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The association of clinical features and laboratory findings of COVID-19 infection with computed pneumonia volume

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Abstract

Coronavirus disease 2019 (COVID-19) was first detected in China in December 2019, and declared as a pandemic by the World Health Organization (WHO) on March 11, 2020.

To study the clinical features of patients with COVID-19, we analyzed the correlation between some inflammation-related indicators in patients' serum and the severity of the disease, especially PV (pneumonia volume under CT scan) and pneumonia volume ratio (PVR).

Sixty-six COVID-19 patients in Huai'an, China were selected as the research subjects. We collected the clinical data, including general characteristics, clinical symptoms, serum test results and CT performance, explored the relationship between inflammation-related indexes, oxygenation index, PV, PVR, while indicators of mild to moderate patients and severe patients were compared.

The most prominent manifestations of COVID-19 patients were fever (47, 71.2%); cough (41, 62.1%), with or without respiratory and other systemic symptoms; There was no difference in gender ($P=.567$) and age ($P=.865$) between mild to moderate and severe groups. High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6) of overall patients were higher than the normal range ($P<.001$, respectively). hs-CRP was negatively correlated with oxygenation index (OI) ($r=-0.55$), whereas positively correlated with PV, PVR and ESR ($r=0.89$; $r=0.87$; $r=0.47$, respectively); ESR was negatively correlated with OI ($r=-0.45$), meanwhile it was positively correlated with PV and PVR ($r=0.44$; $r=0.46$, respectively). OI was negatively correlated with PV and PVR ($r=-0.6$, respectively). PV had a clear correlation with PVR ($r=1$). Severe patients' hs-CRP, PV, PVR were higher than mild to moderate group ($P=.006$; $P=.001$; $P<.001$, respectively), but OI was lower ($P<.001$).

The clinical features of COVID-19 were similar to general viral pneumonia. hs-CRP, ESR showed a certain correlation with the PV and PVR, which might play a certain role in assessing the severity of COVID-19.

Abbreviations: COVID-19 = coronavirus disease 2019, ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, IL = interleukin, OI = oxygenation Index, PV = pneumonia volume under CT scan, PVR = pneumonia volume ratio, RT-PCR = reverse transcription polymerase chain reaction, TLC = total lung capacity, TNF = tumor necrosis factor, Vin = full inspiratory volume.

Keywords: COVID-19, CT, ESR, hs-CRP, pneumonia volume, SARS-CoV-2

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XZ and JZ contributed equally to this work.

All patients included in this study were informed to participate in the survey and signed the consent form.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Highlights

- The characteristics of abnormal indicators and CT pneumonia volume in patients with COVID-19 were studied in this paper.
- Some abnormal indicators correlate with the volume of pneumonia under CT.
- Routine ESR, hs-CRP, IL-6 tests are recommended for all suspected and confirmed patients, with daily assessment of oxygenation index and, if available, software to estimate the volume of pneumonia on CT scan to assist diagnosis and assess the severity of the disease.

1. Introduction

In December 2019, a novel coronavirus appeared in Wuhan, China, which spread rapidly in China and the world. The novel coronavirus was named severe acute respiratory syndrome coronavirus 2 by the International Committee on Taxonomy of Viruses. WHO confirmed its pathogen and named it coronavirus disease 2019 (COVID-19). On March 11, 2020, WHO formally announced that COVID-19 was a pandemic.[1] As of July 26, 2021, Johns Hopkins database showed the global confirmed COVID-19 cases have reached 194,104,829 with the deaths exceeding 4,158,469. The diagnosis of COVID-19 should be based on the comprehensive method such as epidemiology, clinical symptoms, imaging performance, and laboratory tests. Viral nucleic acid detection can confirm the diagnosis of COVID-19. Recently Scherb H showed, COVID-19 death count variability may not only be high between locations but also across periods within locations. Moreover, the observed temporal clustering of the association between positive deaths and positive rate indicates unknown biological, epidemiological, or most likely artefactual determinants of the corona pandemic.[2,3] Therefore, it is important to find additional methods for a more in-depth diagnosis and evaluation of this disease. CT is also a simple and fast supplementary diagnostic method of COVID-19, which can well observe the dynamic changes of patients' lung lesions, and many studies have confirmed this at present.[4–6] Current research is mainly aimed at the clinical features, epidemiology, and imaging features of COVID-19. However, clinical-based research often focuses on the localized analysis of symptoms or positive test results, whereas CT-based research focuses on grading and evaluating the pneumonia range and distribution. Few studies have combined laboratory indicators and CT performance for more in-depth analysis. This article tried to screen out variables that might be related to pneumonia and analyzed their correlation with the lesion volume calculated by CT aimed at better help estimating the severity of pneumonia.

