01			
Platelet	0.601	0.522-0.681	0.016			
Monocyte	0.723	0.653-0.794	<0.01			
Creatinine	0.610	0.529-0.691	<0.01			
NLR	0.574	0.515-0.634	0.019			
ANRI	0.791	0.728-0.854	<0.01	6.03	0.70	0.82
ALRI	0.769	0.698-0.839	<0.01	13.66	0.90	0.55
APRI	0.718	0.640-0.796	<0.01	0.11	0.783	0.645
AMRI	0.812	0.751-0.873	<0.01	36.32	0.853	0.661
ACRI	0.736	0.657-0.815	<0.01	0.31	0.76	0.67

AUC, area under the ROC curve; AST, aspartate aminotransferase; NLR, neutrophil-lymphocyte ratio; ANRI, AST to neutrophil ratio index; ALRI, AST to lymphocyte ratio index; APRI, AST to platelet ratio index; AMRI, AST to monocyte ratio index; ACRI, AST to creatinine ratio index.
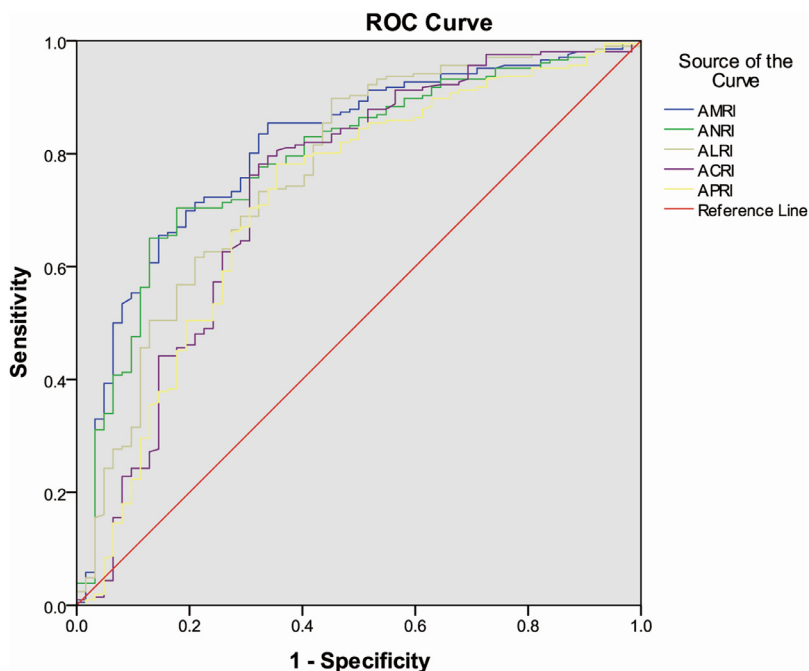
FIGURE 2. Receiver operating characteristic (ROC) curve for hematological parameter prediction of diagnosis with COVID-19. Abbreviations: ANRI, aspartate aminotransferase (AST) to neutrophil ratio index; ALRI, AST to lymphocyte ratio index; APRI, AST to platelet ratio index; AMRI, AST to monocyte ratio index; ACRI, AST to creatinine ratio index.

In our study, the baseline characteristics of COVID-19, such as common comorbidity with hypertension, high proportion of epidemiological exposure histories, symptoms of fever, fatigue and dry cough, and bilateral shadows on CT, were consistent with previous studies on cases in Wuhan City. [8,9] Thus, the included population of our study was somewhat representative of the COVID-19 population to some degree. However, the median age of COVID-19 patients was 43 years old, which was significantly lower than the median age in the above studies (56 and 59 years old). Such a discrepancy might be explained by two reasons. First, the numbers of infected persons and deaths in Sichuan Province were significantly lower than those in Wuhan City. A limited number of patients with severe disease on admission were enrolled in the present study. Then, to eliminate the impact of confounding factors on laboratory examinations, we excluded some patients with chronic disease or those receiving blood transfusion who were predisposed to critical situations. Therefore, it must be noted that our conclusions should be verified in further multicenter studies before being used in clinical practice.

