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Comparison and Analysis of Clinical Characteristics of Common COVID-19 and NSIP Patients

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Abstract: *Objective:* To investigate the relationship between coronavirus disease 2019 (COVID-19) and non-specific interstitial pneumonia (NSIP), with a focus on the clinical features of COVID-19 and NSIP, and the key points of differential diagnosis. *Methods:* The clinical data of 20 patients with common-type COVID-19 and NSIP admitted to Linyi People's Hospital from January 21, 2020, to June 21, 2022, were retrospectively analyzed. Gender, age, history of residence in Hubei province, underlying diseases, clinical manifestations, laboratory test results (including blood routine indexes, inflammatory markers, liver function indexes, and coagulation indexes), and computed tomography (CT) scan images were compared between the two groups. *Results:* COVID-19 patients were younger than NSIP patients ($P < 0.05$). Nine COVID-19 patients had a travel history to Hubei province, while none of the NSIP patients did ($P < 0.05$). Eight COVID-19 patients had underlying chronic conditions, fewer than the NSIP group (12 patients; $P < 0.05$). Both groups experienced symptoms such as shortness of breath, expectoration, fatigue, and runny nose, but fever and cough were more severe and more frequent in the COVID-19 group. Compared to normal reference ranges, both groups exhibited normal white blood cell counts (WBC) and liver function indexes, but elevated lymphocyte counts (LYMP), inflammatory markers, and coagulation indexes, with reduced neutrophil counts (NE). WBC and LYMP were higher in the COVID-19 group compared to the NSIP group. Male patients in the COVID-19 group had higher erythrocyte sedimentation rates and C-reactive protein values than those in the NSIP group, while procalcitonin levels were lower in the COVID-19 group, although the differences were not statistically significant (all $P > 0.05$). The NE count in the COVID-19 group was significantly lower than in the NSIP group ($P < 0.05$). Alanine aminotransferase, total bilirubin, and indirect bilirubin were significantly higher in the COVID-19 group compared to the NSIP group ($P < 0.05$). Chest CT scans of both groups showed bilateral patchy ground-glass opacities, but the lesions in COVID-19 patients were scattered. NSIP patients' chest CTs showed diffuse lesions centered around the hilum or multiple lesions in both lungs, with pleural involvement being rare. *Conclusion:* While there are certain specific clinical, laboratory, and imaging findings in both COVID-19 and NSIP, the specificity of these features is not high. Differentiating the two requires careful consideration of epidemiological history, nucleic acid testing, and antigen-antibody levels.

Keywords: Coronavirus disease 2019; Nonspecific interstitial pneumonia; Clinical features

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1. Introduction

The novel Coronavirus pneumonia (COVID-19) is caused by a new type of Coronavirus (2019-nCoV) that leads to respiratory tract infections. The common symptoms of COVID-19 range from mild to moderate pneumonia-like symptoms such as fever and cough, with some infected individuals remaining asymptomatic and generally having a good prognosis. However, approximately 5% of patients have been reported to develop severe complications [1,2], including respiratory distress syndrome, acute cardiovascular events, and kidney injury. Consequently, the National Health Commission of the People's Republic of China has revised the diagnosis and treatment guidelines for COVID-19 nine times, highlighting the challenges in diagnosis and treatment [3].

At this stage, diagnosing COVID-19 requires a comprehensive consideration of the patient's epidemiological history, symptoms, chest CT scans, and viral nucleic acid test results. However, investigating epidemiological history is complex and prone to oversight. Many reports also indicate that a significant number of asymptomatic COVID-19 patients have had multiple false-negative viral nucleic acid test results [4]. Additionally, it is noteworthy that COVID-19 patients experiencing progressive dyspnea, with mild fever or none at all, and CT findings of diffuse interstitial changes in both lungs, present clinical and imaging characteristics similar to those of patients with nonspecific interstitial pneumonia (NSIP) [5].

Interstitial pneumonia (IP), characterized by diffuse inflammation of the lung parenchyma, alveoli, and pulmonary interstitium, encompasses a wide range of etiologies and prognoses depending on its type. IP is generally classified into usual interstitial pneumonia (UIP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonitis (DIP), acute interstitial pneumonia (AIP), and nonspecific interstitial pneumonia (NSIP). At present, IP has become a significant factor complicating the differential diagnosis of COVID-19, especially as COVID-19 symptoms become more atypical and constantly evolve [6,7]. Among these, NSIP shares the most similarities with COVID-19 in terms of clinical symptoms and imaging findings. Therefore, this study aims to explore the clinical characteristics and risk factors associated with both COVID-19 and NSIP.

