Laboratory Predictors of COVID-19 Pneumonia in Patients with Mild to Moderate Symptoms

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ABSTRACT

Objective: This research aims to develop a laboratory model that can accurately distinguish pneumonia from nonpneumonia in patients with COVID-19 and to identify potential protective factors against lung infection.

Methods: We recruited 50 patients diagnosed with COVID-19 infection with or without pneumonia. We selected candidate predictors through group comparison and punitive least absolute shrinkage and selection operator (LASSO) analysis. A stepwise logistic regression model was used to distinguish patients with and without pneumonia. Finally, we used a decision-tree method and randomly selected 50% of the patients 1000 times from the same specimen to verify the effectiveness of the model.

Results: We found that the percentage of eosinophils, a high–fluorescence-reticulocyte ratio, and creatinine had better discriminatory power than other factors. Age and underlying diseases were not significant for discrimination. The model correctly discriminated 77.1% of patients. In the final validation step, we observed that the model had an overall predictive rate of 81.3%.

Conclusion: We developed a laboratory model for COVID-19 pneumonia in patients with mild to moderate symptoms. In the clinical setting, the model will be able to predict and differentiate pneumonia vs nonpneumonia before any lung computed tomography findings. In addition, the percentage of eosinophils, a high–fluorescence-reticulocyte ratio, and creatinine were considered protective factors against lung infection in patients without pneumonia.

Keywords: COVID-19 infection, pneumonia, non-pneumonia, predictive model, protective factor, laboratory examination

Since the outbreak of COVID-19 in Wuhan, China, in December 2019, the COVID-19 epidemic has developed rapidly.[1] By April 2020, the epidemic had affected most countries and regions in the world.[2] The disease has caused serious global health and social problems.

Abbreviations:

CT, computed tomography; RT-PCR, reverse-transcription polymerase chain reaction; HDL, high-density lipoprotein.

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Patients with COVID-19 with severe symptoms usually die of pneumonia within a short period of time after infection, whereas a small proportion of patients die of other causes.[3] Mild acute respiratory infection symptoms, such as fever, dry cough, and fatigue, usually occur in the early stages of COVID-19,[4] but those who develop acute respiratory distress syndrome, acute respiratory failure, multiple organ failure, and other fatal complications die rapidly.[5] Generally, patients infected with COVID-19 without pneumonia recover, and asymptomatic infection is not life-threatening.[6] However, a specific treatment method for COVID-19 has not been fully developed.[7]

Because of decreased immunity and underlying diseases,[8] the symptoms and mortality associated with COVID-19 in older adults are more serious.[9] Older adult patients are more susceptible to viral infections and death[10] and have more underlying diseases, such as hypertension, hyperlipidemia, diabetes, and rheumatoid arthritis.[10-12] However, it is not clear whether age and underlying disease can predict pneumonia. Current research on COVID-19 has focused on

the epidemiology and clinical characteristics of patients, but information on the susceptibility to pneumonia has not been clear.

Pneumonia clearly plays a vital role in the prognosis of COVID-19. Therefore, we were committed to finding a way to identify whether a patient was susceptible to pneumonia before a chest computed tomography (CT) scan or before symptoms of pneumonia appear. Quickly identifying such patients will help prevent more serious cases of infection. It is a way to fight the death caused by COVID-19 infection. This research aimed to develop a model that can accurately distinguish patients with pneumonia from those without pneumonia in patients with COVID-19 and determine the factors that are significant in fighting infections in the lungs. The study investigated a group of patients at Hefei Second People's Hospital in China. Herein, we report our epidemiological, clinical, radiological, and laboratory examination results.

