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# Comparative study of hematological and radiological feature of severe/critically ill patients with COVID-19, influenza A H7N9, and H1N1 pneumonia

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## Abstract

**Objectives:** This study aimed to explore clinical indexes for management of severe/critically ill patients with COVID-19, influenza A H7N9, and H1N1 pneumonia by comparing hematological and radiological characteristics.

**Methods:** Severe/critically ill patients with COVID-19, H7N9, and H1N1 pneumonia were retrospectively enrolled. The demographic data, clinical manifestations, hematological parameters, and radiological characteristics were compared.

**Results:** In this study, 16 cases of COVID-19, 10 cases of H7N9, and 13 cases of H1N1 who met severe/critically ill criteria were included. Compared with COVID-19, H7N9 and H1N1 groups had more chronic diseases (80% and 92.3% vs. 25%, $p < 0.05$), higher APACHE II scores (16.00 ± 8.63 and 15.08 ± 6.24, vs. 5.50 ± 2.58, $p < 0.05$), higher mortality rates (40% and 46.2% vs. 0%, $p < 0.05$), significant lymphocytopenia ($0.59 \pm 0.31 \times 10^9$/L and $0.56 \pm 0.35 \times 10^9$/L vs. $0.97 \pm 0.33 \times 10^9$/L, $p < 0.05$), and elevated neutrophil-to-lymphocyte ratio (NLR; 14.67 ± 6.10 and 14.64 ± 10.36 vs. 6.29 ± 3.72, $p < 0.05$). Compared with the H7N9 group, ground-glass opacity (GGO) on chest CT was common in the COVID-19 group ($p = 0.028$), while pleural effusion was rare ($p = 0.001$).

**Conclusions:** The NLR can be used as a clinical parameter for the predication of risk stratification and outcome in COVID-19 and influenza A pneumonia. Manifestations of pleural effusion or GGO in chest CT may be helpful for the identification of different viral pneumonia.

**KEYWORDS**
COVID-19, H1N1, hematological, inflammation, influenza A H7N9, radiological

Jindan Kong, Yan Hao and Shan Wan contributed equally to this work.

## 1 | INTRODUCTION

In December 2019, a cluster of pneumonia cases of unknown cause attacked Wuhan city in China. The pathogen was later identified to be a previously unknown beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The World Health Organization (WHO) denominated the new disease as coronavirus disease 2019 (COVID-19) in February and declared COVID-19 outbreak a pandemic in March 2020. COVID-19 infection usually begins with flu-like symptoms,[2] as influenza virus infections. The COVID-19 has caused more than 2.5 million deaths worldwide. Currently, vaccines are being delivered worldwide. There are still reports of confirmed cases in some parts of China. Influenza A virus is another important type of contagious respiratory pathogen, which has caused several global epidemics in history. The Spanish flu in 1918 which caused tens of millions of deaths is mostly considered to be a virus closely related to influenza A H1N1. Novel swine-origin influenza A (H1N1) virus identified in the United States in 2009 also caused a global pandemic.[3] In 2013, the novel avian-origin influenza A (H7N9) virus isolated in China had caused a sporadic epidemic, which was characterized by rapid progression and with a high fatality rate.[4,5]

The confirmed diagnosis of COVID-19 and influenza A pneumonia relies on reverse transcription-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab, which need special laboratory and trained medical staffs. Hematological and radiological examinations are two basic methods for contagious viral pneumonias in clinical practice, which have the advantages of availability and short turnout time. In addition to RT-PCR testing, hematological and radiological examinations can be used for presumptive diagnosis. Although COVID-19 and influenza A pneumonia are caused by two independent pathogens, there is still possibility that superimposed infection of influenza A and SARS-CoV-2 happens in the same patient.[6] Nevertheless, few studies have reported the different clinical features between COVID-19, influenza A H7N9, and H1N1 to date.

In this study, hematological and radiological characteristics of severe/critically ill patients with COVID-19 and influenza A (H7N9 and H1N1) pneumonias in Suzhou were analyzed. In this article, we aimed to find useful index for the management of COVID-19, influenza A H7N9, and H1N1 patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

This retrospective study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Soochow University. Thirty-nine patients with severe/critically ill COVID-19, influenza A H7N9, and H1N1 pneumonia diagnosed by RT-PCR in pharyngeal specimens in Suzhou center for disease control and prevention were included. The severe/critically ill COVID-19 patients were enrolled from January 10 to March 1, 2020. The severe/critically ill influenza A H7N9 and H1N1 patients were enrolled from April 03 to April 30 in 2013 and from November 27 to December 31 in 2009 respectively.

