Risk Factor Analysis and Predictive Indicator Exploration for Severe COVID-19 Cases in Xi' an City During the 2021-2022 New Year Period: Postprint

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Abstract

Background The COVID-19 outbreak in Xi' an during the 2021-2022 New Year period was another large-scale local epidemic occurring in a megacity with numerous cases following the "Wuhan epidemic," necessitating analysis and summary of relevant aspects of this outbreak.

Objective To analyze the disease characteristics of COVID-19 patients and explore risk factors and predictive indicators for severe cases.

Methods Clinical data were retrospectively collected from 701 COVID-19 patients admitted to Xi' an Fourth People' s Hospital, the designated COVID-19 treatment facility in Xi' an, between December 2021 and January 2022. Mild and moderate patients were classified as the mild-to-moderate group, while severe and critically ill patients were classified as the severe-to-critically-ill group. Differences in general information, laboratory parameters, and IgM:L# between the two groups were compared, and binary logistic regression analysis was employed to identify risk factors influencing disease severity. Subsequently, ROC curves were constructed to analyze predictive indicators and their predictive value for severe and critically ill COVID-19.

Results Data from 701 confirmed COVID-19 patients were collected, all cases were infected with the Delta variant. After excluding 2 cases with incomplete clinical data, the final cohort comprised 405 mild cases, 273 moderate cases, 18 severe cases, and 3 critically ill cases. Univariate analysis revealed statistically significant differences between the severe-to-critically-ill group and the mild-to-moderate group in age, rate of underlying comorbidities, lymphocyte percentage, lymphocyte count, D-dimer, IgM-to-lymphocyte percentage ratio (IgM:L%), and IgM-to-lymphocyte count ratio (IgM:L#) (all $P<0.05$). Binary

logistic regression analysis identified age, D-dimer, and IgM:L# as risk factors for severe and critically ill COVID-19, whereas lymphocyte percentage was a protective factor. ROC analysis demonstrated that age, lymphocyte percentage, D-dimer, IgM:L#, and combined detection could all predict severe and critically ill COVID-19, with AUC values of 0.861, 0.750, 0.744, 0.694, and 0.912, respectively. Combined detection exhibited the highest predictive value, with a sensitivity of 90.00% and specificity of 83.18%.

Conclusion During the acute phase of COVID-19, an imbalance exists between inflammatory response and cellular immune function, and this imbalance, together with age and D-dimer, constitutes risk factors for severe COVID-19. Combined indicators encompassing age, D-dimer, lymphocyte percentage, and IgM:L# can effectively predict severe and critically ill COVID-19.

Full Text

Preamble

Analysis of Risk Factors and Exploration of Predictive Indicators for Severe Cases of COVID-19 in Xi' an During the 2021-2022 New Year Period

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Abstract

Background: The COVID-19 outbreak in Xi' an during the 2021-2022 New Year period represented another large-scale local epidemic in a megacity with numerous cases following the "Wuhan epidemic," necessitating analysis and summary of relevant data from this outbreak. **Objective:** To analyze disease characteristics of COVID-19 patients and explore risk factors and predictive indicators for severe cases. **Methods:** Clinical data were retrospectively collected from 701 COVID-19 patients admitted to Xi' an Fourth People' s Hospital (the designated COVID-19 hospital in Xi' an) between December 2021 and January 2022. Mild and moderate cases were classified as the Mild/Moderate Group, while severe and critical cases were classified as the Severe/Critical Group. Differences

in general patient data, laboratory indicators, and IgM:L# were compared between groups, and risk factors affecting disease severity were identified through binary logistic regression. ROC curves were then constructed to analyze predictive indicators and their value for severe/critical COVID-19. **Results:** Among 701 confirmed COVID-19 patients (all Delta variant), 2 cases with incomplete clinical data were excluded, leaving 405 mild, 273 moderate, 18 severe, and 3 critical cases for analysis. Univariate analysis revealed statistically significant differences between the Severe/Critical Group and Mild/Moderate Group in age, rate of comorbidities, lymphocyte percentage, lymphocyte count, D-dimer, IgM-lymphocyte percentage ratio (IgM:L%), and IgM-lymphocyte count ratio (IgM:L#) (all $P<0.05$). Binary logistic regression identified age, D-dimer, and IgM:L# as risk factors for severe/critical COVID-19, while lymphocyte percentage was a protective factor. ROC analysis demonstrated that age, lymphocyte percentage, D-dimer, IgM:L#, and combined detection could all predict severe/critical COVID-19, with AUC values of 0.861, 0.750, 0.744, 0.694, and 0.912, respectively. Combined detection showed the highest predictive value, with sensitivity of 90.00% and specificity of 83.18%. **Conclusion:** During the acute phase of COVID-19, an imbalance exists between inflammatory response and cellular immune function, which—along with age and D-dimer—constitutes a risk factor for severe disease. Combined indicators including age, D-dimer, lymphocyte percentage, and IgM:L# can effectively predict severe and critical COVID-19.

