Original Article

Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus

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Background: The emerging infection of the 2019 novel coronavirus (2019-nCoV) in late December, 2019 in Wuhan, China, has caused an extreme health concern, with many patients having progressed to acute respiratory disease or other complications in a short period. Meanwhile, the risk factors associated with the disease progression still remain elusive.

Methods: A cohort of 17 patients with laboratory-confirmed 2019-nCoV infections who were admitted to the Ninth Hospital of Nanchang between January 28 and February 6, 2020, were enrolled in this study. All the patients received standardized treatment. The disease progression was evaluated every 7 days after admission. The clinical, radiologic, and laboratory characteristics were retrospectively analyzed, and the factors associated with the disease progression were screened by binary logistic regression analysis.

Results: The cohort comprised 11 women (64.7%) and 6 men (35.3%) between the ages of 18 to 70 years old. All patients had a reported history of contact with infection-confirmed patients. Fever (11/64.7%) and cough (8/47.1%) were the most common symptoms, whereas dyspnea (2/11.8%) and fatigue (3/17.6%) were rare, and there was no patient with diarrhea symptoms. There were 5 patients with aggravated disease at the first disease progression evaluation, and no patient received mechanical ventilation, transferred to the intensive care unit (ICU), or progressed to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation dysfunction, or death. Based on the disease progression, patients were divided into the non-aggravation group (12 cases) and the aggravation group (5 cases). There were no significant differences between the 2 groups with respect to their clinical characteristics. Chest computed tomography (CT) on admission revealed there were 8 patients (47.1%) with invasive lesions found bilaterally on the lungs on multiple lobes, 4 patients (23.5%) with invasive lesions on 1 lobe, and 5 patients (29.4%) with normal chest CT. The aggravation group had1 patient (20.0%) with invasive lesions on one lobe, 3 (60.0%) with invasive lesions on multiple lobes, bilaterally, and 1 (20.0%) with normal chest CT; meanwhile, the non-aggravation group had 3 patients (25.0%) with invasive lesions on one lobe, 5 (41.7%) with invasive lesions on multiple lobes, bilaterally, and 4 (33.3%) with normal chest CT. No significant difference was found between the 2 groups. In the aggravation group, the total lymphocyte counts significantly decreased in comparison to that in the non-aggravation group. Further analysis showed that the $CD4^+$ T cell count but not the $CD8^+$ T cell count of the aggravation group was significantly lower than that of the non-aggravation group. Correlation analysis indicated total lymphocyte count was positively correlated with $CD4^+$ T cell count, and no significant differences were found between the 2 groups in other laboratory measurements, including those of white blood cell (WBC) count, C-reactive protein (CRP), albumin, lactate dehydrogenase (LDH), and D-dimer. Finally, a binary logistic regression model was used to identify the factors associated with the disease progression. It was found that total lymphocyte count was a risk factor associated with disease progression in patients infected with 2019-nCoV.

Conclusions: A higher cell count of total lymphocytes may indicate a better outcome of the disease, and immune response may be a vital factor for directing disease progression in the early stage of 2019-nCoV infection.

Keywords: 2019 novel coronavirus (2019-nCoV); disease progression; aggravation; immune response; risk factors

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Introduction

The emerging infection of a novel coronavirus was reported in late December, 2019, in Wuhan, China. The novel coronavirus was subsequently identified and provisionally named the 2019 novel coronavirus (2019-nCoV), and human-to-human transmission was confirmed (1).

Coronaviruses (CoVs) are single-stranded RNA viruses, which circulate in nature, and can infect the respiratory, gastrointestinal, hepatic, and central nervous system tracts of various animal species, including humans, cattle, birds, and bats (2,3). To date, 7 CoVs that can infect humans have been described. Common human CoVs (HCoV-OC43, HCoV-HKU1, and HCoV-229E) cause common colds but also severe lower respiratory tract infections in children and the elderly, while HCoVNL63 is considered to be an essential cause of pseudo-croup and bronchiolitis in children (4). The outbreaks of severe acute respiratory syndrome (SARS) in 2002–2003 (5,6) and Middle East respiratory syndrome (MERS)-CoV in 2012 (7,8) had a serious impact on public health, with these 2 highly pathogenic CoVs causing severe respiratory disease.

The worsening of the clinical status and the complications leading to death in several cases (9-11) provoked a health concern for the current outbreak of 2019-nCoV infection. Genome sequencing and analysis revealed that the genome of 2019-nCoV (GenBank accession MN908947) has the highest similarity (89%) to 2003-SARS (GenBank accession MG772933) (12).