The epidemiological and clinical data, hematological and computed tomography (CT) results of included patients were collected through medical record system and recorded in a standard case questionnaire.

According to the Chinese guidelines for diagnosis and treatment of novel coronavirus infected pneumonia, patients who met one of the following criterions were regarded as severe/critically ill cases: 1) respiratory rate ≥30 bpm; 2) oxygen saturation ≤93%; 3) arterial partial pressure of oxygen ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) <300 mmHg; 4) respiratory failure requires mechanical ventilation, shock, or other organ failures, which requires ICU treatment, and severe/critically ill H7N9 and H1N1 pneumonia patients all met this criterion. Children were excluded. Two neutropenic patients with hematological malignancies after chemotherapy in H1N1 group were excluded.

### 2.2 | Laboratory examination and hospital treatment

The laboratory examination including complete blood count (CBC) and coagulation panel was included for COVID-19, influenza A H7N9, and H1N1 patients. In the ICU, patients were managed with intensive care, which include antivirus, antibiotics, corticosteroids, fluid resuscitation, oxygen support, and other affected vital organs support treatment after multidisciplinary discussions. Appropriate oxygen support methods, including nasal cannula (NC), high flow nasal cannula (HFNC), non-invasive ventilation (NIV), endotracheal intubation invasive mechanical ventilation (MV), and extracorporeal membrane oxygenation (ECMO), were applied according to the clinical condition.

### 2.3 | CT imaging

Patients' CT images were searched in the picture archiving and communication system (PACS). The first chest CT images after symptom onset were collected for analysis in different patients. Time (days) from the onset to CT scan was recorded at the same time. Manifestation of CT images in patients included ground-glass opacity (GGO), consolidation, distribution characteristics, and pleural effusion.

### 2.4 | Statistical analysis

The statistical software SPSS 20.0 (IBM, Armonk, NY, USA) was used for data analysis. Continuous data with normal distribution were presented as mean ± standard deviation, and non-normal distribution was expressed as median (interquartile range). Continuous variables were compared using one-way ANOVA, *t*-test, or Kruskal–Wallis test

(if the test for homogeneity of variance was significant). Categorical variables were presented as a percentage and assessed using $\chi^2$ test and Fisher's exact test. Two-sided $p < 0.05$ indicated statistical significance.

## 3 | RESULTS

### 3.1 | Demographics

A total of 16 cases of COVID-19, 10 cases of influenza A H7N9, and 13 cases of influenza A H1N1 were included. All of the patients met the aforementioned clinical classification criteria. The basic information was listed in Table 1. There was a difference in gender between H7N9 and H1N1 groups ($p = 0.029$). The proportion of patients combined with underlying chronic diseases in H7N9 and H1N1 groups was higher than that in COVID-19 group (80% vs. 25%, $p = 0.014$ and 92.3% vs. 25%, $p = 0.000$).

The common symptoms in the three groups included fever, cough, expectoration, and chest tightness. Cough was less common in the COVID-19 group than the H1N1 group (62.5% vs. 100%, $p = 0.020$). Compared with the COVID-19 group, chest tightness was more common in the H7N9 and H1N1 groups (12.5% vs. 60%, $p = 0.026$, and 12.5% vs. 84.6%, $p = 0.000$). All patients received antivirus, antibiotics, and corticosteroid therapy routinely.