2. Materials and methods

2.1. Subject

This study was approved by the Ethics Committee of Huai'an No .4 People's Hospital (Approval No: 2020001, Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/G627).

All patients included in this study were informed to participate in the survey and signed the consent form. By computer retrieval, 66 patients with COVID-19 diagnosed and isolated in Huai'an and its surrounding areas in Jiangsu, China, from January 23, 2020, to February 20, 2020, were obtained. These patients had clinical symptoms of pneumonia, most of who had a clear contact history, and lung CT showed typical imaging findings. Finally, they were confirmed diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid detection through the throat swab method.

2.2. Data collection

The patient's gender, age, hospital stay, symptoms, epidemiological history, underlying disease, complications, laboratory test data, and other information were collected. CT configuration and method: Philips Ingenuity 64 row spiral CT machine, KV: 120, MAS: 240, layer thickness: 3 mm, layer spacing: 3 mm, screw pitch 1.5: lung window (W: 1500, L: –500), mediastinum window (W: 350, L: 60), thin-layer reconstruction was performed according to the display of the lesion, both the layer thickness and the slice interval of lung window images were 1 mm. The technician carefully trained the patients to take deep breaths and hold breaths before the scan. A patient was placed in a supine position with his hands on his head, and a chest CT scan was performed from the angle of the costal diaphragm to the apex of lung, with the minimized effect of breathing. The workbench was based on an open-source software named MITK (The Medical Imaging Interaction Toolkit, http://www.mitk.org/wiki/MITK) and an open-source convolutional neural networks platform NiftyNet (https://niftynet.io) for medical image analysis and image-guided therapy. A plugin named Lung Kit (GE Healthcare, Shanghai, China) which had been upgraded to version 2.1.1n with the nCov model for COVID-19, was used to outline lung tissue and reconstruct 3D images. Finally, the calculation tool in the software was used to obtain the full inspiratory volume (Vin), which can be used to replace total lung capacity (TLC). We used Vin as an alternative to TLC because there were reports suggesting that Vin and TLC were well correlated ($r=0.89$-0.92).[7,8] Meantime, we also calculated the pneumonia volume under CT scan (PV) and pneumonia volume ratio (PVR, PV/Vin, %). CT was performed by 2 experienced radiologists, who were unaware of patients' age, gender, and other test results except for patients' ID.

2.3. Statistical analyses

Statistical analyses were performed by using Microsoft Excel version15.0 (Microsoft Corporation, Redmond, USA), IBM SPSS Statistics version 20.0 (IBM SPSS Inc., Chicago, USA), and R version 3.6 (Lucent Technologies, Co., Ltd., Beijing, China). Normally distributed quantitative variables were described using mean (SD) and non-normally quantitative variables were described using median (IQR). The *t* test was used to analyze the data. We performed a descriptive analysis of the data to find abnormal variables, and then analyzed the correlation between these variables and PV, PVR. Later, we compared the variables after dividing the patients into mild to moderate and severe groups according to severity. P values $<.05$ were considered statistically significant.