Thus far, the clinical symptoms have been described extensively in the published literature, and include fever, cough, and shortness of breath, with radiographs showing invasive lesions in the lungs. However, there is limited information in the existing literature regarding the influencing factors associated with disease progression in 2019-nCoV-infected patients. The current report analyzed the relationships of several clinical and laboratory factors with the disease progression in a cohort of 17 laboratory-confirmed 2019-nCoV-infected patients. It is hoped that the information described in this report will offer a better understanding on the disease progression occurring after 2019-nCoV infection, and establish a basis to optimize the current therapeutic strategies.

Methods

Patients

A total of 33 patients withlaboratory-confirmed2019-nCoV infections were admitted to the Ninth Hospital of Nanchang between January 28 and Februay 6, 2020. In total,17 patients were included in the analysis, and the disease progress was evaluated every 7 days after the admission. This study was reviewed and approved by the Ethics Committee of the Ninth Hospital of Nanchang, and written informed consent was waived by the Ethics Committee in light of the urgent need to collect clinical data.

Treatment

All the patients were treated in strict accordance with the novel coronavirus infection diagnosis and treatment (the fifth trial version) formulated by the National Health Commission and Health Committee of China. To date, no antiviral treatment for coronavirus infection has been proven to be effective. Lopinavir/Ritonavir was empirically administered as an antiviral therapy, while corticosteroid therapy was given as a combined regimen when severe pneumonia was diagnosed. Oxygen support (e.g., nasal catheter, mask, high-flow oxygen therapy, non-invasive and invasive mechanical ventilation) was administered to patients according to the severity of hypoxaemia.

Data collection

The epidemiological characteristics (including recent exposure history), clinical symptoms and signs, chest computed tomography (CT) characteristics, and laboratory findings were extracted from electronic medical records. Laboratory assessments consisted of white blood cell (WBC) count, C-reactive protein (CRP), D-dimer, albumin, lactate dehydrogenase (LDH), total lymphocyte count, $CD4^+$ cell count, and $CD8^+$cell count. The endpoint was a disease progression to aggravation after admission; because clinical observations were still ongoing, fixed time frame (i.e., within 28 days), admission to ICU, mechanical ventilation, and death, were not applied to these endpoints at the time of the study.

Disease progression evaluation

Disease progression was evaluated every 7 days after admission, and consisted of classification into 1 of 3 grades: (I) improvement: the body temperature is lower than before, respiratory symptoms are relieved, and lung CT shows that the lesion(S) appears to be more absorbed and dissipated than before; (II) no change: no significant change in body temperature, respiratory symptoms, or lung CT; (III) aggravation: the body temperature is higher than before, the respiratory symptoms are more serious, and the lesion(s) on lung CT is larger than before.

Statistical analysis

Continuous variables with Gaussian distribution were expressed as mean ± SD and compared with the independent *t* test, while continuous variables without Gaussian distribution were expressed as median (min, max) and compared with the Mann-Whitney U test. Categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test. Pearson's correlation was used to determine the correlation between total lymphocyte count and $CD4^+$ T cell count. Binary logistic regression was used to screen the factors associated with the disease progression in 2019-nCoV-infected patients.

Results

Demographic and clinical characteristics

A total of 17 patients with confirmed infections were admitted to the Ninth Hospital of Nanchang. There were 11 women (64.7%) and 6 men (35.3%) in this cohort with ages ranging from 18 to 70 years old. All patients had a reported history of contact with infection-confirmed patients. The degree of clinical symptoms varied among this cohort of patients. Fever (11/64.7%) and cough (8/47.1%) were the most common symptoms, whereas dyspnea (2/11.8%) and fatigue (3/17.6%) were rare, and there were no patients with diarrhea symptoms. There were 5 patients (29.4%) with coexisting disorders (e.g., hypertension, others). In this cohort, no patient received mechanical ventilation, transferred to the ICU, or progressed to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction, or death. For the first evaluation of disease progression (7 days after admission), there were 5 patients with aggravation. Based on the disease progression, patients were divided into the non-aggravation group (12 cases, 7 of which showed improvement and 5 of which showed no change) and the aggravation group (5 cases). As shown in *Table 1*, there were no significant differences between the 2 groups with respect to the clinical characteristics.