2. Materials and methods

2.1. General information

The study was conducted on 20 patients diagnosed with COVID-19 (common type) and nonspecific interstitial pneumonia (NSIP) who were admitted to our unit between January 21, 2020, and June 21, 2022. The study subjects met the diagnostic criteria outlined in the "Prevention and Control Program for COVID-19 (8th edition)" and the diagnostic criteria for NSIP. Clinical data were collected and analyzed, including blood cell counts (white blood cells, neutrophils, lymphocytes), C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), liver function tests (including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), conjugated bilirubin (DBIL), and unconjugated bilirubin (IBIL)), fibrinogen (FIB), and D-dimer (D-D) levels. This study was approved by the Ethics Committee of Linyi People's Hospital [Medical Ethics Review No. (YX200417)].

2.2. COVID-19 group inclusion and exclusion criteria

The diagnosis of COVID-19 was based on the "Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial version 6)" [8]. Confirmed cases met one of the following criteria: (1) Positive detection of 2019-nCoV nucleic

acid by real-time fluorescent reverse transcription PCR; (2) Viral gene sequencing showed high homology with known strains of common-type 2019-nCoV.

Exclusion criteria: (1) Repeated negative results for 2019-nCoV nucleic acid by real-time fluorescent reverse transcription PCR; (2) Outpatient death cases; (3) Cases with incomplete data.

2.3. NSIP group inclusion and exclusion criteria

The diagnosis of NSIP was based on the "Chinese Expert Consensus on the Pathological Diagnosis of Nonspecific Interstitial Pneumonia (Draft)" [9]. Confirmed cases exhibited dense fibrous tissue hyperplasia in the lung interstitium, destruction of lung tissue structure with honeycomb lung formation, and patchy lesions, primarily distributed around the lower lobe of the lung and beneath the pleura. Imaging or pathological changes included fibroblastic foci.

Exclusion criteria included five negative findings that were required: no significant inflammatory cell infiltration, no eosinophilic cell infiltration, no granulomas, no asbestos bodies, and no hyaline membranes.

2.4. Methods

2.4.1. Clinical symptoms and epidemiological investigation

Patient data on infection routes, demographic characteristics, SARS-CoV-2 contact history, clinical symptoms at initial admission, and results of nasopharyngeal swab screening were collected by trained personnel.

2.4.2. CT examination method

All patients were protected from radiation exposure, and lead protective clothing was used to shield non-scanned body parts. A Toshiba Aquilion 64-slice spiral CT machine was used for high-resolution CT scanning. Patients were placed in a supine position, and the scan covered the lungs from apex to base. The slice thickness was 0.5 mm, with a slice spacing of 1.0 mm, and the reconstruction slice thickness was 5.0 mm. Relevant scan parameters included a tube voltage of 120 kV, a tube current of 250 mA, a pitch of 1.375:1, a FOV of 300–400 mm, a high-resolution reconstruction algorithm, and lung window settings for observation (window width: 1000 Hu, window level: 700 Hu).

2.4.3. Auxiliary detection equipment

(1) CRP-M100 specific immune protein analyzer (Shenzhen Mindray Biomedical Electronics Co., Ltd.)
(2) Sysmex XN-9000 automatic blood cell analyzer [Sysmex Medical Electronics (Shanghai) Co., Ltd.]
(3) SC-120 automatic blood smear preparation instrument (Shenzhen Mindray Biomedical Electronics Co., Ltd.)
(4) Pylon3D cycle-enhanced fluorescence analyzer [Star Child Medical Technology (Suzhou) Co., Ltd.]
(5) Monitor-100 automatic ESR analyzer (Vital, Italy)
(6) Cobas 8000 e702 automatic biochemical analyzer [Roche Diagnostic Products (Shanghai) Co., Ltd.]