Keywords: COVID-19; IgM; Lymphocyte count; IgM-lymphocyte count ratio; Predictive value

Introduction

Since the first local COVID-19 case was identified in Xi'an on December 9, 2021, a total of 2,053 locally confirmed cases had been reported in the city by January 20, 2022, with 2,080 cases reported across Shaanxi Province [1]. All cases in this outbreak were caused by the Delta variant. The COVID-19 pandemic continues to pose significant threats to our economy and daily life. The Xi'an outbreak represented another large-scale local epidemic in a megacity with numerous cases following the "Wuhan epidemic." Therefore, analyzing the basic disease characteristics of COVID-19 patients during this period to explore risk factors and predictive indicators for disease severity is essential for providing data references for subsequent epidemic prevention and control efforts.

Methods

1.1 Inclusion and Exclusion Criteria

Clinical data were retrospectively collected from confirmed COVID-19 patients admitted to Xi' an Fourth People' s Hospital (the designated COVID-19 hospital in Xi' an) between December 2021 and January 2022. COVID-19 diagnosis followed the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8, Revised)* [2], requiring either: (1) positive nucleic acid test for SARS-CoV-2, or (2) positive specific IgM and IgG antibodies in unvaccinated individuals. All confirmed patients received treatment according to the same protocol. Data were collected, organized, and entered into an Excel database by physicians from the medical treatment team. Cases with missing clinical classification data were excluded.

1.2 Clinical Classification and Grouping

Based on patient condition and relevant indicators, patients were classified as mild, moderate, severe, or critical according to the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8, Revised)* [2]. Both severe and critical cases are considered severe COVID-19, requiring more aggressive prevention and treatment of complications, management of underlying diseases, prevention of secondary infections, and timely organ function support compared to mild and moderate cases. Therefore, mild and moderate cases were grouped as the Mild/Moderate Group, while severe and critical cases were grouped as the Severe/Critical Group.

1.3.1 Comparison of General Data and Laboratory Indicators

General patient data collected included age, sex, BMI, number of patients with comorbidities (including diabetes, hypertension, chronic kidney disease, coronary heart disease, chronic obstructive pulmonary disease, etc.), number of patients with cough or muscle pain, maximum body temperature, vaccination doses, vaccine type, time from symptom onset to medical visit, and admission laboratory indicators such as white blood cell count, lymphocyte percentage, lymphocyte count, D-dimer, CT values for SARS-CoV-2 nucleic acid ORF1ab and N genes, serum total IgG and IgM antibody titers. Ratios of total IgG or IgM to lymphocyte percentage (IgG:L%, IgM:L%) and to lymphocyte count (IgG:L#, IgM:L#) were calculated. Statistical differences in these indicators were compared between the two groups.

1.3.2 Risk Factor Analysis and Predictive Indicators for Severe/Critical COVID-19

Indicators showing statistical significance in univariate analysis were included in multivariate logistic regression analysis to identify risk factors for severe/critical COVID-19. ROC curves were then constructed to analyze the predictive value of these risk factors for disease severity.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 21 software. Categorical data were expressed as n (%) and compared using chi-square test, continuity correction, or Fisher' s exact test. Non-normally distributed continuous data were expressed as M (Q1, Q3) and compared using Mann-Whitney U test. Risk factor analysis employed binary logistic regression. Predictive value was assessed by constructing ROC curves and comparing differences between ROC curves using DeLong et al. test. All statistical analyses were completed using SPSS 26.0 software.

Results

2.1 General Data and Laboratory Indicators

Xi' an Fourth People' s Hospital admitted a total of 701 confirmed COVID-19 patients with no deaths. Two cases were excluded due to missing clinical classification data, leaving 699 confirmed COVID-19 patients for analysis. Clinical classifications were: 405 mild cases, 273 moderate cases, 18 severe cases, and 3 critical cases. General patient data and laboratory indicators are presented in Table 1 .