3. Results

The median age of 66 patients was 49 (36.0-57.3), including 31 males and 35 females. These patients had different degrees of clinical symptoms, the most prominent manifestation were fever 47 (71.2%); cough 41 (62.1%); expectoration 16 (24.2%); muscle ache 15 (22.7%); fatigue 13 (19.7%); sore throat 10 (15.2%); asitia 10 (15.2%); asthma 9 (13.6%). 48 patients (72.1%) had a clear history of living in infected areas or a history of contact with infected ones. According to "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)",[9] mild cases and moderate cases were classified as mild to moderate patients, meanwhile, severe cases and critical cases were classified as severe ones in this study. Most of them were mild to moderate patients (58, 87.9%). The other 8 cases were severe patients, 7 of whom needed to use a ventilator. In addition to general treatment during the hospitalization according to the protocol above, the patients received the following treatments: Recombinant Human Interferon-α1 5 Billion IU nebulized inhaled twice daily; Kaletra (each tablet contains lopinavir 200 mg/ritonavir 50 mg) 500 mg orally twice daily; Abidol hydrochloride 200 mg orally twice daily; A small number of patients used Ribavirin 500 mg intravenously twice daily. The course of medication was not more than 10 days. The median of days in hospital was 15 (10.8-19.0), all 66 patients had achieved good results (Table 1).

Table 1

General characteristics of the patients.

Characteristic	Total (n = 66)
Age, median (IQR)	49 (36.0-57.3)
Gender, no (%)	
Male	31 (47%)
Female	35 (53%)
Clinical features, no (%)	
Fever	47 (47.2%)
Cough	41 (62.1%)
Expectoration	16 (24.2%)
Sore throat	10 (15.2%)
Stuffy nose	1 (1.5%)
Runny	2 (3%)
Headache	4 (6.1%)
Chest distress	1 (1.5%)
Asthma	9 (13.6%)
Muscle ache	15 (22.7%)
Fatigue	13 (19.7%)
Asitia	10 (15.2%)
Vomit	2 (3%)
Diarrhea	3 (4.5%)
Contact history	
Living history of endemic areas	8 (12.1%)
Living in an epidemic-free area, with a history of contact with patients or suspected patients	40 (60%)
Living in an epidemic-free area, no patient or suspected patient contact history	18 (27.3%)
Underlying diseases, no (%)*	20 (30.3%)
Complication, no (%)†	11 (16.7%)
Severity, no (%)	
Mild to moderate	58 (87.9%)
Severe	8 (12.1%)
Use of ventilator, no (%)	7 (10.6%)
Use of antibiotics, no (%)	
No use of antibiotic	54 (81.8%)
Used one antibiotic	8 (12.1%)
Used more than 2 antibiotics	4 (6.1%)
Outcome	All patients were cured or improved
Days in hospital, median (IQR)	15 (10.8-19)

* Underlying diseases include hypertension, coronary heart disease, cerebral infarction, chronic obstructive pulmonary disease, lymphoma, femoral head necrosis, hypothyroidism, and a history of tuberculosis.

† Complications include 10 cases of liver abnormalities, 1 case with impaired liver compounded with kidney function simultaneously.

After a descriptive analysis of the results of the examinations performed within 24 hours, we collated the results in Table 2. These laboratory tests mainly included white blood cells, lymphocytes, neutrophils, and platelets in the blood routine, high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), PCT, lymphocyte subset analysis, and inflammatory factor spectrum analysis. By comparing with the reference range, we found 3 indicators of hs-CRP, ESR, and interleukin 6 (IL-6) in these patients were higher than the normal range ($P < .001$, respectively), other indicators were within normal range.