**TABLE 1** Demographic and clinical characteristic of COVID-19, H7N9, and H1N1 patients

| | COVID−19 $N = 16$ | H7N9 $N = 10$ | H1N1 $N = 13$ | $p$ |
|---|---|---|---|---|
| **Age** (years) | 51.8 ± 12.8 | 62.7 ± 17.8 | 50.8 ± 18.8 | 0.177 |
| **Sex** | | | | **0.042*** |
| Male | 10 (62.5%) | 9 (90%) | 5 (38.5%) | |
| Female | 6 (37.5%) | 1 (10%) | 8 (61.5%) | |
| **Chronic diseases** | 4 (25%) | 8 (80%) | 12 (92.3%) | **0.000*** |
| Hypertension | 2 (12.5%) | 5 (50%) | 5 (38.5%) | 0.110 |
| Diabetes | 1 (6.3%) | 4 (40%) | 3 (23.1%) | 0.109 |
| Respiratory disease | 1 (6.3%) | 2 (20%) | 4 (30.8%) | 0.214 |
| Malignant tumor | 0 (0%) | 1 (10%) | 2 (15.4%) | 0.334 |
| Others | 2 (12.5%) | 3 (30%) | 4 (30.8%) | 0.441 |
| **Symptoms** | | | | |
| Fever | 15 (93.8%) | 10 (100%) | 13 (100%) | 1.000 |
| Cough | 10 (62.5%) | 8 (80%) | 13 (100%) | **0.035*** |
| Expectoration | 7 (43.8%) | 6 (60%) | 10 (76.9%) | 0.232 |
| Chest tightness | 2 (12.5%) | 6 (60%) | 11 (84.6%) | **0.000*** |
| **Days from onset to diagnosis**(days) | 6.1 ± 3.2 | 8.3 ± 4.6 | 8.6 ± 4.4 | 0.208 |
| **APACHE II** | 5.50 ± 2.58 | 16.00 ± 8.63 | 15.08 ± 6.24 | **0.000*** |
| **Death** | 0 (0%) | 4 (40%) | 6 (46.2%) | **0.003*** |
| **Treatment** | | | | |
| Antivirus | 16 (100%) | 10 (100%) | 13 (100%) | |
| Antibiotics | 16 (100%) | 10 (100%) | 13 (100%) | |
| Corticosteroids | 16 (100%) | 10 (100%) | 13 (100%) | |
| Nasal cannula | 9 (56.3%) | 2 (20%) | 4 (30.8%) | 0.163 |
| High flow nasal cannula | 3 (18.8%) | 0 (0%) | 0 (0%) | 0.106 |
| Noninvasive ventilation | 4 (25%) | 1 (10%) | 1 (7.7%) | 0.531 |
| Mechanical ventilation | 0 (0%) | 7 (70%) | 8 (61.5%) | **0.000*** |
| ECMO | 0 (0%) | 2 (20%) | 0 (0%) | 0.061 |
| Vasoactive drugs | 1 (6.3%) | 5 (50%) | 6 (46.2%) | **0.016*** |
| CRRT | 0 (0%) | 4 (40%) | 5 (38.5%) | **0.008*** |

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

* $p < 0.05$.

Bold indicates significant $p$ values.

Besides, the H7N9 and H1N1 groups had higher *Acute Physiology and Chronic Health Evaluation* (APACHE)-II scores than the COVID-19 group (16.00 ± 8.63 vs. 5.50 ± 2.58, $p = 0.001$; 15.08 ± 6.24 vs. 5.50 ± 2.58, $p = 0.000$). The proportion of mechanical ventilation in H7N9 and H1N1 groups was significantly higher compared with the COVID-19 group (70% vs. 0%, $p = 0.000$; 61.5% vs. 0%, $p = 0.000$). The application of vasoactive drugs (50% vs. 6.3%, $p = 0.018$, and 46.2% vs. 6.3%, $p = 0.026$) and *continuous renal replacement therapy* (CRRT) (40% vs. 0%, $p = 0.014$, and 38.5% vs. 0%, $p = 0.011$) was more common in H7N9 and H1N1 groups than the COVID-19 group. Among 16 COVID-19 patients, no one died during the time of observation, while four patients in the H7N9 group ($n = 10$) and six patients in the H1N1 group ($n = 13$) died during the same period. Above all, there was a difference in mortality between the three groups; the mortality rate in the COVID-19 group was significantly lower than the H7N9 group ($p = 0.014$) and the H1N1 group ($p = 0.004$).

### 3.2 | Hematological examination

The results of complete blood count and coagulation panel on admission of all patients were summarized in Table 2. Although lymphopenia was detectable in all three groups, it was more pronounced in the H7N9 ($p = 0.008$) and H1N1 ($p = 0.002$) groups. The neutrophil-to-lymphocyte ratio (NLR) was higher in the H7N9 group (Fold change = 1.33, $p = 0.006$) and the H1N1 group (Fold change = 1.33, $p = 0.003$). However, monocyte count in the COVID-19 group was significantly higher than the other two groups (Fold change = 1.21 and 1.79, $p = 0.000$). In the coagulation panel, fibrinogen level was slightly elevated in the COVID-19 group (Fold change = 0.77, $p = 0.001$), which was not detectable in the H7N9 and H1N1 groups.