Methods

Study Design and Participants

We enrolled 50 patients who were diagnosed with COVID-19 at Hefei Second People's Hospital and Affiliated Hospital of Anhui Medical University. The inclusion criteria were as follows: patients with a confirmed diagnosis of COVID-19, patients with mild to moderate symptoms, men or women, patients with or without underlying diseases, and patients without any signs of death, including any symptoms of acute respiratory distress and/or failure of any organ. Patients with mild to moderate symptoms were defined by fever, fatigue, and smell and taste disorders, with or without respiratory symptoms (ie, coughing, sputum, and lung CT or X-ray showing pneumonia). They were managed in the hospital from January 2020 to April 2020, and as the final outcome all patients were discharged from the hospital. Patients were defined as having COVID-19 infection if they met any of the following criteria: (i) respiratory tract or blood specimens that were positive for SARS-CoV-2 per nucleic acid test using real-time fluorescent reverse-transcription polymerase chain reaction (RT-PCR) and/or (ii) through the SARS-CoV-2 gene sequencing method, a new virus found in the respiratory tract or blood specimens that was highly homologous to COVID-19.

These data were used to construct a predictive model of pneumonia. The research was approved by the Institutional Review Board of Anhui Medical University and complied with the Declaration of Helsinki. Patients were told verbally that their data would be used for medical research anonymously. After obtaining their permission, we collected written informed consent.

Variable Measurement

Previous medical history, age, and symptoms (fever, fatigue, smell and taste disorders, and respiratory symptoms) were recorded daily by resident physicians and nurses. The laboratory data after hospital admission were collected. Routine blood tests were performed multiple times over the course of the disease, and they were a part of the patient's standard care and testing. The blood test used 2 mL of blood from the cubital vein of the patient, and the blood was stored in an EDTA-dipotassium anticoagulation tube. Routine blood tests were completed using an automatic blood analyzer (Hitachi 7600 automatic analyser, Japan) and electrical impedance methods. The items obtained included the number of red blood cells, hemoglobin, white blood cells, platelet counts, absolute lymphocyte values, absolute intermediate cells, absolute neutrophils, lymphocyte percentage, intermediate cell percentage, percentage of neutral granulocytes, hematocrit, average red blood cell volume, average red blood cell hemoglobin, average hemoglobin concentration, red blood cell distribution width, average platelet volume, platelet distribution width, and platelet hematology.

For blood biochemistry indexes, 4 mL of venous blood was drawn, and the supernatant was removed and put into an automatic biochemical instrument (Hitachi, Japan) for analysis. Enzyme assay was used to obtain the reaction rate data for enzyme kinetic analysis, which was used to test the myocardial enzyme spectrum and adenosine dehydrogenase. Total bile acid was detected using an enzymatic cycle method. γ-glutamyltransferase was measured using the gamma-glutamyl-p-nitroanilide (GPNA) substrate method. Carbon dioxide was measured using a phosphoenolpyruvate carboxylase (PEPC) enzymatic method. Uric acid was measured using the oxidase method. Apolipoprotein A1 and apolipoprotein B were measured using the immunoturbidimetric method. Inorganic phosphorus was measured using the phosphomolybdate method.

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High-density lipoprotein (HDL) cholesterol and C-reactive protein were measured using the immunoturbidimetric method. Magnesium was measured using the xylene blue method. Creatinine was measured using the sarcosine oxidase method. Urea was measured using the urease-glutamate dehydrogenase method. Triglycerides were measured using the glycerol phosphate oxidase (GPO-PAP) method. Cystatin C was measured using a latex-enhanced immunoturbidimetric method. Total bile acid was measured using an enzyme cycle method. Total bilirubin was determined by using the vanadate oxidation method. Albumin was determined by using the bromocresol green method. Total protein was determined by using the biuret method. Hypersensitive C-reactive protein was determined by using immunofluorescence chromatography.

Lung CT Scan

Using the Siemens Somatom definition 64-row spiral CT scan, with patients in the supine position and the head at an incline, the researchers told patients to hold their breath during the scan. The scanning range was from the top to the bottom of both lungs and the cross-sectional area. The scanning parameters were as follows: tube voltage 120 kV, tube current 320 mA, matrix 512 × 512, layer thickness and layer moment 5 mm.[13]

Statistical Analysis

For data analyses, we selected the examination data taken at the most severe time in the course of the disease (that is, when the patient's self-reported symptoms, including fever, cough, chest pain, and/or muscle weakness, were the most severe).