Figure 1 showed the scope of pneumonia of 2 patients under CT and 3D models, respectively. After processing by computer software, we obtained PV, Vin, and PVR of each patient. According to the results in Table 2, we chose 3 indicators above the upper of normal value (hs-CRP, ESR, IL-6) for comparison. Correlation analysis results were shown in in Figure 2. hs-CRP was negatively correlated with oxygenation index (OI) (r = –0.55, $P < .001$), positively correlated with PV, PVR, and ESR (r = 0.89, $P < .001$; r = 0.87, $P < .001$; r = 0.47, $P < .001$, respectively). ESR was negatively correlated with OI (r = –0.45, $P < .001$), positively correlated with PV and PVR (r = 0.44, $P < .001$; r = 0.46, $P < .001$, respectively). There was also a good negative correlation between OI and PV, OI and PVR (r = –0.6, $P < .001$; r = –0.6, $P < .001$, respectively). A very obvious positive correlation between PV and PVR was displayed (r = 1, $P < .001$). However, IL-6 did not show a correlation with other parameters.

After classifying and comparing patients of different genders and severity, we found there was no statistical difference in the severity of the disease between different genders ($\chi^2 = 0.328$, $P = .865$, 95% CI: –0.22 to 0.12, Fig. 3A). No statistically significant difference was found in the age between the 2 groups after comparing the age distribution of patients in 2 groups of different severity ($P = .865$, 95% CI: –0.67 to 0.80, Fig. 3B). This suggested the 2 groups are comparable.

All indicators which were analyzed according to grouped severity, led to results in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A892 after those 6 indicators above were drawn into box-violin plots (Fig. 3C-H). As we can see from the picture, hs-CRP ($P = .006$, 95% CI: –2.19 to 0.65, Fig. 3C), PV ($P = .001$, 95% CI: –2.93 to –1.3, Fig. 3G), and PVR ($P < .001$, 95% CI: –3.22 to –1.54, Fig. 3H) of severe patients were higher than mild to moderate patients, whereas OI was lower ($P < .001$, 95% CI: 2.92 to 4.91, Fig. 3D).

4. Discussion

In our study, the indicators of ESR, hs-CRP, IL-6, pneumonia volume, and oxygenation index in COVID-19 patients can reflect the severity of COVID-19. And ESR and hs-CRP correlated well with the volume of pneumonia measured by CT.

Severe acute respiratory syndrome coronavirus 2 has spread rapidly around the world since it was first detected in late 2019. According to the current diagnostic criteria, nucleic acid testing is the gold standard for the diagnosis of COVID-19.[10] For some patients who had been diagnosed and hospitalized, other laboratory indicators have been found abnormal besides CT and nucleic acid positive. The most common laboratory abnormalities were hypoalbuminemia, lymphopenia, decreased percentage of lymphocytes and neutrophils, decreased CD8 count, elevated IL-6, lactate dehydrogenase, and C-reactive protein.[11,12] Strangely, most of the patients in our study had not only normal lymphocytes but also normal lymphocyte subset analysis, most of the interleukins (except IL-6), tumor necrosis factor (TNF)-α and interferon-γ were not significantly abnormal. This is an interesting phenomenon. This may be related to the absolute advantage of mild to moderate patients. In a study on risk factors associated with disease progression, Zhou et al[13] also confirmed that 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.[14] The majority of our 66 patients had normal lymphocyte counts and had a better prognosis, which is consistent with the final conclusion of Zhou et al. In another study focused on investigating critically patients in ICU, Huang et al[15] pointed out that compared with non-ICU patients, ICU patients had higher plasma levels of IL-2, IL-7, IL-10, MIP1-A, and TNF-α. The vast majority of patients in this study belong to non-ICU. We also found the patient's ESR, hs-CRP, and IL-6 were elevated, which was consistent with Zhu et al's[14] study.

Table 2

Comparison of laboratory results with normal reference ranges.

