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Original Research

Association Between Clinical Manifestations and Prognosis in Patients with COVID-19



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ABSTRACT

Purpose: The purpose of this study was to determine the risk factors associated with pneumonia, acute respiratory distress syndrome (ARDS), and clinical outcome among patients with novel coronavirus disease 2019 (COVID-19).

Methods: This was a cross-sectional multicenter clinical study. A total of 95 patients infected with COVID-19 were enrolled. The COVID-19 diagnostic standard was polymerase chain reaction detection of target genes of 2019 novel coronavirus (2019-nCoV). Clinical, laboratory, and radiologic results, as well as treatment outcome data, were obtained. ARDS was defined as an oxygenation index (arterial partial pressure of oxygen/fraction of inspired oxygen) ≤ 300 mm Hg.

Findings: Multivariate analysis showed that older age (odds ratio [OR], 1.078; $p = 0.008$) and high body mass index (OR, 1.327; $p = 0.024$) were independent risk factors associated with patients with pneumonia. For patients with ARDS, multivariate analysis showed that only high systolic blood pressure (OR, 1.046; $p = 0.025$) and high lactate dehydrogenase level (OR, 1.010; $p = 0.021$) were independent risk factors associated with ARDS. A total of 70 patients underwent CT imaging repeatedly after treatment. Patients were divided in a disease exacerbation group ($n = 19$) and a disease relief group ($n = 51$). High body mass index (OR, 1.285; $p = 0.017$) and tobacco smoking (OR, 16.13;

$p = 0.032$) were independent risk factors associated with disease exacerbation after treatment.

Implications: These study results help in the risk stratification of patients with 2019-nCoV infection. Patients with risk factors should be given timely intervention to avoid disease progression. (*Clin Ther.* 2020;42:964–972) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key words: 2019-nCoV, Acute respiratory distress syndrome, COVID-19, Pneumonia, Risk factors.

INTRODUCTION

Since December 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, Hubei Province, of China.¹ Those cases have been confirmed as acute respiratory infections caused by a novel coronavirus infection. To date, confirmed cases have been found in many countries worldwide.^{2,3} Until now, however, the source of the virus and the pathogenesis of the disease are unknown. Early detection, quarantine, and timely treatment are the keys to better controlling the epidemic and reducing the spread of the disease.

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Coronaviruses are RNA viruses and can be divided into 4 genera according to the genomic characteristics: α , β , γ , and ξ .⁴ Among these, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus are known coronaviruses.^{4,5} The new virus recently discovered in China is now recognized to be a novel coronavirus named 2019-nCoV. The coronavirus isolated from patients with this novel pneumonia in Wuhan is a coronavirus of genus β .⁵

This sudden infectious disease mainly manifests as fever, fatigue, and cough.^{6–8} Upper respiratory symptoms such as nasal congestion and runny nose are rare. About one half of the patients develop dyspnea after 1 week.⁹ In severe cases, patients progress rapidly to acute respiratory distress syndrome (ARDS), sepsis, and coagulopathy. Some patients have mild symptoms with no fever or without pneumonia and usually recover after 1 week. However, some patients may suddenly worsen and develop ARDS.⁹ At present, how to stratify high-risk

and low-risk patients is an important but unresolved issue.

In the present study, the clinical manifestations and clinical outcomes of patients with 2019 novel coronavirus disease (COVID-19) were evaluated. The purpose of this study was to identify the risk factors associated with pneumonia, ARDS, and clinical outcomes.

PATIENTS AND METHODS

Patients

This cross-sectional multicenter clinical study was approved by the institutional ethics board of the Nanfang Hospital, Southern Medical University. All consecutive patients with confirmed 2019-nCoV infections who were diagnosed in the Dongguan People's Hospital and Nanfang Hospital, Southern Medical University, from January 2020 to February 2020 were enrolled. The study population comprised hospitalized patients. Because COVID-19 is an infectious disease, all outpatients were required to be

Table I. Demographic and clinical characteristics in patients with coronavirus disease 2019 (COVID-19) with or without pneumonia. Values are given as mean (SD) unless otherwise indicated.