In the H7N9 and H1N1 groups, patients were evaluated and regrouped according to their survivals. After a further statistical analysis of their hematological examination, it was found that NLR was significantly higher in the group with patient death, compared to the group without patient death (Fold change = 0.66, $p = 0.033$; Table 3). The ROC and AUC of lymphocytes, neutrophils, and NLR between the two groups were calculated (Figure 1). The AUC of NLR is 0.7615, and the AUC of lymphocytes and neutrophils is 0.6731 and 0.6154, respectively.

### 3.3 | CT image findings

Sixteen cases of COVID-19, 8 cases of H7N9, and 7 cases of H1N1 patients had received chest CT examinations. The CT manifestations of typical patients were shown in Figure 2. In most patients with severe/critically ill viral pneumonia, the lesions dispersed in bilateral lungs ($n = 30$). Compared with H7N9 group, GGO was more common in the COVID-19 group ($p = 0.028$), while pleural effusion was relatively rare in the COVID-19 group ($p = 0.001$). From the onset of symptoms to the first CT examination, the days in the COVID-19 group were significantly shorter than the other two groups (Median: 5.13 ± 3.22 days vs. 14.13 ± 10.01 days and 16.00 ± 9.15 days, $p < 0.05$).

## 4 | DISCUSSION

The SARS-CoV-2, influenza A H7N9, and H1N1 viruses all belong to the RNA viruses, which spread through the respiratory tract or contact, and damage multiple organs including the lungs. The RT-PCR is widely used for the diagnosis of patients with SARS-CoV-2 infection. However, the quantification of viral genomes cannot be used to evaluate the severity of pneumonia when planning management for patients. Nevertheless, the routine examination of patients with pneumonia through the hematological and radiological methods helps clinicians to assess risk and predict prognosis of patients, which show special advantage when treating the patients with uncleared etiology. In this article, the clinical parameters of hematological and radiological examinations were comprehensively compared in-between COVID-19 and H7N9/H1N1 pneumonia, which indicate the different clinical characteristics of the three pneumonias.

In this research, we found the higher proportion of male patients in the H7N9 group, which was similar to the data from some previous clinical studies and which can be explained by more involvement of males in poultry breeding and slaughtering.[5,7–9] By comparison, cough and chest tightness were more common in the influenza groups compared with the COVID-19 group. However, these symptoms belong to the common symptoms of pneumonia, which are unspecific parameters useless for the distinguishing of different viral pneumonia. Therefore, careful inquiries of epidemiological history and clinical manifestations may be helpful. Interestingly, our research showed that those symptoms of COVID-19 patients were milder and had better prognosis compared with the influenza groups. The patients with COVID-19 had less underlying chronic disease and lower APACHE II score (within 24 h) compared with the influenza groups. For this reason, the patients in the COVID-19 group received less life support treatment and consequently had lower mortality compared with the influenza group. Similar to our findings, a case-control study found that the preexisting comorbidities (hypertension excluded) were significantly associated with human infection with H7N9.[10] Moreover, a Spanish study in H1N1 showed that independent factors, including hospital-acquired infection, APACHE II score, underlying hematological diseases, continuous veno-venous hemofiltration, and mechanical ventilation, were associated with higher mortality.[11] Two severe/critically ill H1N1 patients (15.4%) in 2009 were hospital-acquired infections, while the proportion in the Spanish study was 9.3%, which may contribute to the high mortality rate in this study. The COVID-19 group had milder symptoms and better survivals, which can be explained by the early diagnosis of COVID-19 due to the rapid response of medical system facing the urgent event.[12] Another explanation for this is the development of molecular medicine and emergency medicine from the prevalence year of H1N1 pneumonia (2009) to the outbreak of COVID-19