Test parameter	Total (n = 66) Median (range)/mean (SD)	IQR/95%CI	Reference range	*P* value
WBC (10^9/L)	5.09 (8.97)	3.98-6.96	4-10	/
NEUT (10^9/L)	3.09 (9.38)	2.37-5.32	2-7	/
NEUT (%)	64.38 (14.03)	60.93-67.83	50-70	/
LYM (10^9/L)	1.36 (0.65)	1.20-1.52	0.8-4	/
LYM (%)	26.84 (13.17)	23.60-30.08	20-40	/
PLT (10^9/L)	208.36 (88.01)	186.73-230	100-300	/
*hs-CRP (mg/L)	7.94 (192.02)	1.39-32.84	0-4	<.001*
*ESR (mm/h)	30.5 (98)	14-51.5	0-15	<.001*
PCT (ng/mL)	0.26 (0.13)	0.23-0.29	0-0.5	/
$CD3^+$ (cells/μL)	1554 (521)	1426-1682	955-2660	/
$CD3^+$ (%)	78.9 (5.9)	77.4-80.4	59.4-84.6	/
$CD4^+$ (cells/μL)	902 (334)	820-984	550-1440	/
$CD4^+$ (%)	49.8 (6.7)	48.1-51.4	28.5-60.5	/
$CD8^+$ (cells/μL)	516 (1346)	405-696	320-1250	/
$CD8^+$ (%)	28.2 (30)	26.1-30.3	11.1-38.3	/
$CD4^+/CD8^+$	1.8 (2.66)	1.4-2.4	0.9-3.6	/
$CD19^+$ (cells/μL)	257 (452)	157-363	90-560	/
$CD19^+$ (%)	12.8 (15.5)	9.4-16.6	6.4-22.6	/
NK (cells/μL)	191 (307)	109-270	150-1100	/
NK (%)	12.9 (28.1)	9.0-20.3	5.6-30.9	/
IL-2 (pg/mL)	0 (1.28)	0-0	0-5.71	/
IL-4 (pg/mL)	0 (1.69)	0-0	0-3	/
*IL-6 (pg/mL)	5.68 (59.33)	1.16-20.05	0-5.3	<.001*
IL-10 (pg/mL)	2 (7.04)	0-3.39	0-4.91	/
TNF-α (pg/mL)	0.10 (1.07)	0-1.07	0-4.6	/
INF-γ (pg/mL)	0 (0)	0-0	0-7.42	/
OI (mm Hg)	277.6 (518.3)	226.7-318.2	400-500	/

* indicates exceeding the Reference range.

$CD3^+$ means T lymphocyte; $CD19^+$ means B lymphocyte. OI = oxygenation index, which means PaO2/FiO2.

ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, INF = interferon, IL = interleukin, LYM = lymphocyte, NEUT = neutrocyte, NK = natural killer cell, PCT = procalcitonin, PLT = platelet, TNF = tumor necrosis factor, WBC = white blood cell.

The current nucleic acid test is relatively time-consuming and may yield false-negative results due to laboratory error or insufficient viral material in the specimen.[16,17] Therefore, PCR still needs to be combined with CT examination to more accurately assist diagnosis. An updated systematic review and meta-analysis from Bao et al[18] underscored, the most common CT features in patients affected by COVID-19 included ground-glass opacities and consolidation involving the bilateral lungs in a peripheral distribution, and the detection of COVID-19 chest CT imaging was very high among symptomatic individuals at high risk, especially using thin-section chest CT. It is worth noting that different PCR reagents may lead to false-positive results. In a study on PCR, Konrad et al[19] noted even using the same primers and probes, there are differences in detection efficacy using different PCR systems. This may lead to false positivity, which can produce false signals from other coronaviruses in the order of magnitude as large as 50%. As an auxiliary examination method for pneumonia, the importance of CT cannot be ignored. Current research on CT is mainly based on lung scans to describe the location of pneumonia, and evaluate the severity of the disease, which has certain limitations. Through a retrospective study re-evaluating the diagnostic value of RT-PCR and CT, Long et al[20] believed CT was more sensitive than RT-PCR, which meant it was relatively difficult to miss a diagnosis, but still had a certain degree of defects. The imaging manifestations of early-stage COVID-19 are relatively mild, and the imaging findings of some patients are not typical, which can easily lead to missed diagnoses.[21] In addition, studies have demonstrated CT was of great significance in evaluating the severity of disease,[22,23] moreover some scholars are interested in the 3D CT imaging performance of COVID-19 patients.[24] Indeed we believed it