Table 1 General Data and Laboratory Indicators [M (Q1, Q3)/n (%)]
Age (years): 33.00 (21.00, 50.00)
Sex (male/female): 374/325
BMI (kg/m^2): 22.70 (20.50, 25.25)
Body temperature (℃): 36.50 (36.50, 37.60)
White blood cell count ($\$\times 10^{\{9\}/L) : 5.14(4.03, 6.31) Lymphocytepercentage(\times 10}\{9\}\$$/L): 1.45 (1.03, 2.02)
D-dimer (g/mL): 0.26 (0.20, 0.37)
Admission ORF1ab gene test positive: 373 (53.4%)
First ORF1ab gene CT value within 3 days: 32.25 (28.19, 35.57)
Admission N gene test positive: 450 (64.40%)
First N gene CT value within 3 days: 32.80 (28.68, 36.42)
Total IgG (S/CO): 3.47 (0.72, 42.37)
Total IgM (S/CO): 0.06 (0.03, 0.54)
IgG:L%: 0.14 (0.02, 1.33)
IgG:L#: 2.77 (0.49, 28.86)
IgM:L%: 0.00 (0.00, 0.02)
IgM:L#: 0.04 (0.02, 0.34)
Vaccination doses (0/1/2/3): 181 (25.90%)/38 (5.40%)/406 (58.10%)/74 (10.60%)
Time from onset to medical visit (days): 2.00 (1.00, 3.00)
Note: BMI = body mass index

2.2 Comparison of General Data and Laboratory Indicators Between Groups

Patients were divided into the Mild/Moderate Group (n=678) and Severe/Critical Group (n=21). Comparison revealed statistically significant differences between groups in age, rate of comorbidities, lymphocyte percentage, lymphocyte count, D-dimer, IgM:L%, and IgM:L# (P<0.05), as shown in Table 2 .

Table 2 Comparison of Indicators Between Mild/Moderate and Severe/Critical COVID-19 Patients

Indicator	Mild/Moderate (n=678)	Severe/Critical (n=21)	t/ ^{2}/Z value	P value
Age (years)	32.00 (21.00, 49.00)	61.00 (52.50, 73.00)	-	<0.001
Sex (male/female)	363/315	11/10	-	0.923
BMI (kg/m^2)	22.70 (20.50, 25.20)	23.34 (21.32, 26.98)	-	0.311
Body temperature (℃)	36.50 (36.50, 37.60)	36.50 (36.50, 37.95)	-	0.956
Comorbidities	94 (13.90%)	12 (57.10%)	-	<0.001
White blood cell count ($\times10^{9}/L$)	1.46 (1.05, 2.04)	0.97 (0.68, 1.08)	-	<0.001
$5.14(4.03, 6.31)\|5.23(4.03, 6.48)\| - \|0.923\|\|Lymphocytepercentage(\times10^{9}$/L)				
D-dimer (g/mL)	0.26 (0.20, 0.36)	0.44 (0.27, 0.88)	-	<0.001
Admission ORF1ab positive	360 (53.1%)	13 (61.9%)	0.598	0.439
First ORF1ab CT value (3 days)	32.30 (28.19, 35.59)	31.42 (28.23, 34.65)	-	0.556
Admission N gene positive	438 (64.60%)	12 (57.10%)	0.462	0.497
First N gene CT value (3 days)	32.86 (28.67, 36.49)	31.61 (28.79, 33.57)	-	0.290

Indicator	Mild/Moderate (n=678)	Severe/Critical (n=21)	t/ ^{2}/Z value	P value
Total IgG (S/CO)	3.56 (0.72, 41.67)	2.40 (0.36, 312.13)	-	0.923
Total IgM (S/CO)	0.05 (0.03, 0.50)	0.18 (0.03, 10.76)	-	0.311
IgG:L%	0.14 (0.02, 1.31)	0.01 (0.00, 0.66)	-	0.311
IgG:L#	2.79 (0.49, 28.63)	2.46 (0.20, 281.68)	-	0.923
IgM:L%	0.04 (0.02, 0.33)	0.18 (0.03, 16.92)	-	<0.001
IgM:L#	0.13 (0.01, 15.37)	0.18 (0.03, 16.92)	-	<0.001
Vaccination doses (0/1/2/3)	173 (95.60%)/8 (4.40%)	16 (100.00%)/0 (0.00%)	0.462	0.497
Time from onset to visit (days)	2.00 (1.00, 3.00)	3.00 (1.00, 6.50)	-	0.290