The baseline demographic and clinical characteristics of all participants at the time of enrollment are presented as continuous variables and categorical variables (**Table 1**). The CT scan results divided all patients into 2 groups: patients with pneumonia and patients without pneumonia. The χ^2 test, 1-way analysis of variance, and Kruskal-Wallis tests were used to analyze the differences in these variables between the 2 groups. We used SPSS version 24 was used for statistical analyses, and G-power was used to determine whether each step in the statistics reached sufficient power.

In the initial factor selection step, we selected potential predictors by comparing the 2 groups, and the factors showing group differences were considered candidate predictors. In the second factor selection step, regularized regression with least absolute shrinkage and selection operator (LASSO) variable selection was used.[14] The LASSO penalization selected important predictors by shrinking the coefficients of weaker predictors to zero and excluded predictors with estimated zero coefficients from the final sparse prediction model. To avoid model overfitting in the training samples, the variable selection used 10-fold cross-validation[15] to select the best adjustment or penalty level, which was measured by the Bayesian information criterion.[16]

In the model development step, a stepwise logistic regression generalized an estimating equation, with the factors selected above entered as independent variables and the CT scan results entered as dependent variables. In the final validation step, a decision tree with the growth method of Chi-square automatic interaction detector (CHAID) and split sample tests were conducted, and random allocation of the whole sample (including all patients) was 50% for training and 50% for test sampling for 1000 times. The logistic model derived from the above was applied in the 50% randomly selected validation sample to calculate the predicted probabilities for each patient.

Hospitalization and Laboratory Tests

All patients were actively treated after admission, with daily droplet isolation, contact isolation, and routine care for Class A infectious diseases. The daily medication regimen of patients included lopinavir/ritonavir tablets 1000 mg (500 mg tablet × 2), 2 mL nebulized saline by inhalation, injection of 5 million units of recombinant human interferon alpha 2b, Chinese medicine decoction, vitamin C tablet 0.2 g, arbidol tablet 0.2 g, thymosin enteric-coated tablet 15 mg, and chloroquine hydrogen sulfate tablet 300 mg. Patient symptoms all improved after 4 to 34 days of treatment, and all patients were discharged home from the hospital.

The oropharyngeal swab nucleic acid test was assessed by the Centers for Disease Control and Prevention in Yaohai District, Hefei City. By using a fluorescent PCR method, a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) was used to extract RNA from the specimens from each patient into 50 μL of eluate. Forward (5′-CCT ACTAAATTAAATGATCTCTGCTTTACT-3′) and reverse (5′-CAAGCTATAACGCAGCCTGTA-3′) primers targeted the S gene of COVID-19 for determination of viral RNA. Real-time nucleic acid amplification tests were performed

Table 1: Baseline demographic and clinical characteristics of all participants

	Non-Pneumonia		Pneumonia			
	Mean or %	SD	Mean or %	SD	*t* or χ2	Sig.
Number	24	∅	26	∅		
Age (years)	40.25	18.32	50.42	14.18	-2.02	.05[a]
Hospital Stay (days)	20.83	19.50	17.32	10.59	0.60	.56
Nucleic acid test (times)	5.83	4.67	2.92	0.64	2.16	.05
Gender					0.10	.75
Male	50%	∅	55%	∅		
Female	50%	∅	45%	∅		
Underlying Disease					0.04	.85
Yes	42%	∅	45%	∅		
No	58%	∅	55%	∅		
Family cluster outbreak					3.29	.07
Yes	100%	∅	76%	∅		
No	0	∅	24%	∅		

SD, standard deviation; Sig., significance.
[a]*P < .05.*

using the QuantiNovaSYBR Green RT-PCR Kit (Qiagen) in a LightCycler 480 Real-Time PCR System (Roche, Basel, Switzerland). Reactions were incubated at 50°C for 10 minutes and 95°C for 2 minutes, followed by 45 cycles at 95°C for 5 seconds and 60°C for 30 seconds and then subjected to melting curve analysis (95°C for 5 seconds, 65°C for 1 minute, followed by a gradual increase in temperature to 97°C with continuous recording of fluorescence).