Radiologic characteristics

Chest CT on admission revealed that there were 8 patients (47.1%) with invasive lesions found bilaterally on multiple lobes of the lungs, 4 patients (23.5%) with invasive lesions on 1 lobe, and 5 patients (29.4%) with normal chest CT. As shown in *Figure 1*, the aggravation grouphad1 patient (20.0%) with invasive lesions on one lobe, 3 (60.0%) with invasive lesions on multiple lobes, bilaterally, and 1 (20.0%) with normal chest CT. Meanwhile, the non-aggravation group had 3 patients (25.0%) with invasive lesions on one lobe, 5 (41.7%) with invasive lesions on multiple lobes, bilaterally, and 4 (33.3%) with normal chest CT. No significant difference was found between the 2 groups (P=0.777). Some representative radiologic features of Chest CT are shown in *Figures 2-4*.

On admission, chest CT showed a patchy shadow on the dorsal segment of the lower left lung with fuzzy edge. After 7-day treatment, the shadow on the dorsal segment of the lower left lung was reduced.

On admission, chest CT showed multiple patchy shadows on both lungs with fuzzy edges. After 7-day treatment, multiple patchy shadows on both lungs were enlarged.

On admission, chest CT showed patchy ground-glass

Table 1 Clinical characteristics of the two groups

Clinical characteristics	Non-aggravation group (n=12)	Aggravation group (n=5)	P
Age (year)	41.50±14.31	42.20±14.91	0.929
Gender (n/%)			0.102
Female	6/50.0%	5/100.0%	
Male	6/50.0%	0/0.0%	
Fever (n/%)			1.000
Yes	8/66.7%	3/60.0%	
No	4/33.3%	2/40.0%	
Cough (n/%)			0.131
Yes	4/33.3%	4/80.0%	
No	8/66.7%	1/20.0%	
Dyspnea (n/%)			1.000
Yes	2/16.7%	0/0.0%	
No	10/83.3%	5/100.0%	
Fatigue (n/%)			0.191
Yes	1/8.3%	2/40.0%	
No	11/91.7%	3/60.0%	
Coexisting disorders (n/%)			0.600
Yes	3/25.0%	2/40.0%	
No	9/75.0%	3/60.0%	

shadow on the middle lobe and lower lobe of the right lung. After 7-day treatment, the shadow on the middle lobe and lower lobe of the right lung showed no obvious changes.

Laboratory findings

The laboratory findings are summarized in *Table 2*. In the aggravation group, the total lymphocyte counts significantly decreased in comparison with that in the non-aggravation group, with the difference being statistically significant (P=0.021). The cell count of lymphocyte subtype $CD4^+$ T cell and $CD8^+$ T cell were then further analyzed. It was found that the $CD4^+$ T cell count in the aggravation group was significantly lower than that of the non-aggravation group with a statistical significance (P=0.034). Meanwhile, there was no significant difference between the 2 groups regarding the$CD8^+$ T cell count. In addition, no significant differences were found between the 2 groups in other

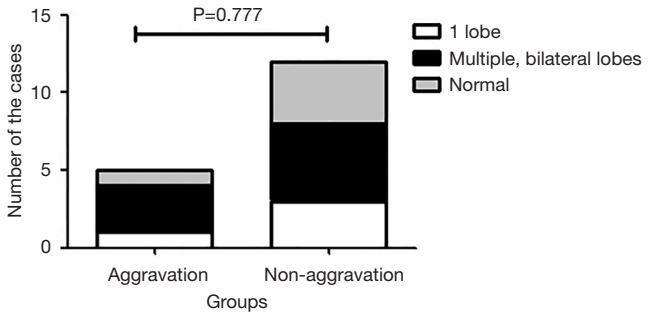

Figure 1 Radiologic characteristics of the two groups.

laboratory measurements, including those of WBC count, CRP, albumin, LDH, and D-dimer.

We further analyzed the correlation between total lymphocyte count and $CD4^+$ T cell count. As shown in *Figure 5*, $CD4^+$ T cell count was positively correlated with total lymphocyte count with a statistical significance (r=0.940, P<0.0001).

Logistic analysis of factors associated with disease progression

A binary logistic regression model was used to identify the factors associated with the disease progression in patients infected with 2019-nCoV. As shown in *Table 3*, several independent variables were included in this model, and the univariate logistical analysis indicated that total lymphocyte count was a factor associated with disease progression in patients infected with 2019-nCoV.