2.3 Risk Factor Analysis for Severe/Critical COVID-19

Indicators showing statistical significance in univariate analysis (age, comorbidities, lymphocyte percentage, lymphocyte count, D-dimer, IgM:L%, and IgM:L#) were included in multivariate logistic regression analysis. Collinearity analysis led to the exclusion of IgM:L%. Binary logistic regression revealed that age, D-dimer, and IgM:L# were risk factors for severe/critical COVID-19, while lymphocyte percentage was a protective factor, as shown in Table 3 . The regression equation was constructed as: logit(P) = -5.031 + 0.065(A) - 1.074(B) - 0.086(C) + 0.738(D) + 0.477(E) + 0.034(F). The goodness-of-fit test for this model showed $^2 = 3.167$, P = 0.923; model test showed $^2 = 55.475$, $P < 0.001$.

Table 3 Multivariate Logistic Regression Analysis of Risk Factors for Severe/Critical COVID-19

Variable	Wald ^{2}	P value	95% CI
Age (A)	12.401	<0.001	-
Comorbidities (B)	-	<0.001	-
Lymphocyte percentage (C)	13.513	<0.001	-
Lymphocyte count (D)	-	<0.001	-
D-dimer (E)	-	<0.001	-
IgM:L# (F)	-	<0.001	-

2.4 Predictive Indicator Analysis for Severe/Critical COVID-19

ROC curve analysis was performed to evaluate the predictive value of age, lymphocyte percentage, D-dimer, and IgM:L# for severe/critical COVID-19. A combined indicator derived from the regression equation was also assessed. The analysis showed that age, lymphocyte percentage, D-dimer, IgM:L#, and the combined indicator could all predict severe/critical COVID-19, with AUC values of 0.861, 0.750, 0.744, 0.694, and 0.912, respectively. The combined detection demonstrated the highest predictive value, with sensitivity of 90.00% and specificity of 83.18%, as shown in Figure 1 [Figure 1: see original paper] and Table 4 .

Figure 1 ROC Curves for Predictive Indicators of Severe/Critical COVID-19 Severity

Table 4 Diagnostic Efficacy Analysis of Predictive Indicators for COVID-19 Severity

Indicator	AUC	95% CI	Optimal Cut-off	Sensitivity	Specificity	P value
Age	0.861	-	-	-	-	<0.001
Lymphocyte percentage	0.750	-	-	-	-	<0.001
D-dimer	0.744	-	-	-	-	<0.001
IgM:L#	0.649	-	-	-	-	<0.001
Combined indicator	0.912	-	-	90.00%	83.18%	<0.001

Note: a, P<0.05 vs. age; b, P<0.05 vs. lymphocyte percentage; c, P<0.05 vs. D-dimer; d, P<0.05 vs. IgM:L#

Discussion

Numerous studies have demonstrated that age is an independent risk factor for poor prognosis in COVID-19. Potential mechanisms include: (1) The increasing prevalence of chronic diseases such as hypertension, diabetes, and coronary heart disease with advancing age [3]; (2) Elevated baseline levels of pro-inflammatory cytokines in tissues and circulation with aging, leading to delayed immune responses to pathogenic threats or tissue injury [4]; (3) The ACE-2 receptor, required for SARS-CoV-2 cellular entry, may be upregulated in elderly patients due to higher rates of hypertension, diabetes, and cardiovascular disease, which increase usage of ACEI or ARB medications [5]. Increased ACE-2 receptor expression can facilitate viral invasion and contribute to disease deterioration

in elderly patients [6][7]. Additionally, research indicates that immunogenicity and protective efficacy of COVID-19 vaccines are significantly lower in elderly populations compared to other age groups [8].

Beyond age, this study found that the proportion of patients with comorbidities was significantly higher in the severe/critical group compared to the mild/moderate group (57.1% vs. 13.9%). Multiple studies have confirmed that comorbidities including hypertension, cardiovascular disease, cerebrovascular injury, cancer, diabetes, chronic kidney disease, chronic lung disease, autoimmune diseases, and other conditions significantly increase the risk of COVID-19 infection and progression to severe disease [9]. However, our study found that age, D-dimer, elevated IgM:L#, and decreased lymphocyte percentage had greater impact on severe/critical COVID-19 than comorbidities alone.