Respiratory specimens from the patients were collected separately and tested for influenza A and B viruses and respiratory syncytial virus using the Xpert Xpress Flu/RSV assay (GeneXpert System, Cepheid, Sunnyvale, CA). Specimens were tested with the BioFire FilmArray Respiratory Panel 2 Plus (bioMérieux, Marcy l'Etoile, France) to detect the presence of respiratory microbial pathogens, including coronavirus, adenovirus, respiratory syncytial virus, influenza A virus, influenza B virus, parainfluenza virus, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila.*

Routine urine analysis was completed using urine dip strips and a dry chemical method, along with a urine analyzer and colorimetry. The main parameters evaluated in the urine included urine color, urine pH, urine specific gravity, qualitative protein, and microscopic examination. Routine fecal examination was the direct microscopic examination of slides under a microscope. The main parameters analyzed in feces included stool color and hardness, mucus, and a microscopic examination of the stool for helminthiasis (hookworm eggs, roundworm eggs, and whipworm eggs) and other parasites.

Results

Among 50 patients with COVID-19 with mild to moderate symptoms, 26 had positive signs on lung CT leading to a COVID-19 pneumonia diagnosis, and 24 were diagnosed with COVID-19 infection without pneumonia. Twenty-three patients had underlying diseases before they entered the hospital, including hypertension (n = 10), hyperlipidemia (10), diabetes (5), rheumatoid arthritis (1), chronic bronchitis with emphysema (2), cervical spondylosis (1), femoral head necrosis (1), cerebral infarction (1), chronic hypothyroidism (1), fatty liver (1), and chronic superficial gastritis (2); in addition, 1 patient was pregnant and another was breastfeeding. The demographic characteristics of the two groups are shown in **Table 1**. Patients with pneumonia (ages 50.42 ± 14.18 years) were older than the patients without pneumonia (ages 40.25 ± 18.32 years) ($P < 0.05$). Otherwise, the 2 groups were similar regarding the time of hospital stay, sex composition, ratio of underlying disease, and ratio of family cluster outbreaks.

In the initial factor selection step, we found that patients without pneumonia had a greater number of lymphocytes

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Table 2: Group Differences on Blood Cell and Biochemistry Measures

	Non-Pneumonia		Pneumonia			
Blood Cells	**Mean**	**SD**	**Mean**	**SD**	***t***	**Sig.**
Lymphocytes	1.73	0.66	1.36	0.50	2.07	.04
Eosinophils	0.12	0.08	0.03	0.04	5.12	.00
Eosinophils%	2.09	0.83	0.62	0.52	5.12	.00
Basophils	0.40	0.26	0.31	0.18	2.10	.04
Reticulocyte absolute value	58.59	25.56	40.51	16.71	2.77	.01
Reticulocyte%	1.40	0.89	0.90	0.40	2.65	.01
High fluorescence reticulocyte ratio	1.34	0.91	0.15	0.41	2.40	.02
Biochemistry	**Mean**	**SD**	**Mean**	**SD**	***t***	**Sig.**
Calcium	2.32	0.09	2.20	0.15	2.46	.02
Creatinine	52.61	18.00	66.08	17.62	-2.22	.03
Urea/Creatinine	0.08	0.02	0.06	0.02	2.77	.01
Globulin	22.99	5.51	26.30	2.95	-2.63	.05
Albumin/Globulin	1.92	0.58	1.51	0.23	3.54	.00
Creatine kinase	46.00	14.03	77.11	15.92	-3.27	.00
Lactate dehydrogenase	178.91	47.05	251.24	76.92	-2.95	.01
HDL/CHOL	28.58	6.40	23.32	5.76	2.59	.01
Prealbumin	211.72	73.67	158.57	55.04	2.60	.01
Apolipoprotein A1	1.18	0.19	1.00	0.21	2.47	.02
SAA	45.46	72.78	110.63	69.04	-2.72	.01

HDL/CHOL, high-density lipoprotein/cholesterol; SAA, serum amyloid A; SD, standard deviation; Sig., significance.