**TABLE 2** Laboratory examination and chest CT findings of COVID-19, H7N9, and H1N1 patients

| | COVID–19 | H7N9 | H1N1 | *p* |
|---|---|---|---|---|
| **CBC** | *N* = 16 | *N* = 10 | *N* = 13 | |
| Leukocyte (×$10^9$/L) | 7.14 ± 3.61 | 9.03 ± 5.36 | 7.05 ± 2.82 | 0.414 |
| Neutrophil (×$10^9$/L) | 5.63 ± 3.50 | 8.17 ± 4.97 | 6.21 ± 2.81 | 0.243 |
| Lymphocyte (×$10^9$/L) | 0.97 ± 0.33 | 0.59 ± 0.31 | 0.56 ± 0.35 | **0.004*** |
| Monocyte (×$10^9$/L) | 0.53 ± 0.14 | 0.24 ± 0.23 | 0.19 ± 0.17 | **0.000*** |
| Hemoglobin (g/L) | 135.88 ± 16.46 | 133.70 ± 19.98 | 112.23 ± 30.90 | 0.128 |
| Platelets (×$10^9$/L) | 191.69 ± 59.30 | 157.40 ± 58.24 | 152.08 ± 82.62 | 0.249 |
| **NLR (%)** | 6.29 ± 3.72 | 14.67 ± 6.10 | 14.64 ± 10.36 | **0.004*** |
| **Coagulation panel** | | | | |
| PT (s) | 12.07 ± 0.81 | 12.51 ± 1.52 | 11.48 ± 6.69 | 0.499 |
| APTT (s) | 24.64 ± 3.32 | 35.21 ± 26.35 | 32.71 ± 21.09 | 0.335 |
| Fibrinogen (g/L) | 5.31 ± 1.58 | 2.78 ± 1.51 | 3.32 ± 1.85 | **0.001*** |
| **Chest CT finding** | *N* = 16 | *N* = 8 | *N* = 7 | |
| Days from onset to CT (days) | 5.13 ± 3.22 | 14.13 ± 10.01 | 16.00 ± 9.15 | **0.002*** |
| Distribution | | | | 0.484 |
| Unilateral lung | 0 (0%) | 1 (12.5%) | 0 (0%) | |
| Bilateral lungs | 16 (100%) | 7 (87.5%) | 7 (100%) | |
| GGO | 16 (100%) | 5 (62.5%) | 5 (71.4%) | **0.028*** |
| Consolidation | 10 (62.5%) | 6 (75%) | 5 (71.4%) | 0.884 |
| Pleural effusion | 1 (6.3%) | 6 (75%) | 3 (42.9%) | **0.001*** |

Abbreviations: CBC, complete blood count; NLR, neutrophil-lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CT, computed tomography; GGO, ground-glass opacity.

*$p < 0.05$.

Bold indicates significant *p* values.

**TABLE 3** Laboratory examination of patients in influenza survival group and death group

| | Influenza survival group *N* = 13 | Influenza death group *N* = 10 | *p* |
|---|---|---|---|
| **CBC** | | | |
| Leukocyte(×$10^9$/L) | 7.07 ± 2.72 | 8.99 ± 5.44 | 0.327 |
| Neutrophil (×$10^9$/L) | 6.17 ± 2.54 | 8.23 ± 5.14 | 0.267 |
| Lymphocyte (×$10^9$/L) | 0.65 ± 0.35 | 0.47 ± 0.27 | 0.182 |
| Monocyte (×$10^9$/L) | 0.21 ± 0.19 | 0.22 ± 0.21 | 0.922 |
| Hemoglobin (g/L) | 120.54 ± 32.92 | 122.90 ± 22.66 | 0.848 |
| Platelets (×$10^9$/L) | 165.08 ± 88.86 | 140.50 ± 40.06 | 0.427 |
| **NLR (%)** | 11.37 ± 5.81 | 18.93 ± 9.97 | **0.033*** |
| **Coagulation panel** | | | |
| PT (s) | 10.40 ± 4.88 | 13.92 ± 4.80 | 0.099 |
| APTT (s) | 32.81 ± 26.88 | 35.08 ± 18.03 | 0.820 |
| Fibrinogen (g/L) | 2.89 ± 1.89 | 3.34 ± 1.47 | 0.538 |

Abbreviations: CBC, complete blood count; NLR, neutrophil-lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time.

* $p < 0.05$.

Bold indicates significant *p* values.

(2020). COVID-19 patients received more advanced testing method of RT-PCR, as well as better intensive care for critically ill patients, which accounts for the much better prognosis of COVID-19 compared with H1N1 or H7N9 patients.