2.5. Statistical analysis

SPSS 26.0 software was used for statistical analysis. Measurement data with normal distribution were represented as mean ± standard deviation (SD), and comparisons between groups were analyzed using the t-test. Measurement data with a skewed distribution were represented as the median (P25, P75), and comparisons were analyzed using

the Mann-Whitney U test. Count data were expressed as the number of cases (percentage), and comparisons between groups were analyzed using the chi-square test. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of general conditions and clinical manifestations

Among the 20 patients in the COVID-19 group, 13 were male (65%) and 7 were female (35%). In the NSIP group, there were 10 males and 10 females, representing 50% of the patients. There was no significant difference in the male-to-female ratio between the two groups ($\chi^2 = 0.921$, $P = 0.337$). In terms of age, the median age of patients in the COVID-19 group was 48.50 (36.50, 56.00) years, which was younger than that of the NSIP group, where the median age was 63.00 (53.00, 74.75) years. This difference was statistically significant ($Z = 3.344$, $P < 0.01$). Nine patients (45%) in the COVID-19 group had a history of traveling to Hubei province, while none of the NSIP patients had such a history, a statistically significant difference ($\chi^2 = 9.176$, $P < 0.01$). Furthermore, 8 patients (40%) in the COVID-19 group had chronic underlying conditions, compared to 12 patients (60%) in the NSIP group. Both groups exhibited symptoms such as shortness of breath, expectoration, fatigue, and runny nose, but there were no significant differences in the number of patients with these symptoms (all $P > 0.05$). However, the number of patients with fever and cough was significantly higher in the COVID-19 group than in the NSIP group ($P < 0.05$). Detailed data are presented in **Table 1**.

Table 1. Comparison of general conditions and clinical manifestations [*n* (%)]

Groups	COVID-19 group (*n* = 20)	NSIP group (*n* = 20)	χ^2 value	*P* value
Gender				
Male	13 (65)	10 (50)	0.921	0.337
Female	7 (35)	10 (50)		
Age	48.50 (36.50, 56.00)	63.00 (53.00, 74.75)	3.344	0.001
History of traveling to Hubei province	9 (45)	0 (0)	9.176	0.001
Chronic underlying conditions	8 (40)	12 (60)	1.6	0.206
Clinical manifestations				
Fever	15 (75).	6 (30)	8.12	0.004
Cough	19 (95).	14 (70).	4.329	0.037
Shortness of breath	10 (50)	11 (55)	0.1	0.752
Expectoration	7 (35)	8 (40)	0.107	0.744
Fatigue	4 (20)	1 (5)	0.914	0.151
Runny nose	3 (15)	0 (0)	1.441	0.072

3.2. Comparison of laboratory test data

The laboratory test results of the COVID-19 and NSIP groups were compared. In the blood test results, the white blood cell (WBC) and lymphocyte (LYMP) counts were higher in the COVID-19 group than in the NSIP group, although the differences were not statistically significant (all $P > 0.05$). The neutrophil count (NE) was significantly lower in the COVID-19 group compared to the NSIP group ($P < 0.05$). In the analysis

of inflammatory markers, the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were higher in both male and female patients in the COVID-19 group compared to the NSIP group, while procalcitonin (PCT) levels were lower in the COVID-19 group; however, these differences were not statistically significant (all $P > 0.05$).

Regarding liver function, both groups showed some degree of liver function impairment upon admission. The alanine aminotransferase (ALT), total bilirubin (TBIL), and indirect bilirubin (IBIL) levels were significantly higher in the COVID-19 group than in the NSIP group ($P < 0.05$). There were no significant differences in other liver function markers, such as aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ-GT), and direct bilirubin (DBIL) (all $P > 0.05$).

In the comparison of coagulation markers, the fibrinogen (FIB) value in the COVID-19 group was within the normal range, while the D-dimer (D-D) level was elevated. Both FIB and D-D levels were higher in the NSIP group compared to the COVID-19 group, but the differences were not statistically significant (all $P > 0.05$). Detailed results are provided in **Table 2**.