Characteristic	Patients With COVID-19		<i>P</i>
	With Pneumonia	Without Pneumonia	
Sample size, n	73	22	—
Male sex	39 (53.4%)	14 (63.6%)	0.398
Age, y	42.66 (17.93)	23.86 (13.88)	<0.001
SBP, mm Hg	126.41 (16.01)	120.95 (14.90)	0.175
DBP, mm Hg	83.69 (10.26)	79.90 (8.60)	0.138
BMI, kg/m ²	23.71 (3.41)	20.78 (3.15)	0.001
Serum lactic acid, mmol/L	1.51 (0.71)	1.61 (0.59)	0.608
Neutrophil count, $\times 10^9$	3.32 (1.52)	3.33 (1.29)	0.972
Lymphocyte count, $\times 10^9$	1.25 (0.94)	1.81 (0.87)	0.014
Hemoglobin, g/L	139.07 (18.07)	143.41 (13.01)	0.298
Platelet count, $\times 10^9$	196.27 (56.67)	251.50 (77.46)	<0.001
Serum creatinine, $\mu\text{mol/L}$	68.60 (41.11)	60.95 (17.97)	0.400
ALT, U/L	21.33 (12.00)	22.77 (24.75)	0.718
AST, U/L	23.97 (10.48)	18.75 (7.72)	0.041
LDH, IU/L	204.04 (67.44)	154.32 (34.88)	0.003
Tobacco smoking	5 (6.8%)	3 (13.6%)	0.315

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; SBP = systolic blood pressure.

quarantined in the hospital if infection with 2019-nCoV was confirmed. The 2019-nCoV infection diagnostic standard was polymerase chain reaction detection of 2 target genes of 2019-nCoV, open reading frame 1 ab (ORF1ab) and nucleocapsid protein. A positive result was determined to be 2019-nCoV infection.

Ethics, Consent, and Permissions

The Institutional Review Board of Nanfang Hospital, Southern Medical University, approved this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the 1975 Declaration of Helsinki as revised in 2008. Oral consent was obtained from patients.

Data Collection

All patients' clinical, laboratory, and radiologic characteristics, as well as treatment outcome data, were obtained through medical record extraction. Data were reviewed by a team of trained physicians. The recorded information included demographic

data, medical history, contact history, potential comorbidities, symptoms, laboratory test results, and chest computed tomography (CT) scans. ARDS was defined as an acute-onset oxygenation index (arterial partial pressure of oxygen/fraction of inspired oxygen) ≤ 300 mm Hg and a chest radiograph showing patchy shadows.¹⁰

Real-Time Polymerase Chain Reaction Assay for 2019-nCoV

All patients had pharyngeal swab samples collected to detect 2019-nCoV. The specific steps were as follows: The throat swab was placed into a collection tube containing 150 μ L of virus preservation solution, and a respiratory sample RNA isolation kit (Zhongzhi, Wuhan, China) was used to extract total RNA within 2 h. Forty microliters of cell lysate were transferred to a collection tube and vortexed for 10 s. It was centrifuged after incubation at room temperature for 10 min. Real-time polymerase chain reaction was then performed, and 2 target genes (ORF1ab and nucleocapsid protein) were detected. Target 1 (ORF1ab): forward primer

Table II. Factors associated with pneumonia in patients with coronavirus disease 2019.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Sex	0.655	0.245–1.751	0.400			
Age	1.073	1.034–1.112	<0.001	1.078	1.020–1.140	0.008
SBP	1.023	0.990–1.057	0.176			
DBP	1.040	0.987–1.095	0.141			
BMI	1.298	1.103–1.527	0.002	1.327	1.038–1.697	0.024
Serum lactic acid	0.815	0.376–1.765	0.603			
Neutrophil count	0.994	0.717–1.378	0.972			
Lymphocyte count	0.548	0.305–0.986	0.045			
Hemoglobin	0.986	0.959–1.013	0.301			
Platelet count	0.987	0.979–0.995	0.002			
Serum creatinine	1.011	0.986–1.036	0.387			
ALT	0.994	0.965–1.025	0.716			
AST	1.080	1.001–1.165	0.048			
LDH	1.023	1.007–1.039	0.004			
Tobacco smoking	0.466	0.102–2.127	0.324			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; OR = odds ratio; SBP = systolic blood pressure.

CCTGGTGGGTTTTACTTAA; reverse primer ACGATTGTGCATCAGCTGA; probe 5'-VIC-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. Target 2 (N protein): forward primer GGGGAACCTTCTCCTGCTAGAAT; reverse primer CAGACATTTTGCTCTCAAGCTG; probe 5'-FAM-TTGCTGCTGCTTACAGATT-TAMRA-3'. The diagnostic criteria were based on the recommendations of the National Institute of Viral Disease Prevention and Control (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html).

Statistical Analysis

Continuous data are reported as mean (SD), and categorical data are expressed as percentages. The significance of differences was tested by using either the Student's *t* test (for continuous variables) or the χ^2 test (for categorical variables). Univariable and multivariable regression analyses were performed by

using logistic regression analysis, and the results are expressed as odds ratio (OR) and 95% CIs. All analyses were performed by using SPSS version 13.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) with an alpha level of 0.05.