Discussion

As of February 12, 2020, more than 40,000 cases have been confirmed as 2019-nCoV infection, with more than 1,000 fatal cases being reported throughout mainland China, and an increasing number of laboratory-confirmed cases being identified globally, including in the USA, Vietnam, Germany, etc. (13-16). The World Health Organization (WHO) has recently declared 2019-nCoV to be a public health emergency of international concern (16).

In an earlier published study (17) of a 41-patient cohort with laboratory-confirmed 2019-nCoV infection, the mortality rate for 2019-nCoV was as high as 15% (6 deaths among 41 patients). The high mortality maybe due to the fact that most of patients admitted had serious, sometimes fatal pneumonia, with some developing ARDS and

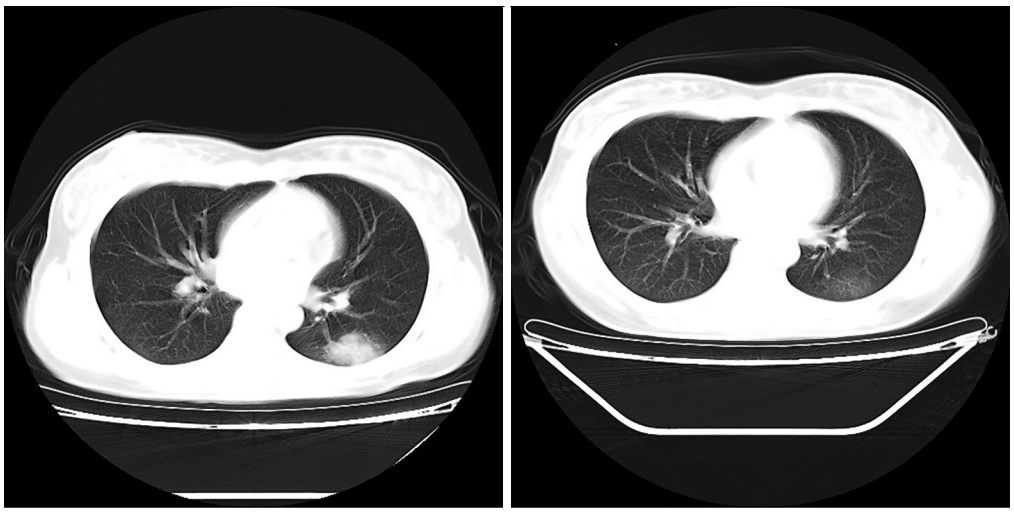

Figure 2 Representative radiologic features for improved patients.

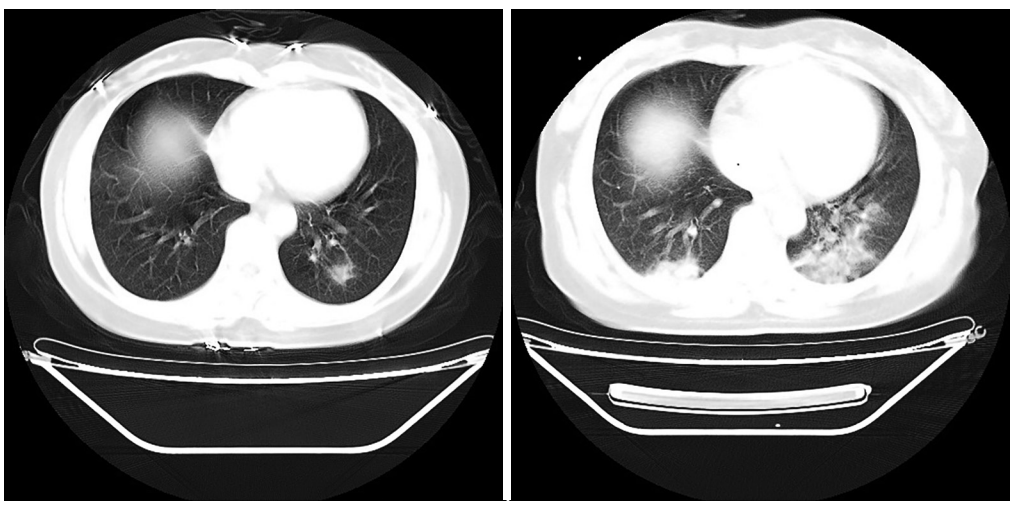

Figure 3 Representative radiologic features for aggravated patients.

requiring rapid ICU admission and oxygen therapy. The time between admission and ARDS was as short as 2 days in some cases. In the current study, we reported a cohort of 17 patients with laboratory-confirmed 2019-nCoV infection, who were admitted to the designated hospital (the Ninth Hospital of Nanchang) after January 28, 2020. By the first evaluation (7 days after admission) no patients had received mechanical ventilation, transferred to the ICU, or progressed to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation dysfunction, or death. This may be due to the fact that most patients in this cohort did not have severe illness, or the observation period of patients was too short (7 days) with the disease still ongoing. Despite a hospitalization period of only 7 days, the patients in this cohort experienced different illness outcomes, and 5 patients in this cohort progressed to aggravated illness.