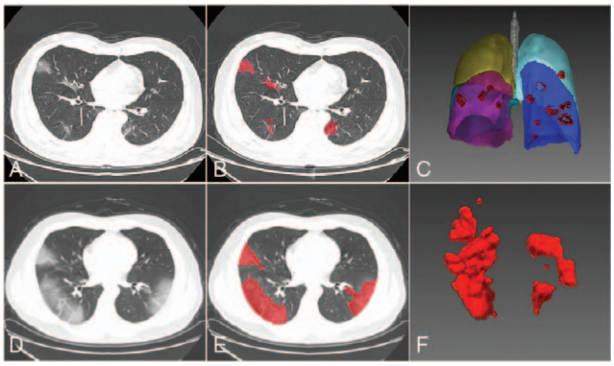

Figure 1. Pulmonary and pneumonia of different layers under CT. A and D are different scan layers, B and E correspond to the lesion areas of A and D at the same layer, marked with red; C is the 3D model of the 2 lungs, the total volume represents the value of Vin, and the red parts represent the focus of pneumonia; F displays the 3D model of the pneumonia lesions. The computer software can calculate PV and PVR according to C and F. PV = pneumonia volume under CT scan, PVR = pneumonia volume ratio, Vin = full inspiratory volume.

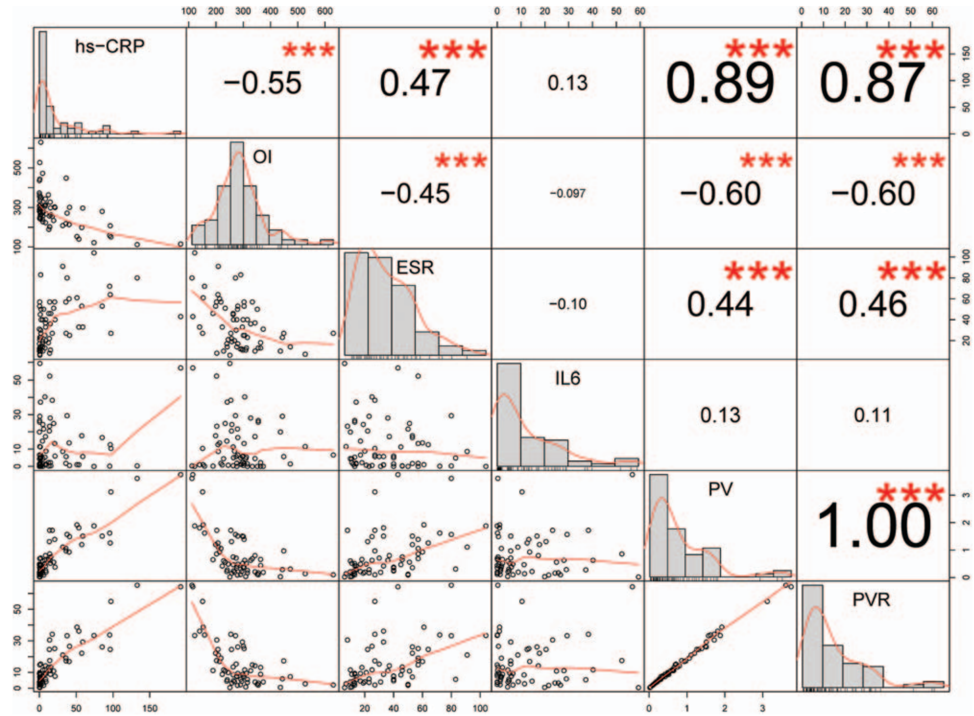

Figure 2. Correlation analysis between 6 parameters. 6 * 6 scatterplot matrix is used for correlation analysis, which has histograms of the variables in the diagonal, and correlation coefficients in the upper part of the matrix. The values shown in the table are correlation coefficients, where positive values are positively correlated and negative values are negatively correlated, and the larger the absolute value of the correlation coefficient, the larger the font. ***: $P < .001$. ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, IL = interleukin, OI = oxygenation Index, PV = pneumonia volume under CT scan, PVR = pneumonia volume ratio.

could be feasible to carry out more detailed quantification and evaluation of CT monitoring for COVID-19 by computer software. In this study, we introduced a method of 3D reconstruction to assess the volume of pneumonia and more refined management of CT detection. Thus, we hoped to further study the relationship between CT and laboratory indicators through methods other than mainstream detection. Finally, the results implicated hs-CRP and ESR had a good correlation with PV and PVR estimated by CT. On the other hand, hs-CRP of severe patients was significantly higher than those in mild to moderate patients, whereas no significant difference between these patients in ESR. Although hs-CRP, ESR, and IL-6 were higher than the reference range in all patients, only hs-CRP and ESR might have a good correlation with the severity of the disease yet. The ionizing radiation of CT is harmful to the human body, consequently, it is not appropriate to evaluate the changes