RESULTS

Characteristics of Patients With COVID-19

A total of 95 patients infected with 2019-nCoV were enrolled. Seventy-three had pneumonia based on the CT findings, and 22 did not have pneumonia. Demographic and clinical characteristics are shown in Table I. Patients with pneumonia were significantly older than the other patients ($p < 0.001$). The body mass index (BMI) ($p = 0.001$), aspartate aminotransferase levels ($p = 0.041$), and lactate dehydrogenase (LDH) levels ($p = 0.003$) were significantly higher in patients with pneumonia. However, lymphocyte count ($p = 0.014$) and platelet

Table III. The demographic and clinical characteristics in patients with coronavirus disease 2019 (COVID-19) with and without acute respiratory distress syndrome (ARDS). Values are given as mean (SD) unless otherwise indicated.

Characteristic	Patients With COVID-19		<i>P</i>
	With ARDS	Without ARDS	
Sample size, n	24	71	—
Male sex	14 (58.3%)	39 (54.9%)	0.772
Age, y	45.92 (18.44)	35.73 (13.32)	0.021
SBP, mm Hg	130.96 (14.62)	123.15 (15.87)	0.038
DBP, mm Hg	84.92 (10.42)	82.12 (9.93)	0.245
BMI, kg/m ²	24.26 (3.32)	22.64 (3.55)	0.053
Serum lactic acid, mmol/L	1.49 (0.51)	1.55 (0.74)	0.703
Neutrophil count, $\times 10^9$	3.21 (1.34)	3.36 (1.51)	0.656
Lymphocyte count, $\times 10^9$	1.05 (0.48)	1.49 (1.04)	0.046
Hemoglobin, g/L	141.46 (12.47)	139.61 (18.41)	0.648
Platelet count, $\times 10^9$	193.67 (67.23)	214.27 (65.15)	0.187
Serum creatinine, μ mol/L	81.42 (65.91)	61.90 (18.02)	0.025
ALT, U/L	23.83 (14.07)	20.91 (16.05)	0.439
AST, U/L	25.49 (11.68)	21.92 (9.48)	0.146
LDH, IU/L	228.86 (80.21)	181.79 (55.17)	0.003
Tobacco smoking	1 (4.2%)	7 (9.9%)	0.385

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; SBP = systolic blood pressure.

count ($p < 0.001$) were significantly lower in patients with pneumonia.

Univariate and Multivariate Analyses of Factors Associated With Pneumonia

Univariate and multivariate analyses were conducted to analyze the risk factors associated with 2019-nCoV–infected patients developing pneumonia. Univariate results showed that older age, high BMI, low lymphocyte count, low platelet count, high aspartate aminotransferase level, and high LDH level were risk factors associated with patients developing pneumonia. However, multivariate analysis showed that only older age (OR, 1.078; $p = 0.008$) and high BMI (OR, 1.327; $p = 0.024$) were independent risk factors associated with patients developing pneumonia (Table II).

Differences in Characteristics Between the ARDS Group and the Non-ARDS Group

Using the ARDS definition, patients were divided into an ARDS group ($n = 24$) and a non-ARDS group ($n = 71$) (Table III). Patients with ARDS

were older than those without ARDS ($p = 0.021$). Moreover, systolic blood pressure (SBP) ($p = 0.038$), serum creatinine ($p = 0.025$), and LDH ($p = 0.003$) levels were significantly higher in patients with ARDS. However, lymphocyte counts were lower in patients with ARDS than in others ($p = 0.046$).

Univariate and Multivariate Analyses of Factors Associated With ARDS

Logistic regression was used to identify factors that were significantly associated with ARDS in patients with COVID-19. In multivariate analysis, high SBP level (OR, 1.046; $p = 0.025$) and high LDH level (OR, 1.010; $p = 0.021$) were found to be independent risk factors associated with ARDS among patients with COVID-19 (Table IV).