and eosinophils, a higher percentage of eosinophils, a greater number of basophils, a greater absolute value of reticulocytes, a higher percentage of reticulocytes, and a higher ratio of high-fluorescent reticulocytes than patients with pneumonia, $P < .05$ (**Table 2**). G-power analyses determined that the effect size of these factors between the 2 groups ranged from 0.63 to 1.28, and the power of each comparison ranged from 0.49 to 0.97. Patients without pneumonia also had higher levels of calcium, lower creatinine, a higher urea/creatinine ratio, lower globulin, a higher albumin/globulin ratio, lower creatine kinase, lower lactate dehydrogenase, a higher HDL/cholesterol ratio, higher pre-albumin, higher apolipoprotein A1, and lower serum amyloid A (SAA) levels in blood than patients with pneumonia ($P < .05$; **Table 2**). G-power analyses determined that the effect size of these factors between the 2 groups ranged from 0.75 to 0.93, and the power of each comparison ranged from 0.60 to 0.75. In the second factor selection step, we observed that the percentage of eosinophils, the absolute value of reticulocytes, the high–fluorescence-reticulocyte ratio, creatinine, the albumin/globulin ratio, and lactate dehydrogenase survived the LASSO penalty and were selected as potential predictive factors (see **Tables 3** and **4**).

With a backward stepwise logistic regression model (see **Table 5**), age, the percentage of eosinophils, the absolute value of reticulocytes, the high–fluorescence-reticulocyte ratio, creatinine, the albumin/globulin ratio, and lactate dehydrogenase were entered as independent variables, and the pneumonia group was entered as the dependent variable. We found that the percentage of eosinophils, the high–fluorescence-reticulocyte ratio, and creatinine had better discriminatory power than the other factors. The predictive rate of the model was 77.1%, with $\chi^2 = 35.25$, Cox-Snell $R^2 = .52$, and $P < .05$.

In the final validation step, a decision tree with the growth method of CHAID and split sample (ie, all patients) tests were conducted. The logistic model derived from above was applied in the 50% randomly selected validation sample to calculate predicted probabilities for each patient for 1000 times. We observed that the validation samples had an overall predictive rate of 81.3%.

Table 3: Lasso coefficient (the factors left in rows 28-31 were selected as the potential predictors)

No.	Number of selected predictors	Number of lymphocytes	Eosinophils	Eosinophils%	Basophils	Reticulocytes absolute value	Reticulocytes percentage	High fluorescent reticulocytes ratio
1	7	0.322	-0.271	0.733	-0.334	0.164	0.089	0.353
2	7	0.301	-0.148	0.629	-0.301	0.165	0.043	0.341
3	7	0.281	-0.029	0.527	-0.268	0.16	0.004	0.329
4	6	0.263	0.037	0.47	-0.238	0.146	0	0.309
5	6	0.245	0.03	0.469	-0.207	0.138	0	0.289
6	6	0.225	0.024	0.47	-0.172	0.132	0	0.262
7	6	0.206	0.017	0.472	-0.138	0.126	0	0.236
8	5	0.149	0	0.488	0.022	0.125	0	0.153
9	5	0.142	0	0.482	0.013	0.12	0	0.146
10	7	0.136	0.001	0.473	0.003	0.11	0.006	0.141
11	4	0.127	0	0.471	0	0.111	0	0.133
12	5	0.12	0.002	0.461	0	0.104	0	0.129
13	4	0.111	0	0.46	0	0.101	0	0.119
14	4	0.104	0	0.454	0	0.096	0	0.112
15	4	0.096	0	0.449	0	0.092	0	0.105
16	4	0.088	0	0.443	0	0.087	0	0.098
17	4	0.08	0	0.438	0	0.082	0	0.091
18	4	0.074	0	0.43	0	0.075	0	0.088
19	4	0.065	0	0.427	0	0.072	0	0.077
20	4	0.058	0	0.421	0	0.066	0	0.072
21	4	0.05	0	0.416	0	0.063	0	0.063
22	4	0.042	0	0.411	0	0.058	0	0.056
23	4	0.034	0	0.405	0	0.053	0	0.049
24	4	0.027	0	0.4	0	0.047	0	0.043
25	4	0.019	0	0.395	0	0.044	0	0.035
26	4	0.011	0	0.389	0	0.039	0	0.028
27	4	0.004	0	0.384	0	0.034	0	0.021
28	3	0	0	0.378	0	0.028	0	0.014
29	3	0	0	0.37	0	0.022	0	0.009
30	3	0	0	0.363	0	0.016	0	0.003
31	3	0	0	0.354	0	0.008	0	0
32	2	0	0.002	0.345	0	0	0	0
33	1	0	0	0.336	0	0	0	0
34	1	0	0	0.326	0	0	0	0
35	1	0	0	0.316	0	0	0	0
36	1	0	0	0.306	0	0	0	0
37	1	0	0	0.296	0	0	0	0
38	1	0	0	0.286	0	0	0	0
39	1	0	0	0.276	0	0	0	0
40	1	0	0	0.266	0	0	0	0
41	1	0	0	0.256	0	0	0	0