of pneumonia by giving patients frequent CT examinations. In brief, hs-CRP and ESR may play a guiding role in assessing the changes in the severity of patients' condition during the interval between 2 CT examinations. When the dynamic increase of these 2 indicators occurs— it may mean aggravation of pneumonia, even fatal consequences may occur in a short time— clinicians should pay enough attention to the patients, if necessary, needs to recheck CT and strengthen intensive supervision. Using the software to perform 3D processing on the images obtained by CT scanning is conducive to clinicians to carry out a more detailed quantitative assessment of pneumonia. Since nucleic acid testing still has certain defects, there is currently no kind of test which is perfect for diagnosis, so it is necessary to combine nucleic acid, CT, and some other laboratory indicators for comprehensive diagnosis and monitoring.

5. Limitations

There are some deficiencies in our study. First, the difference in patient's breathing amplitude will affect the measured CT value and lung volume, after all, some subjects in this research might not really achieve a deep exhalation state, which might interfere with the inspection results; What is more, the total number of samples is small and mild to moderate patients had an absolute advantage, which might bring a certain degree of uncertainty to the conclusion— for instance, Lymphocytes, TNF-α, and some other indicators were inconsistent with the conclusions of many studies— it still requires a larger sample for further verification. There are currently a large number of cases worldwide, hence we hope more researchers can conduct multicenter and large-scale sample studies to demonstrate these indicators.

6. Conclusion

On the whole, ESR, hs-CRP, and IL-6 increased in patients with COVID-19, while ESR and hs-CRP were positively correlated with the pneumonia volume estimated by CT. The larger the pneumonia volume, the more obvious the decrease in oxygenation index. PV, PVR, and hs-CRP were higher in severe patients than those mild to moderate patients, and OI decreased significantly. These indicators can show the severity of COVID-19 to a certain extent. We recommend routine ESR,