For laboratory parameters, compared with RT-PCR negative patients, COVID-19 patients had lower WBC counts, neutrophil counts, lymphocyte counts, eosinophil counts, monocyte counts, and higher AST levels, which was also in line with previous studies. [10,11] Zhao et al. compared COVID-19 and other pneumonia patients and demonstrated that COVID-19 patients had remarkably more abnormal AST and alanine aminotransferase (ALT) levels, which means that liver function damage was more common in COVID-19 patients. [12] Our study had a larger sample size and further showed that platelet counts and glucose levels were also significantly different between the two groups. These differences in the laboratory data were understandable given that previous studies have indicated the roles of the systemic inflammatory response, innate immunity dysfunction and

TABLE 3. Correlation between variables.

	ANRI		ALRI		APRI		AMRI		ACRI	
	r	P	r	P	r	P	r	P	r	P
ANRI	1		0.577	<0.01	0.684	<0.01	0.676	<0.01	0.597	<0.01
ALRI	0.577	<0.01	1		0.712	<0.01	0.632	<0.01	0.625	<0.01
APRI	0.684	<0.01	0.712	<0.01	1		0.559	<0.01	0.582	<0.01
AMRI	0.676	<0.01	0.632	<0.01	0.559	<0.01	1		0.638	<0.01
ACRI	0.597	<0.01	0.625	<0.01	0.582	<0.01	0.638	<0.01	1	

Data were analyzed by Pearson or Spearman correlation analysis.

TABLE 4. Risk factors associated with confirmed cases among patients with suspected COVID-19.

Risk factors	Univariate		Multivariate[#]	
	OR (95% CI)	P value	OR	P value
ANRI ≥ 6.03	9.09 (4.71-17.55)	<0.01	3.26 (1.02-10.40)	0.046
ALRI ≥ 13.66	5.40 (3.34-8.73)	<0.01	2.00 (0.71-5.67)	0.19
APRI ≥ 0.11	4.49 (2.75-7.31)	<0.01	0.35 (0.11-1.16)	0.09
AMRI ≥ 36.32	6.48 (3.85-10.92)	<0.01	3.64 (1.24-10.68)	0.02
ACRI ≥ 0.31	5.18 (3.12-8.58)	<0.01	1.77 (0.74-4.23)	0.20

OR, odds ratio; CI, confidence interval.

[#] Adjusted by age, history of alcohol use, epidemiological exposure histories, hypertension, diabetes mellitus, heart rate, rhinorrhea, dry cough, weakness/fatigue and bilateral pneumonia.

immunosuppression in the development and progression of COVID-19.[13] Moreover, some specific clinical features, such as lymphopenia, thrombocytopenia, and elevated transaminase were also found in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[14,15] On the other hand, it should also be noted that although some parameters, such as WBC, platelet, creatinine and AST, were altered between the groups, they remained within the reference values. Therefore, the detailed impacts of COVID-19 on these parameters and relevant pathogenesis remain to be clarified.