In determining which patients progress to severe illness,

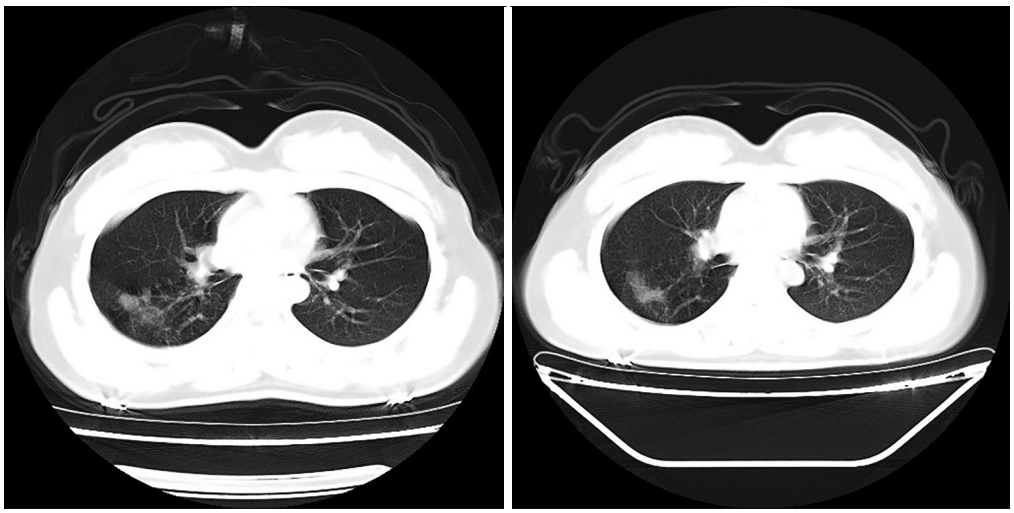

Figure 4 Representative radiologic features for patients without obvious change.

Table 2 Laboratory findings of the two groups

Laboratory measurements	Non-aggravation group (n=12)	Aggravation group (n=5)	P
WBC (10^9/L)	5.65±2.08	3.53±1.60	0.059
CRP (mg/L)	1.8 (0.5, 82.5)	4.8(1.5, 8.2)	0.162
Albumin (g/L)	44.91±2.97	46.00±3.24	0.510
LDH (U/L)	180 (137, 320)	157 (148, 246)	0.792
D-Dimer (mg/L)	0.29±10.11	0.28±0.11	0.922
Total lymphocyte (10^6/L)	1,223.0±442.7	650.0±339.3	0.021
$CD4^+$ T cell (10^6/L)	698.2±267.4	377.2±229.6	0.034
$CD8^+$ T cell (10^6/L)	364 (111, 799)	147 (116, 446)	0.102

WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase.

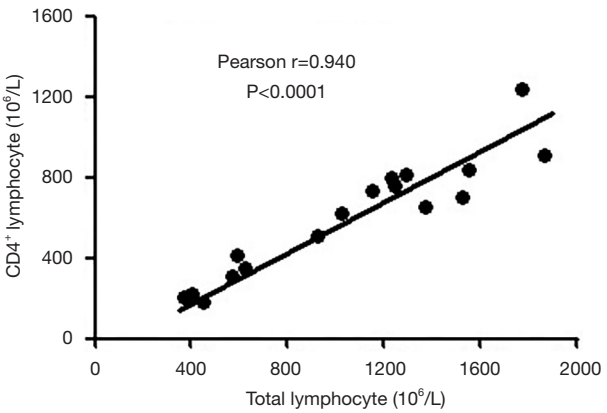

Figure 5 Correlation between total lymphocyte count and $CD4^+$ T cell count.