Table 3. Continued

No.	Number of selected predictors	Number of lymphocytes	Eosinophils	Eosinophils%	Basophils	Reticulocytes absolute value	Reticulocytes percentage	High fluorescent reticulocytes ratio
42	1	0	0	0.246	0	0	0	0
43	1	0	0	0.236	0	0	0	0
44	1	0	0	0.226	0	0	0	0
45	1	0	0	0.216	0	0	0	0
46	1	0	0	0.206	0	0	0	0
47	1	0	0	0.196	0	0	0	0
48	1	0	0	0.186	0	0	0	0
49	1	0	0	0.176	0	0	0	0
50	1	0	0	0.166	0	0	0	0
51	1	0	0	0.156	0	0	0	0

Table 4: Lasso coefficient (the factors left in rows 39-45 were selected as the potential predictors)

No.	Number of selected predictor	Calcium	Creatinine	Urea/ creatinine	Globulin	Albumin/ globulin	Creatine kinase	Lactatede hydrogenase	HDL/CHOL	Prealbumin	Apolipoprotein A1	SAA
1	11	0.228	0.146	0.33	-0.507	0.125	-0.245	-0.181	0.434	-0.276	-0.2	-0.137
2	11	0.202	0.065	0.29	-0.453	0.124	-0.228	-0.206	0.36	-0.161	-0.155	0.032
3	11	0.158	-0.006	0.255	-0.405	0.121	-0.223	-0.194	0.332	-0.117	-0.145	0.005
4	10	0.136	-0.026	0.235	-0.372	0.124	-0.213	-0.181	0.312	-0.08	-0.127	0
5	10	0.113	-0.046	0.216	-0.346	0.122	-0.203	-0.175	0.29	-0.048	-0.107	0
6	10	0.091	-0.069	0.196	-0.317	0.121	-0.194	-0.169	0.267	-0.013	-0.086	0
7	8	0.086	0	0.215	-0.325	0.114	-0.2	-0.165	0.27	0	-0.093	0
8	8	0.079	0	0.201	-0.313	0.11	-0.189	-0.168	0.251	0	-0.072	0
9	8	0.073	0	0.187	-0.302	0.106	-0.179	-0.171	0.233	0	-0.052	0
10	8	0.069	0	0.174	-0.291	0.103	-0.168	-0.172	0.216	0	-0.032	0
11	8	0.047	-0.113	0.122	-0.253	0.102	-0.135	-0.175	0.182	0	0	0
12	8	0.041	-0.113	0.112	-0.242	0.104	-0.126	-0.174	0.173	0	0	0
13	8	0.035	-0.114	0.103	-0.231	0.107	-0.117	-0.172	0.164	0	0	0
14	8	0.03	-0.115	0.094	-0.22	0.109	-0.108	-0.17	0.155	0	0	0
15	8	0.025	-0.116	0.085	-0.21	0.112	-0.099	-0.167	0.147	0	0	0
16	8	0.021	-0.117	0.077	-0.199	0.115	-0.09	-0.164	0.139	0	0	0
17	8	0.017	-0.117	0.068	-0.19	0.117	-0.081	-0.16	0.131	0	0	0