The white blood cell count (WBC) is a sensitive indicator to reflect systemic infection and inflammation control. Similarly, AST is a sensitive and reliable biomarker of liver injury. The liver might also be a target organ of SARS-CoV-2. The exact effects of SARS-CoV-2 on the liver are not well understood. It is speculated that the pathological changes include hepatocytes degeneration, focal necrosis, microthrombosis and lymphocytic infiltration. The underlying mechanisms include psychological stress, systemic activated inflammatory response and drug toxicity.[16] Xie and colleagues showed that over thirty percent of non-ICU hospitalized COVID-19 patients had liver injury and that liver injury predicted prolonged hospital stay.[17] Among COVID-19 patients, it has also been indicated that AST levels are higher in refractory patients (median value: 37 U/L) and patients who die (median value:34 U/L) than in typical patients (median value:32 U/L) and patients who recover (median value:22 U/L) among COVID-19 patients.[18,19] Another possible mechanism of liver tissue injury is the upregulation of angiotensin-converting enzyme II (ACE2) expression in liver tissue due to the compensatory proliferation of hepatocytes.[20,21] However, these assumptions need further investigation. Although we did not find differences in albumin between the two groups on admission, other researchers have observed a continuous decrease in serum albumin levels in those patients who progressed to critical illness.[22] The damage of liver synthetic function and the influence of the patients' nutritional status should also be considered seriously. The early recognition and intense monitoring and evaluation of liver function is crucial and essential for the timely management of patients with COVID-19. Considering that the current study was conducted in Sichuan Province, a relatively low-risk area, further studies could focus on the subsequent prognostic value of liver injury during hospitalization, especially in severe COVID-19 patients.

Other combinations of hematological and biochemical parameters in the development and progression of COVID-19 have also been evaluated. A previous study enrolled 245 COVID-19 patients and reported that the NLR is an independent risk factor for in-hospital mortality in COVID-19 patients.[23] Yang et al. also found that elevated NLR (HR 2.46, 95% CI 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) were independent factors for poor clinical outcomes of COVID-19.[24] Qu and colleagues demonstrated that a higher platelet-to-lymphocyte ratio (PLR) was associated with a longer average hospitalization duration.[25]

As new inflammatory biomarkers, the AMRI and ANRI both take the levels of AST and WBC into account. The indexes could be quickly calculated to help physicians identify patients at a high risk for COVID-19 at admission. A high AMRI and ANRI result from increased AST and decreased neutrophil or monocyte counts. In previous studies, the predictive and prognostic values of the ANRI and AMRI were evaluated in liver diseases. It has been reported that a higher preoperative ANRI (cut-off value of 7.8) is an independent predictor of poorer outcomes in patients with hepatocellular carcinoma (HCC).[26] Similar findings (cut-off value of ANRI: 6.7) have been reported for patients with intrahepatic cholangiocarcinoma (ICC) after hepatectomy.[27] The cut-off value of ANRI in the current study was 6.03, which was slightly lower than that in the above studies. The optimal cut-off values of AMRI and ANRI, as well as the critical roles of AST, neutrophils and monocytes in the pathophysiological mechanisms, immune response and systemic inflammation of COVID-19, remain to be confirmed in future studies with larger populations.

Some parameters that were significantly different between the two groups, however, were not included in the final combination indexes. We believe that the eosinophil count is relatively low and is probably affected by several confounding factors regardless of the pathophysiological mechanisms of COVID-19. In addition, the

white blood cell count represents the summation of various immune cells, and the serum glucose level is often affected by the existence of diabetes, differences of diets, use of corticoids, etc. Finally, we chose suitable parameters and adjusted the baseline features to minimize the potential impact of confounding factors. The AMRI and ANRI were positively correlated and were both independent risk factors for the occurrence of COVID-19.

There are still several limitations of the study. First, this was a retrospective observational study, and unavoidable subjective selection bias was present. Second, the sample size was relatively small, and the number of patients was not equal between the confirmed group and the control group. Third, the use of drugs and therapies before admission might have influenced our results. Fourth, we did not explore the variation trends of the laboratory examination data in the few days after admission among the suspected patients. Fifth, our results were not externally validated. Further well-designed, multicenter studies with better comparative ability are warranted to confirm the utility and validity of our findings.

CONCLUSIONS

In the current study, we explored two novel indexes with promising predictive capacities for COVID-19. The ANRI and AMRI might be used as cost-effective and convenient alternatives to RT-PCR for the early identification of COVID-19 among all suspected patients. Our findings need to be confirmed in further studies.

DECLARATION OF COMPETING INTEREST

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

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