the progression at the early stage is likely very important to the outcome or the prognosis of the disease. We thus analyzed the differences between the aggravated patients and the non-aggravated patients in regards to the several clinical, radiologic, and laboratory findings, and attempted to identify the factors associated with disease progression. We found that clinical symptoms and signs had nothing to do with disease progression, and neither did the radiologic features of chest CT. Analysis of laboratory findings showed that the cell count of total lymphocyte and $CD4^+$ T cells in the aggravated patients was significantly reduced. Furthermore, a binary logistic regression model was used to screen the factors associated with disease progression; it was found that total lymphocyte count was the factor associated with the progression in 2019-CoV-infected patients. A higher cell count of total lymphocyte indicated a better outcome of the disease. However, $CD4^+$ T cell count was not a factor associated with disease progression, and this may be due to the small number of patients in this study. Correlation analysis indicated that $CD4^+$ T cell count was

Table 3 Screening of factors associated with disease progression

Factors	B	S.E.	Wals	df	Sig.	Exp(B)	95% CI	
							Lower	Upper
WBC (10^9/L)	–1.020	0.559	3.336	1	0.068	0.036	0.121	1.077
CRP (mg/L)	–0.050	0.065	0.601	1	0.438	0.951	0.837	1.080
Albumin (g/L)	0.131	0.181	0.489	1	0.484	1.140	0.790	1.646
LDH (U/L)	–0.004	0.012	0.095	1	0.758	0.996	0.974	1.020
D-Dimer (mg/L)	–0.551	5.204	0.011	1	0.916	0.576	0.000	15504.426
Total lymphocyte (10^6/L)	–0.003	0.002	3.912	1	0.048	0.997	0.993	0.999
$CD4^+$ T cell (10^6/L)	–0.005	0.003	3.707	1	0.054	0.995	0.989	1.000
$CD8^+$ T cell (10^6/L)	–0.007	0.005	2.554	1	0.110	0.993	0.984	1.002

WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase.

positively correlated with total lymphocyte count in this cohort of patients. This suggests that $CD4^+$ T cells may be lymphocytes that regulate the immune response against 2019-nCoV in these patients; therefore, an in-depth study with a large sample size should be conducted to verify this.

It is well known that during virus infection, host factors trigger an immune response against the virus. Immune insufficiency or misdirection may increase viral replication and cause tissue damage. It has been reported that MERS-CoV and SARS-CoV can cause fatal lower respiratory tract infections and extrapulmonary manifestations (18-20). Lymphocytes, especially $CD4^+$ T cells and $CD8^+$ T cells, have been shown to play a significant antiviral role by managing the fight against pathogens (21). $CD4^+$ T cells promote the production of virus-specific antibodies by activating T-dependent B cells. $CD8^+$ T cells, meanwhile, are reported to play a vital role in eliminating CoVs in infected cells and inducing immune injury. In MERS-CoV, $CD4^+$ T cells were found to be more susceptible to infection (22). In SARS-CoV, however, depletion of $CD8^+$ T cells did not affect viral replication of SARS-CoV (23,24), while depletion of $CD4^+$ T cells was associated with reduced pulmonary recruitment of lymphocytes and the neutralizing of antibody and cytokine production, resulting in a strong immune-mediated interstitial pneumonitis and delayed clearance of SARS-CoV from the lungs (25).

Based on the information from previous reports combined with the findings in this study, we believe that immune response is a vital factor directing disease progression. To our knowledge, this is the first study to report that total lymphocyte count and $CD4^+$ T cell count are related with the outcome of the disease, with total lymphocyte count being a risk factor associated with the outcome of the disease. This suggests that immune response may be critical in directing disease progression at the early stage of 2019-nCoV infection. We hope the findings of this study are helpful for optimizing the current therapeutic strategies in the treatment of 2019-nCoV infection.

Some limitations in this study should also be addressed. Firstly, a number of cases might have caused statistical bias in the results. Moreover, the risk factors associated with disease progression were not assessed extensively. Secondly, few patients with severe illness were admitted, which made it difficult to assess the risk factors for mortality. Thirdly, the immune response in this cohort of patients was not studied in depth. However, the findings of this research may still provide some insight for future studies to identify which cell types, cytokines/chemokines, underlying mechanisms, etc. figure prominently in the disease severity, outcome, and prognosis of this infection. More effort should be made to answer these questions in future studies. To conclude, a higher cell count of total lymphocytes may indicate a better outcome of the disease, and immune response may be a vital factor directing disease progression at the early stage of 2019-nCoV infection.

Acknowledgments

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Footnotes

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by the Ethics Committee of the Ninth Hospital of Nanchang (No. 20200224), and written informed consent was waived by the Ethics Committee in light of the urgent need to collect clinical data.

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