Previous observations showed that severe influenza A H1N1 infections had marked lymphopenia detected by hematological examination.[13,14] Another case report detected more lymphocyte infiltration in the lung tissue from an autopsy of H1N1 patients.[15]

Clinical studies also reported marked lymphopenia in patients with H7N9 infection, among which two death cases showed diffuse alveolar injury with lymphocyte and monocyte infiltration in percutaneous lung biopsies.[7–9] In the case of COVID-19, it was reported that hospitalized patients had some extent of lymphopenia, which was even more obvious in the patients with disease progression.[16,17] In our study, the lymphopenia was less obvious in the COVID-19 patients compared with the influenza groups, which is in consistent with the observations in other studies. A systematic review and meta-analysis suggested that peripheral blood leucocyte ratio was useful infection parameter for the distinguish between bacterial and viral infection.[18] NLR is a marker of inflammation and has been shown to be associated with COVID-19.[19] Not only COVID-19 but also other inflammatory conditions, such as type 2 diabetes mellitus,[20] thyroiditis,[21] and ulcerative colitis,[22] are associated with increased NLR levels. Given the similar hemogram of patients with viral infections, a higher NLR was detected in the two influenza groups, especially in the influenza groups with patient death. A multi-center retrospective study also reported the NLR was an independent risk factor for patient survivals in H7N9 pneumonia.[5] A retrospective observational study found that the NLR was an easily measurable, available, cost-effective, and reliable parameter, which continuous monitoring may be useful for the diagnosis and treatment of COVID-19.[23] Taken together, these results reveal that the NLR in hematological examination is an important clinical parameter for the prediction of patient prognosis in the pneumonia caused by viral infections, including the influenza and COVID-19.

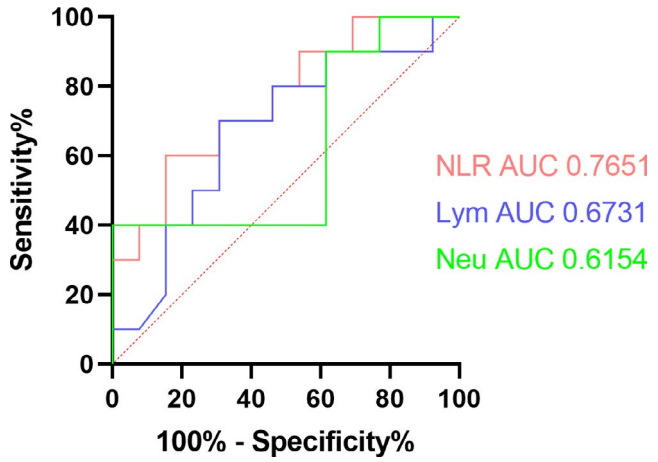


**FIGURE 1** Receiver operating curve of lymphocyte, neutrophil, and neutrophil-to-lymphocyte ratio (NLR) for death prediction of influenza A H7N9 and H1N1

A single-center retrospective study of 242 COVID-19 cases with 52 patient deaths, found that the median absolute monocyte count, was significantly reduced in the death group, while the NLR was significantly increased in the survival group.[24] In our research, there was no patient died in the COVID-19 group, with the median