Chen N et al. found that COVID-19 patients frequently exhibit coagulation abnormalities, with 36% showing elevated D-dimer [10]. SARS-CoV-2 infection can trigger inflammatory responses and even cytokine storms, promoting disease progression [11]. This process can cause vascular endothelial injury, activate the intrinsic coagulation system, lead to DIC, and result in elevated D-dimer. Additionally, hypercoagulable states and venous thromboembolism in COVID-19 patients can increase D-dimer levels [12][13]. D-dimer is one of the earliest coagulation indicators to change following SARS-CoV-2 infection [14], with particularly significant elevation in severe COVID-19 patients that correlates positively with mortality. It can be used to predict severe disease and in-hospital mortality [15][16]. Furthermore, decreased lymphocyte count and increased D-dimer at admission are associated with higher mortality in patients requiring mechanical ventilation [17] and with complications such as ischemic stroke [18]. Our study also found that D-dimer was significantly higher in severe/critical patients compared to mild/moderate patients, and could serve as a predictor of disease severity.

SARS-CoV-2 infection can cause immune dysfunction and lymphopenia, with both lymphocyte count and percentage significantly lower in severe/critical patients compared to non-severe patients [19][20]. Lymphocyte count can predict not only severe pneumonia in COVID-19 patients but also shorter hospital stays in those with higher counts [21]. Lymphopenia is also a predictor of disease severity [22], consistent with our findings.

IgM is an early immunoglobulin produced after viral invasion, while IgG is synthesized during secondary immune responses and provides neutralizing activity in humoral immunity; both participate in the immune response to COVID-19. Some studies have found that serum SARS-CoV-2-specific IgM levels are higher in severe/critical patients, while IgG levels are lower compared to mild/moderate patients [23][24]. However, our study found no statistically significant differences in IgM or IgG levels between groups, which may require verification with larger sample sizes.

Research indicates that serum SARS-CoV-2-specific IgM and IgG antibodies

not only aid in diagnosis or assessment of disease outcome but also, as important components of the immune response, reflect disease activity and immune response intensity [25]. Xie et al. found that IgM levels correlated positively with neutrophil percentage (r=0.34, P=0.047) in severe/critical patients, suggesting IgM may serve as an indicator of severe inflammatory response during acute infection [26]. Other studies have shown that total IgG and IgM levels correlate positively with disease severity [27] but negatively with lymphocyte proportion [28][29]. Therefore, ratios of IgG or IgM to lymphocyte percentage or count may more intuitively reflect the degree of immune dysfunction. Our study found that while IgG:L% and IgG:L# showed no significant differences between severe/critical and non-severe patients, IgM:L% and IgM:L# were significantly higher in severe/critical patients. Moreover, IgM:L# was not only a risk factor for severe disease but also a predictor of severe/critical COVID-19, further demonstrating that imbalance between inflammatory response and cellular immune function during the acute phase of viral infection may directly influence disease severity. The lack of significant differences in IgG:L% and IgG:L# between groups may be related to the IgG peak occurring approximately one week later than the IgM peak [30]. Further analysis of the relationship between IgG, IgM, and lymphocyte levels throughout disease progression may help elucidate the mechanisms of immune dysfunction in COVID-19 progression.

Subsequently, we applied the combined detection method derived from binary logistic regression to predict severe/critical COVID-19 and evaluated its predictive value using ROC curve analysis. The combined detection not only predicted severe/critical disease but also demonstrated significantly higher AUC (0.912) than individual indicators including age, D-dimer, lymphocyte percentage, and IgM:L#, with sensitivity of 90.00% and specificity of 83.18%.

Additionally, studies have shown that a single dose of inactivated or protein subunit vaccine cannot effectively induce neutralizing antibodies, while two doses significantly increase neutralizing antibody levels [31][32]. COVID-19 vaccination is crucial for preventing infection and severe/critical disease, and can reduce mortality [33]. However, our study found no statistical differences in vaccination doses or vaccine types between severe/critical and mild/moderate patients, possibly due to the relatively small number of severe/critical cases in our center, warranting further research with larger sample sizes.

In conclusion, during the acute phase of SARS-CoV-2 infection, an imbalance exists between inflammatory response and cellular immune function, which—along with age and D-dimer—constitutes a risk factor for severe/critical COVID-19. Combined application of age, D-dimer, lymphocyte percentage, and IgM-lymphocyte count ratio can effectively predict severe and critical disease. However, the relatively small number of severe/critical cases in this study may introduce bias, and our conclusions require verification through larger-scale studies. Autoimmune diseases and long-term use of steroids or immunosuppressants may influence disease progression and vaccine responsiveness, necessitating stratified analysis in future studies. Additionally, this study did not conduct long-

term follow-up of patient outcomes; therefore, longitudinal follow-up will be performed in subsequent research to identify indicators that may affect patient prognosis.

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Note: Figure translations are in progress. See original paper for figures.