Differences in Characteristics Between Patients With Pneumonia Exacerbation and Relief

A total of 70 patients underwent CT scanning repeatedly after 1 week of treatment. Based on the findings obtained after comparison with the first CT

Table IV. Factors associated with acute respiratory distress syndrome in patients with coronavirus disease 2019.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Sex	1.149	0.450–2.930	0.772			
Age	1.031	1.004–1.058	0.025			
SBP	1.033	1.001–1.066	0.042	1.046	1.006–1.089	0.025
DBP	1.029	0.981–1.079	0.244			
BMI	1.147	0.996–1.320	0.057			
Serum lactic acid	0.865	0.416–1.801	0.699			
Neutrophil count	0.927	0.665–1.292	0.652			
Lymphocyte count	0.359	0.141–0.918	0.032			
Hemoglobin	1.006	0.980–1.034	0.645			
Platelet count	0.995	0.987–1.003	0.188			
Serum creatinine	1.021	0.995–1.048	0.116			
ALT	1.011	0.983–1.040	0.443			
AST	1.033	0.988–1.080	0.154			
LDH	1.011	1.003–1.018	0.007	1.010	1.001–1.019	0.021
Tobacco smoker	0.398	0.046–3.408	0.400			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; OR = odds ratio; SBP = systolic blood pressure.

scan, patients were divided into the pneumonia exacerbation group ($n = 19$) and the pneumonia relief group ($n = 51$). The characteristics were compared, and the results showed that patients with pneumonia exacerbation were significantly older ($p = 0.021$), with a higher BMI ($p = 0.003$) and a higher proportion of tobacco smokers ($p = 0.006$) (Table V).

Univariate and Multivariate Analyses of Factors Associated With Pneumonia Exacerbation

Logistic regression was used to identify factors that were associated with pneumonia exacerbation in patients with COVID-19. Multivariate analysis showed that a high BMI (OR, 1.285; $p = 0.017$) and tobacco smoking (OR, 16.13; $p = 0.032$) were independent risk factors associated with 2019-nCoV-infected patients with pneumonia exacerbation after treatment (Table VI).

DISCUSSION

The present study found that older age and high BMI were independent risk factors associated with patients with pneumonia. Furthermore, high SBP level and high LDH level were independent risk factors associated with ARDS among patients with COVID-19. High BMI and tobacco smoking were independent risk factors associated with pneumonia exacerbation after treatment in patients with COVID-19. These results help in the risk stratification of patients with COVID-19. Timely intervention should be initiated in patients with risk factors to avoid disease progression. In addition, the results of this study may have implications for the pathogenesis of COVID-19.

Most patients with COVID-19 will develop pneumonia.¹¹ However, a small proportion of patients have negative radiographic findings. The largest study sample to date showed that among the 3665 confirmed cases, 95.5% ($n = 3498$) of patients were diagnosed with pneumonia.¹² According to the

Table V. Demographic and clinical characteristics in patients with coronavirus disease 2019 (COVID-19) with pneumonia exacerbation or relief.

Characteristic	Patients with COVID-19		<i>P</i>
	Pneumonia Exacerbation	Pneumonia Relief	
Sample size, <i>n</i>	19	51	—
Male sex	11 (57.9%)	24 (47.1%)	0.420
Age, <i>y</i>	49.58 (22.16)	38.37 (15.80)	0.021
SBP, mm Hg	127.63 (13.11)	125.39 (17.43)	0.614
DBP, mm Hg	81.26 (10.95)	84.14 (10.58)	0.322
BMI, kg/m ²	25.38 (2.49)	22.95 (3.61)	0.003
Serum lactic acid, mmol/L	1.53 (0.75)	1.56 (0.72)	0.896
Neutrophil count, × 10 ⁹	3.47 (1.62)	3.29 (1.58)	0.679
Lymphocyte count, × 10 ⁹	1.13 (0.58)	1.31 (1.05)	0.481
Hemoglobin, g/L	139.68 (13.46)	137.92 (19.83)	0.722
Platelet count, × 10 ⁹	184.95 (50.78)	207.19 (60.51)	0.159
Serum creatinine, μmol/L	81.74 (73.92)	61.76 (17.34)	0.073
ALT, U/L	19.38 (11.03)	21.78 (12.55)	0.477
AST, U/L	23.26 (12.71)	23.80 (10.05)	0.856
LDH, IU/L	201.16 (80.15)	200.40 (64.92)	0.968
Tobacco smoking	4 (21.1%)	1 (2.0%)	0.006

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; SBP = systolic blood pressure.

Table VI. Factors associated with pneumonia exacerbation in patients with coronavirus disease 2019.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Sex	1.547	0.534–4.482	0.422			
Age	1.037	1.004–1.071	0.026			
SBP	1.009	0.976–1.042	0.608			
DBP	0.974	0.926–1.025	0.319			
BMI	1.253	1.049–1.497	0.013	1.285	1.045–1.581	0.017
Serum lactic acid	0.949	0.440–2.047	0.894			
Neutrophil count	1.072	0.774–1.485	0.674			
Lymphocyte count	0.746	0.325–1.714	0.490			
Hemoglobin	1.005	0.977–1.034	0.718			
Platelet count	0.993	0.983–1.003	0.161			
Serum creatinine	1.014	0.990–1.039	0.244			
ALT	0.982	0.936–1.031	0.472			
AST	0.995	0.945–1.048	0.854			
LDH	1.000	0.992–1.008	0.967			
Tobacco smoking	6.667	1.110–40.04	0.038	16.13	1.275–204.16	0.032

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; OR = odds ratio; SBP = systolic blood pressure.

Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia recommended by The National Health Commission of China, these patients only exhibited low fever and mild fatigue with no pneumonia manifestations, and they usually recovered after 1 week. Our study confirmed these results. We found that some patients had negative CT scan results, although the throat swabs confirmed infection with 2019-nCoV. Most previous studies were conducted in Wuhan Province with patients enrolled from Wuhan, and the symptoms of those first-generation patients were relatively severe. The patients enrolled in the present study were from Guangdong Province, which is not the first generation of infected patients. In our study, the patients' symptoms were relatively mild, which is in line with the results of patients from Zhejiang Province.¹³ Symptoms of patients outside Hubei Province are relatively mild.

Some 2019-nCoV–infected patients will rapidly become critically ill.^{9,14} Previous research reported that the mortality rate of 2019-nCoV–infected patients is 4%–15%.^{7,9} In our study, only one patient

aged 75 years (BMI, 29.37 kg/m²) died (mortality rate, 1.05%). Therefore, early detection of this population is very important. However, this subpopulation of patients who have severe disease may have moderate to low fever in the development of the disease. It is still difficult to screen out these patients. Our research may provide a sign. According to the results of our study, the 2019-nCoV–infected patients who developed ARDS were older and had higher SBP, serum creatinine, and LDH levels. This group of people also had lower lymphocyte counts. However, multivariate analysis suggested that only high SBP level and high LDH level were independent risk factors associated with ARDS among patients with COVID-19.

Previous research implied that some patients' conditions will change dramatically in ~1 week.⁹ In our study, we performed repeated CT examinations on 70 patients after 1 week of treatment and found that those with imaging findings suggesting exacerbations had clinical baseline data significantly different from patients with reduced disease. Tobacco smoking has been confirmed to be associated with many diseases.^{15,16} In our study, multivariate analysis

suggests that high BMI and tobacco smoking were independent risk factors associated with disease exacerbation in 2019-nCoV–infected patients after treatment.

Until now, there have been no antiviral drugs specifically approved for treating 2019-nCoV–infected patients. Although reports have suggested the potential antiviral effects of lopinavir/ritonavir, it remains controversial.¹⁴ Remdesivir has shown strong potential antiviral effects in previous reports but has not yet been approved by the US Food and Drug Administration, and large clinical research results are lacking to support its application.^{2,17} Finding an effective treatment plan is a particularly important clinical problem.

The present study discusses the evolution of CT findings for patients with COVID-19. However, CT scans are not frequently used for assessment of patients with complicated pneumonia or ARDS. CT scan findings cannot completely identify exacerbation or relief of the disease. The CT scan results can only reflect some aspects in the development of the disease. The findings from our study may not have clinical relevance across different parts of the world.

This study has limitations. First, it involved a cross-sectional investigation. Second, the relative sample size was limited. The potential limitations of the present report could be overcome in future studies by enrolling more patients. In our study, there was no control group, and there was no comparator virus-infected group. Most of these findings are the same as would be seen with influenza, respiratory syncytial virus, and human metapneumovirus. The results from our study may imply that high-risk patients are at high risk of complications because of who they are (their specific characteristics), and not because of the specific nature of the individual pathogen. The airway inflammation coupled with their clinical factors is the real issue. In addition, prognostic outcomes were assessed. In the present study, all patients diagnosed with ARDS were admitted to the intensive care unit to continue further treatment. However, other prognostic outcomes, including length of stay data, in this study are missing because some patients are still in the hospital. Further study is needed to determine mortality and length of stay data.

CONCLUSIONS

Older age and high BMI were independent risk factors associated with pneumonia in patients with COVID-19. High SBP and LDH levels were independent risk factors associated with ARDS, whereas high BMI and tobacco smoking were independent risk factors associated with disease exacerbation after treatment. For such patients, stratification by using independent risk factors could help with the management of their disease.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Drs. S. Cai, Yin, Xu, and Peng designed and guided the study; Drs. S. Cai and Yu wrote the main manuscript text; and Drs. Zheng, Liu, and X. Cai prepared all tables and data analysis. All authors reviewed the manuscript.

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