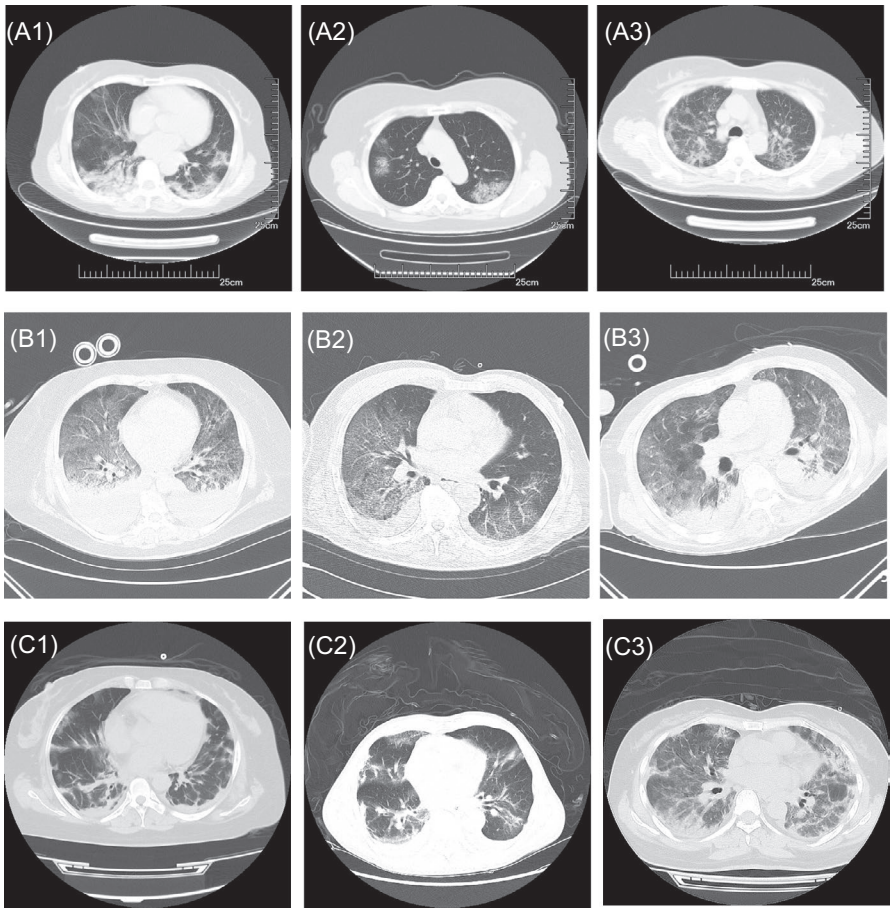


**FIGURE 2** Representative chest CT images of severe/critically ill patients with COVID-19, influenza A H7N9, and H1N1

monocyte count within the normal range. One study conducted multivariate logistic regression analysis demonstrated that age, lymphocyte percentage, and monocyte count were non-specific laboratory markers predictive for COVID-19.[25] As a result, the relevance of monocytes in prediction of severity of COVID-19 demands further research.

Studies had reported that COVID-19 patients had increased D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time, and platelet counts were relatively rare.[26,27] Three- to four-fold increase in D-dimer levels was detected in the early stages of COVID-19 patients, which was associated with poor prognosis of COVID-19 patients.[27] Measuring the level of D-dimer and coagulation parameters from the early stage can also be useful in controlling and managing of COVID-19 disease.[27] Our data also showed that fibrinogen was elevated in the COVID-19 group, which suggest an activation of coagulation in the patients. Due to the lack of D-dimer data in the influenza groups, it was impossible to further compare the levels of D-dimer between the COVID-19 and the influenza groups.

A retrospective study of 1014 patients, which compared the accuracy between chest CT and RT-PCR in the diagnosis of potential COVID-19 patients, reported 59% positivity in RT-PCR and 88% positivity in chest CT, in which the chest CT had 97% accuracy in reference to the results of RT-PCR, which demonstrated the value of chest CT in diagnosis and monitoring the injury of COVID-19.[28] Studies comparing the different manifestations of CT imaging between different viral pneumonia showed that the COVID-19 had areas of rounded opacity and septal thickening in peripheral regions of lungs, while the influenza A showed diffused distribution of lesions, including multiple nodules and "tree-in-bud" sign.[29] Another study compared the CT feature of H7N9 and H1N1 patients with *acute respiratory distress syndrome* (ARDS), which showed common manifestations, such as consolidation, GGO, air bronchogram, interlobular septal thickening, and nodular shadow, while pleural effusion was more specific in H7N9 pneumonia.[30] Compared with those studies, our study showed more GGO in the COVID-19 group, while pleural effusion was rare in COVID-19 group, but more common in the H7N9 group. The days from the onset to the first CT examination were shorter in the COVID-19 group, due to the active response strategy and screening of patients with fever or respiratory symptoms in COVID-19, which led to the early diagnosis of COVID-19 with milder injury in the lungs.

The limitations of this study were the small number of included cases, the long-time span, the lack of comparison of the characteristics in mild cases, and the lack of inflammatory factors and infection markers.

In summary, patients with H7N9 and H1N1 had a more critical and complex condition. They had received more life support treatment in the ICU and had a higher mortality rate. In the COVID-19 group, hematological examination showed slight decrease in lymphocytes, increase in monocytes, and slight increase in fibrinogen compared with the influenza groups. The NLR in the influenza groups was significantly increased, especially in the subgroup with patient death. These results suggest that NLR can be used as an important indicator to distinguish the severity of viral pneumonia and predict the prognosis of influenza pneumonia. The comparison of chest CT showed that pleural effusion and GGO may be helpful for distinguishing of the COVID-19 and the influenza pneumonia.

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## CONFLICT OF INTERESTS

The authors declare no conflict of interests.