Table 2. Comparison of laboratory test data

Laboratory tests		COVID-19 group	NSIP group	Z / *t* value	*P* value
Routine blood tests					
WBC (3.50–9.50×10^9/L)		9.13 (5.66, 12.21)	7.71 (5.28, 11.35)	0.649	0.516
LYMP (1.10–3.20×10^9/L)		7.57 (3.47, 11.09)	5.05 (3.58, 9.06)	0.825	0.409
NE (1.80–6.30×10^9/L)		0.99 (0.73, 1.57)	1.71 (1.07, 2.27)	2.300	0.021
Inflammatory factor indicators					
CRP (0.00–8.00 mg/L)		30.69 ± 26.18	27.92 ± 33.91	0.289	0.774
PCT (0.00–0.05 ng/mL)		0.20 ± 0.54	0.33 ± 1.10	0.460	0.649
ESR	Male (0–15 mm/h)	50.50 (24.25, 67.75)	24.50 (3.25, 57.25)	1.389	0.165
	Female (0–20 mm/h)	47.00 (25.00, 59.00)	38.00 (21.00, 62.00)	0.159	0.874
Liver function indicators					
ALT (9–50 U/L)		44.53 ± 34.58	24.10 ± 22.54	2.213	0.034
AST (15–40 U/L)		28.78 ± 16.63	27.57 ± 18.61	0.217	0.830
Gamma GT (10–60 U/L)		35.05 ± 25.29	37.05 ± 31.44	0.222	0.826
TBIL (2–24 μmol/L)		20.40 (16.48, 29.58)	8.40 (6.93, 11.10)	5.032	0.0001
DBIL (0–5 μmol/L)		4.25 (3.10, 5.18)	3.25 (2.03, 4.75)	1.800	0.072
IBIL (1.70–20.60 μmol/L)		16.50 (13.63, 22.68)	5.20 (3.88, 6.60)	5.143	0.0001
Blood coagulation indicators					
FIB (2.00–4.00 g/L)		3.59 (2.63, 4.66)	4.39 (3.22, 5.56)	1.600	0.11
D-D (0.0–0.5 μg/mL)		0.63 ± 0.49	1.40 ± 1.62	1.527	0.155

Abbreviation: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; DBIL, Direct bilirubin; D-D, D-dimer; ESR, Erythrocyte sedimentation rate; FIB, Fibrinogen; Gamma GT, Gamma-glutamyl transpeptidase; IBIL, Indirect bilirubin; LYMP, Lymphocyte; NE, Neutrophil; PCT, Procalcitonin; TBIL, Total bilirubin; WBC, White blood cell.

3.3. Comparison of CT features

The Chinese Medical Association has provided detailed descriptions of the CT diagnostic criteria for COVID-19 and NSIP. Based on these guidelines, this paper selects four cases to illustrate lung lesion changes at different stages and compares their CT imaging characteristics with relevant literature reports [10,11]. The findings are summarized as follows:

(1) Differences in lesion characteristics between COVID-19 and NSIP: In COVID-19 patients, chest CT showed scattered patchy ground-glass opacities (GGO) in both lungs (**Figures 1A, 1B**), along with areas of consolidation (**Figure 1B**) and linear opacities (**Figures 1A, 1B**). Other literature reports mention rare CT findings such as "halo signs" and "mosaic perfusion patterns" in a small number of patients. In NSIP patients, chest CT revealed increased lesion density and size, with GGOs (**Figure 1C**) and consolidation (**Figures 1C, 1D**) predominantly located under the pleura, accompanied by nodules and reticular opacities (**Figure 1C**).

(2) Differences in the number and distribution of lesions between COVID-19 and NSIP: COVID-19 patients typically presented with a single localized lesion at the onset of the disease, which rapidly progressed to multiple lesions in both lungs (**Figure 1A**) or diffuse lesions (**Figure 1B**). The distribution was not segmental, differing from the CT findings typically seen in community-acquired or bacterial pneumonia. In contrast, NSIP patients had diffuse lesions in both lungs (**Figures 1C, 1D**), some of which were symmetrically distributed along the subpleural regions or bronchovascular bundles (**Figure 1D**).