Table 4: Continued

No.	Number of selected predictor	Calcium	Creatinine	Urea/ creatinine	Globulin	Albumin/ globulin	Creatine kinase	Lactatede hydrogenase	HDL/CHOL	Prealbumin	Apolipoprotein A1	SAA
18	8	0.014	-0.118	0.059	-0.181	0.118	-0.071	-0.157	0.123	0	0	0
19	8	0.011	-0.119	0.049	-0.173	0.118	-0.061	-0.155	0.114	0	0	0
20	8	0.008	-0.119	0.04	-0.164	0.118	-0.051	-0.152	0.106	0	0	0
21	8	0.005	-0.12	0.031	-0.156	0.119	-0.042	-0.149	0.098	0	0	0
22	8	0.002	-0.121	0.022	-0.147	0.119	-0.032	-0.146	0.091	0	0	0
23	7	0	-0.122	0.013	-0.139	0.12	-0.023	-0.142	0.083	0	0	0
24	7	0	-0.122	0.004	-0.131	0.12	-0.013	-0.139	0.075	0	0	0
25	6	0	-0.121	0	-0.123	0.121	-0.004	-0.135	0.067	0	0	0
26	5	0	-0.116	0	-0.116	0.121	0	-0.129	0.059	0	0	0
27	5	0	-0.111	0	-0.107	0.124	0	-0.123	0.051	0	0	0
28	5	0	-0.106	0	-0.098	0.127	0	-0.116	0.044	0	0	0
29	5	0	-0.1	0	-0.09	0.129	0	-0.109	0.036	0	0	0
30	5	0	-0.095	0	-0.082	0.131	0	-0.102	0.029	0	0	0
31	5	0	-0.09	0	-0.074	0.133	0	-0.096	0.022	0	0	0
32	5	0	-0.085	0	-0.067	0.134	0	-0.089	0.015	0	0	0
33	5	0	-0.08	0	-0.057	0.138	0	-0.082	0.007	0	0	0
34	5	0	-0.075	0	-0.051	0.138	0	-0.076	0	0	0	0
35	4	0	-0.069	0	-0.026	0.161	0	-0.064	0	0	0	0
36	4	0	-0.062	0	-0.017	0.162	0	-0.057	0	0	0	0
37	4	0	-0.056	0	-0.009	0.164	0	-0.05	0	0	0	0
38	4	0	-0.049	0	-0.001	0.166	0	-0.043	0	0	0	0
39	3	0	-0.042	0	0	0.162	0	-0.036	0	0	0	0
40	3	0	-0.035	0	0	0.156	0	-0.03	0	0	0	0
41	3	0	-0.028	0	0	0.15	0	-0.024	0	0	0	0
42	3	0	-0.021	0	0	0.145	0	-0.018	0	0	0	0
43	3	0	-0.014	0	0	0.139	0	-0.012	0	0	0	0
44	3	0	-0.007	0	0	0.134	0	-0.006	0	0	0	0
45	3	0	0	0	0	0.128	0	0	0	0	0	0
46	1	0	0	0	0	0.118	0	0	0	0	0	0
47	1	0	0	0	0	0.108	0	0	0	0	0	0
48	1	0	0	0	0	0.098	0	0	0	0	0	0
49	1	0	0	0	0	0.088	0	0	0	0	0	0
50	1	0	0	0	0	0.078	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0

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Table 5: The Stepwise Regression Model

	B	S.E.	Wald	DoF	Sig.	Exp (B)	CI of EXP(B)	
							Lower limit	Upper limit
Eosinophil%	5.154	1.839	7.853	1	.005	173.047	4.707	6361.383
High fluorescent reticulocyte ratio	1.039	0.583	3.174	1	.075	2.827	0.901	8.865
Creatinine	-0.124	0.06	4.297	1	.038	0.883	0.785	0.993
Constant	-0.764	2.938	0.068	1	.795	0.466		

B, coefficients; S.E., standard error; Wald, Wald test; DoF, degree of freedom; Sig., significance; Exp (B), exponentiation of the B coefficient; CI, confidence interval.

Discussion

The study included 50 patients with mild to moderate symptoms of COVID-19. We have established a laboratory model that can predict pneumonia through readily available laboratory measures. The model showed good discrimination, and external verification was satisfactory. This is the first study to determine the important factors that may fight COVID-19 pneumonia or potential protective factors in patients with mild to moderate symptoms.