## AUTHOR CONTRIBUTION

J. Kong, J. Fu, Y Hao, and S. Wan designed the work and performed patient data collection, analyzed the data, and wrote the article. D. Zou, Z Li, L Zhang, Y Lu, and J Wang performed patient data collection in this retrospective clinical study. X. Chen revised the article. All authors approved the submission.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

1. Zhu NA, Zhang D, Wang W, et al. A novel Coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.
2. Aktas G. A comprehensive review on rational and effective treatment strategies against an invisible enemy; SARS Cov-2 infection. *Exp Biomed Res*. 2020;3:293-311.
3. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med*. 2009;360(25):2605-2615.
4. Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med*. 2013;368(20):1888-1897.
5. Zhang Y, Zou P, Gao H, et al. Neutrophil-lymphocyte ratio as an early new marker in AIV-H7N9-infected patients: a retrospective study. *Ther Clin Risk Manag*. 2019;15:911-919.
6. Wu X, Cai Y, Huang XU, et al. Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China. *Emerg Infect Dis*. 2020;26(6):1324-1326.
7. Gao H-N, Lu H-Z, Cao B, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. *N Engl J Med*. 2013;368(24):2277-2285.
8. Wan DM, Kang XH, Bai W, Zeng ZG, Zhang W. The clinical characteristics and prognosis of 20 patients with H7N9 avian influenza. *Chin J Tuberc Respir Dis*. 2019;42(10):750-754.
9. Yu WQ, Ding MD, Dai GH, et al. Analysis of 15 cases of avian influenza virus (H7N9) infection. *Chin J Tuberc Respir Dis*. 2018;41(7):534-538.
10. Ai J, Huang Y, Xu K, et al. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. *Eurosurveillance*. 2013;18(26):20510.

11. Álvarez-Lerma F, Marín-Corral J, Vilà C, et al. Characteristics of patients with hospital-acquired influenza A (H1N1) pdm09 virus admitted to the intensive care unit. *J Hosp Infect*. 2017;95(2):200-206.
12. Pan AN, Liu LI, Wang C, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA*. 2020;323(19):1915-1923.
13. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med*. 2009;361(7):680-689.
14. Cui W, Zhao H, Lu X, et al. Factors associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China. *BMC Infect Dis*. 2010;10:145.
15. Denney L, Aitken C, Li CK-F, et al. Reduction of natural killer but not effector CD8 T lymphocytes in three consecutive cases of severe/lethal H1N1/09 influenza A virus infection. *PLoS One*. 2010;5(5):e10675.
16. Guan W-J, Ni Z-Y, Hu YU, et al. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
17. Zheng Y, Zhang Y, Chi H, et al. The hemocyte counts as a potential biomarker for predicting disease progression in COVID-19: a retrospective study. *Clin Chem Lab Med*. 2020;58(7):1106-1115.
18. Russell CD, Parajuli A, Gale HJ, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. *J Infect*. 2019;78(5):339-348.
19. Aktas G. Hematological predictors of novel Coronavirus infection. *Rev Assoc Méd Bras*. 2021;67(Suppl 1):1-2.
20. Bilgin S, Aktas G, Zahid Kocak M, et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. *Aging Male*. 2020;923-927.
21. Aktas G, Sit M, Dikbas O, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. *Rev Assoc Med Bras*. 2017;1065-1068.
22. Posul E, Yilmaz B, Aktas G, Kurt M. Does neutrophil-to-lymphocyte ratio predict active ulcerative colitis? *Wien Klin Wochenschr*. 2015;127(7-8):262-265.
23. Jimeno S, Ventura PS, Castellano JM, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. *Eur J Clin Invest*. 2020;51(1):e13404.
24. Pakos IS, Lo KB, Salacup G, et al. Characteristics of peripheral blood differential counts in hospitalized patients with COVID-19. *Eur J Hematol*. 2020;105(6):773-778.
25. Wang L, Liu Y, Zhang T, et al. Differentiating between 2019 Novel Coronavirus pneumonia and influenza using a nonspecific laboratory marker-based dynamic nomogram. *Open Forum Infect Dis*. 2020;7(5):ofaa169.
26. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033-2040.
27. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. *Expert Rev Hematol*. 2020;13(11):1265-1275.
28. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in Coronavirus Disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology*. 2020;296(2):E32-E40.
29. Liu M, Zeng W, Wen Y, Zheng Y, Lv F, Xiao K. COVID-19 pneumonia: CT findings of 122 patients and differentiation from influenza pneumonia. *Eur Radiol*. 2020;30(10):5463-5469.
30. Li H, Weng H, Lan C, et al. Comparison of patients with avian influenza A (H7N9) and influenza A (H1N1) complicated by acute respiratory distress syndrome. *Medicine*. 2018;97(12):e0194.


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