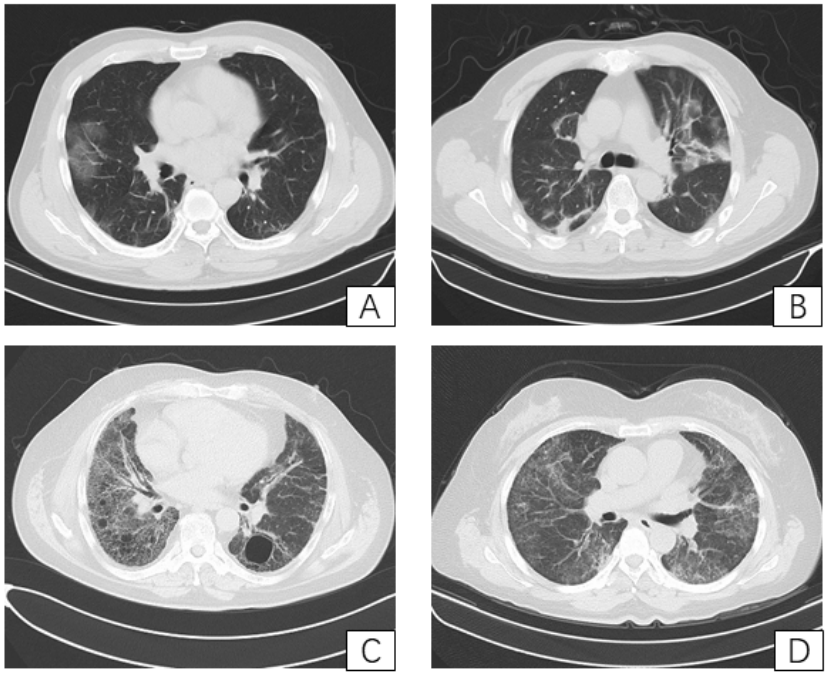

Figure 1. Chest CT findings of patients with COVID-19 and interstitial pneumonia. **(A)** A 33-year-old female diagnosed with COVID-19 on the 5th day after symptom onset; **(B)** A 41-year-old male diagnosed with COVID-19 on the 10th day after symptom onset; **(C)** A 65-year-old male diagnosed with NSIP based on chest CT findings at 2 and 5 weeks after symptom onset; **(D)** A 48-year-old female diagnosed with NSIP of unknown etiology after experiencing shortness of breath for 3 weeks.

4. Discussion

COVID-19 continues to spread globally, with new variants constantly emerging from different countries. These new strains are becoming increasingly difficult to detect, and the epidemiological history is becoming more obscure. Under the current "dynamic COVID-zero" policy, diagnosing COVID-19 remains challenging. The initial viral nucleic acid screening has a positive rate of only 30%–50%, often requiring multiple rounds of testing. Clinically, symptoms such as cough and dyspnea lack specificity. As the virulence of the virus changes, the number of patients presenting without significant fever is increasing [12]. Furthermore, some NSIP patients may present with acute onset, progressive dyspnea, and interstitial lung changes on CT, making their clinical and imaging manifestations very similar to those of COVID-19. Therefore, distinguishing between COVID-19 and NSIP is crucial.

The results of this study indicate that COVID-19 affects people of all age groups, demonstrating that 2019-nCoV exhibits general susceptibility across all ages. However, the average age of patients in the COVID-19 group was younger than that of the NSIP group. Additionally, 45% of the patients in the COVID-19 group had a history of travel to Wuhan, while no patients in the NSIP group had such a history. These differences may be related to variations in social activities across different age groups.

The white blood cell (WBC) counts and liver function indices of both COVID-19 and NSIP patients were normal during the course of the disease, though the liver function of COVID-19 patients was worse than that of NSIP patients, potentially due to the toxicity of 2019-nCoV or the effects of related drug treatments. Lymphocyte (LYMP) counts, inflammatory markers, and hemagglutination indices were elevated in both groups but showed no significant differences, suggesting that COVID-19 and NSIP are highly similar and difficult to distinguish. However, neutrophil (NE) levels in both groups were below normal, with a more pronounced decrease in the COVID-19 group, indicating that 2019-nCoV has a greater impact on NE levels during the disease course.

This study analyzed chest CT scans of 20 COVID-19 patients and 20 NSIP patients. In COVID-19 patients, early-stage imaging showed small patchy shadows and interstitial changes, particularly in the peripheral lobes of the lungs (**Figure 1A**). In advanced stages, the disease often progresses to multiple ground-glass opacities (GGOs) and infiltrates in both lungs. In severe cases, lung consolidation may occur, but pleural effusion is rare. Advanced patients may develop pulmonary interstitial fibrosis, which appears as reticular or linear shadows on CT, while critical patients may present with "white lungs" on CT [13]. In NSIP patients, CT often revealed consolidation along the bronchovascular bundles or subpleural distribution (Figure 1D), with or without traction bronchiectasis, accompanied by GGOs [14].

In conclusion, China is currently managing COVID-19 under a situation of "overall control, with occasional local outbreaks." It is essential to remain vigilant in the prevention and control of COVID-19 to avoid missed diagnoses. At the same time, more attention should be given to the differential diagnosis of COVID-19 and other lung diseases, particularly NSIP, to ensure timely treatment and avoid delays [15]. With collective efforts, the challenges posed by COVID-19 will eventually be overcome. By continually summarizing the clinical experiences in diagnosing and treating COVID-19 and NSIP, more effective approaches to managing these diseases can be developed, ultimately benefiting patients with other lung conditions and improving outcomes.

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Disclosure statement

The authors declare no conflict of interest.

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