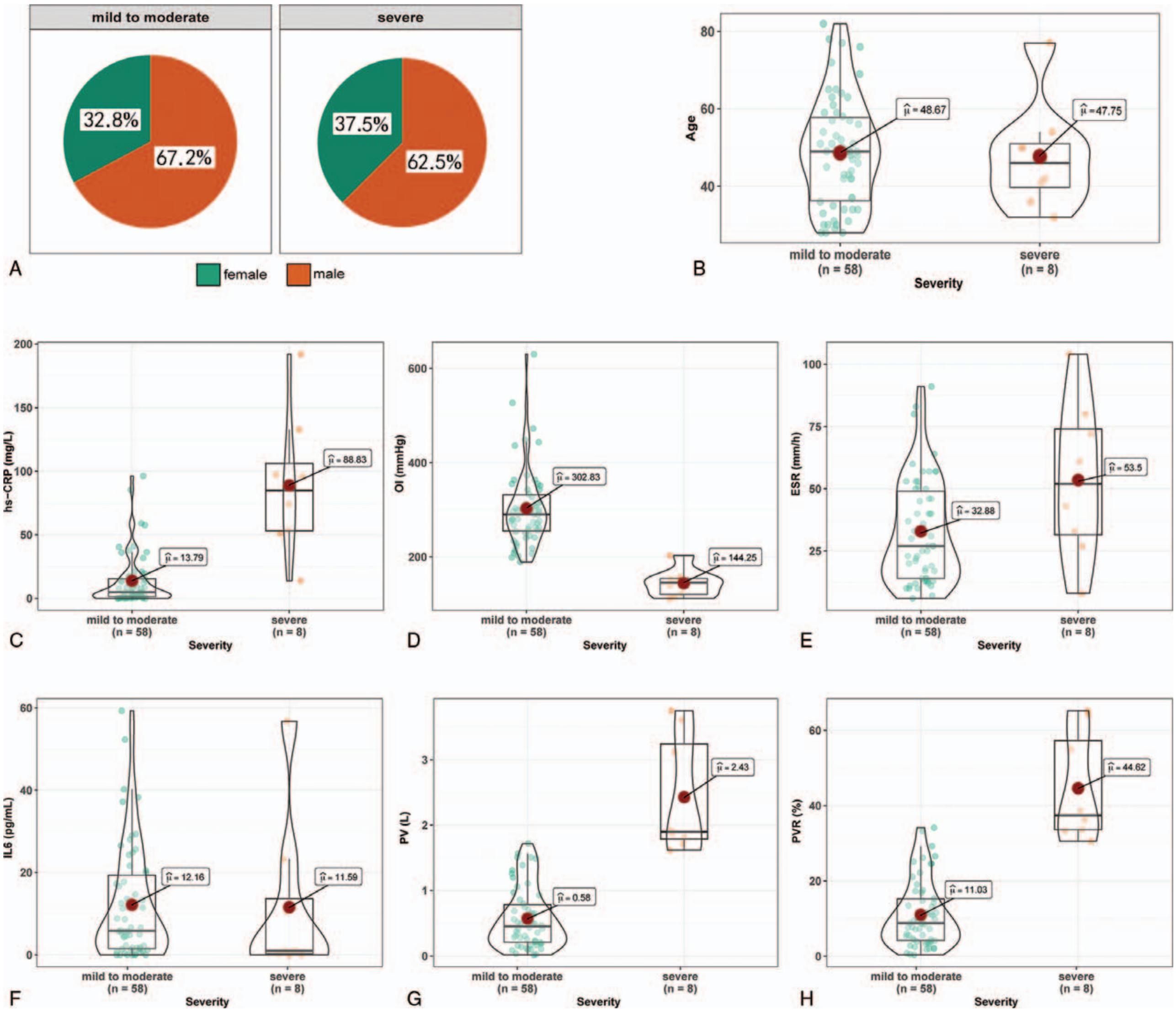

Figure 3. Comparison between the mild to moderate group and the severe group. (A) Comparison of severity by sex; (B) The box-violin plots showed the distribution of age between the 2 groups; (C-H) The box-violin plots showed the distribution of the 6 parameters in different severity. ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, OI = oxygenation Index, PV = pneumonia volume under CT scan, PVR = pneumonia volume ratio.

hs-CRP, and IL-6 examinations for all suspected and confirmed patients, daily assessment of oxygenation index, furthermore, the software can be used to estimate the volume of pneumonia under CT scans to assist in diagnosis and evaluation of the severity if available.

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