Generally, age and underlying disease are regarded as risk factors for COVID-19 pneumonia. Older adults are generally at higher risk of chronic diseases and are more susceptible to infection.[17] Age is a risk factor for poor prognosis in patients with COVID-19, partly because age-related immune dysfunction is caused by low-grade chronic inflammation.[18] In addition, older adult patients may also have other risk factors, such as comorbidities and sarcopenia.[19,20] For example, a history of hypertension is an important risk indicator of the MuLBSTA score, a viral pneumonia death warning model.[21] Hypertension has been found to be a predictor of death in patients with COVID-19.[18] However, in this study, neither age nor underlying disease was an important factor in distinguishing the pneumonia group. Although the age of patients with pneumonia was relatively higher than for those without pneumonia, this finding may have been because our patients had mild to moderate symptoms rather than severe symptoms, different from previous studies.

With the predictive model, we found that the percentage of eosinophils, the high–fluorescence-reticulocyte ratio, and creatinine in the blood were good predictors or discriminators for patients with and without pneumonia. Patients without pneumonia had a higher percentage of eosinophils, a greater high–fluorescence-reticulocyte ratio, and lower creatinine levels than patients with pneumonia.

Eosinophils are produced by bone marrow stem cells and account for 1% to 5% of the total number of white blood cells in the blood.[22] Eosinophils play an important role in adaptive immune function, specifically resisting viruses.[23] As immune modulators, eosinophils are not only associated with the effector arm of adaptive immunity but also trigger a polarized adaptive response process.[24] In diseases caused by respiratory viruses, the blood and immune organs are severely damaged[25] and viruses directly inhibit the proliferation of bone marrow cells. Some clinical studies have found that viral infections cause a decrease in the percentage of eosinophils in routine blood tests.[26] The relatively higher percentage of eosinophils in our patients without pneumonia may indicate better adaptive immunity and a better polarized adaptive response process, which helped these patients avoid lung infection.

Studies have shown that a variety of viral infections cause bone marrow hematopoietic arrest and inhibit bone marrow cell proliferation.[27–29] After the virus invades, it binds to red blood cell membrane proteins and damages red blood cell production, resulting in a decrease in the number of red blood cell lines and reticulocytes in the blood.[30] The number of reticulocytes has been used to clinically judge the severity of viral infections and the hematopoietic function of bone marrow.[31] Viral infection in this study was associated with decreased reticulocytes, and the relatively higher level of the high–fluorescence-reticulocyte ratio indicated better bone marrow cell proliferation, which was also a factor that helped patients without pneumonia avoid lung infection.

The abnormal levels of urea, creatinine, and the urea/creatinine ratio were clinically indicative of impaired renal

function.[32,33] In addition to damaging the respiratory system, COVID-19 has also been found to harm the kidneys and liver.[34] One study showed that approximately 3% to 10% of patients with COVID-19 had abnormal renal function, including a significant increase in creatinine and/or blood urea nitrogen.[35] In this study, patients without pneumonia had a lower level of creatinine, indicating a better kidney function.

Conclusion

The laboratory model showed good discriminatory power with a predictive rate of 77.1%, a sensitivity of 100.00%, and a negative predictive value of 100.00%. The validation samples (ie, patients) had an overall predictive rate of 81.3%. Among the patients with mild to moderate symptoms of COVID-19, age and underlying diseases were not significant in the discrimination between the pneumonia and nonpneumonia groups. The percentage of eosinophils, the high–fluorescence-reticulocyte ratio, and creatinine in the blood were good discriminators between the 2 groups. Patients without pneumonia had a higher percentage of eosinophils, a greater high–fluorescence-reticulocyte ratio, and lower creatinine levels than patients with pneumonia. The relatively higher percentage of eosinophils may indicate better adaptive immunity and a better polarized adaptive response process. The relatively higher level of the high–fluorescence-reticulocyte ratio indicated better bone marrow cell proliferation, and the lower level of creatinine may have indicated better kidney function. These factors may be protective factors for patients without pneumonia against lung infection. **LM**

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Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest.

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