Correlation between lung infection severity and clinical laboratory indicators in patients with COVID-19: A cross-sectional study based on machine learning

Xingrui Wang (787229957@qq.com)
Northwest University
Qinglin Che
Jingmen First People's Hospital
Xiaoxiao Ji
Northwest University
Xinyi Meng
Northwest University
Lang Zhang
Northwest University
Rongrong Jia
Northwest University
Hairong Lyu
Northwest University
Weixian Bai
Northwest University
Lingjie Tan
Northwest University
Yanjun Gao
Northwest University

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Abstract

Background: New coronavirus disease (COVID-19) has caused a global pandemic that has raised worldwide concern. This study aims to investigate the correlation between the extent of lung infection and relevant clinical laboratory testing indicators in COVID-19 and to analyse its underlying mechanism.

Methods: Chest high-resolution computer tomography (CT) images and laboratory examination data of 31 patients with COVID-19 were extracted, and the lesion areas in CT images were quantitatively segmented and calculated using the deep learning (DL) system. A cross-sectional study method was used to explore the differences among the proportions of lung lobe infection and to correlate the percentage of infection (POI) of the whole lung in all patients with clinical laboratory examination values.

Results: No significant difference in the proportion of infection was noted among various lung lobes ($P > 0.05$). The POI of total lung infection was negatively correlated with the peripheral blood lymphocyte percentage (L%) ($r = -0.633$, $P < 0.0001$) and lymphocyte count (LY) ($r = -0.555$, $P = 0.001$) but positively correlated with the neutrophil percentage (G%) ($r = 0.565$, $P = 0.001$). Otherwise, the POI was not significantly correlated with the peripheral blood leukocyte count (WBC), monocyte percentage (M%) or haemoglobin content (HGB). In some patients, the G% increased continuously and was accompanied by a progressive decrease in the L% and LY.

Conclusions: No significant difference in infection propensity was noted among the lung lobes in COVID-19 patients. The peripheral blood lymphocyte and neutrophil levels are significantly correlated with the extent of lung lesions, and related indicator abnormalities serve as a warning, thus guiding the implications of clinical interventions in patients.

Background

In December 2019, several cases of pneumonia of unknown causes were reported in Wuhan, Hubei Province, China [1]. It was confirmed that the pathogenic microorganism causing this pneumonia was a new coronavirus. Later, the International Committee on Taxonomy of Viruses (ICTV) officially named the new coronavirus severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Studies have shown that SARS-CoV-2, which is a beta genera coronavirus, shares similarity with the viruses that cause SRAS and MERS; however, SARS-CoV-2 is more severely contagious [2]. SARS-CoV-2 is mainly transmitted through respiratory droplets (cough, sneeze) and contact, and people of all ages are generally susceptible. The symptoms after infection mainly include fever, dry cough and fatigue. Most patients have a good prognosis, and a few quickly progress to acute respiratory distress syndrome (ARDS), sepsis shock, and multiple organ failure, which heralds a poor prognosis. On March 11, 2020, the WHO announced that COVID-19 has caused a global pandemic. As of March 15, 2020, COVID-19 had spread in 135 countries and regions around the world. The cumulative number of confirmed cases was greater than 330,000, and the death toll was greater than 14,000 [3].

COVID-19 generally attacks within 14 days after infection, and its diagnosis depends on viral nucleic acid testing, which is susceptible to interference by many factors. Moreover, the sensitivity of nucleic acid testing is much lower than that of computer tomography (CT) (98% vs. 71%) [4]. CT is recommended for clinical screening and observation of COVID-19 patients due to its high efficiency and objectivity. However, visual inspection of CT imaging cannot attain a quantitative assessment of the infected area and is incapable of accurately judging the patient's progress. At present, artificial intelligence (AI) technology is becoming increasingly mature. This technology is adept in automatically identifying complex patterns in imaging data, can quantitatively evaluate specific imaging features, and has been widely used in the field of medical imaging [5].

Current evidence shows that the primary diseased region of COVID-19 patients is the lungs, and normal or decreased peripheral leukocytes as well as reduced lymphocyte counts are noted [6, 7]. To further clarify the dynamic changes of relevant clinical laboratory test indicators and their significance in the diagnosis and treatment of COVID-19, this study intends to use AI technology to quantitatively evaluate the extent of pulmonary lesions in COVID-19 patients and to explore the correlation between the two factors in combination with their respective blood observation indexes, so as to provide a clinical reference.

Methods

Study design

Chest high-resolution CT images and laboratory examination data of COVID-19 patients were extracted, and lesion areas in the CT images were quantitatively segmented and calculated using the deep learning (DL) system. A cross-sectional study was conducted to investigate the correlation between lung infection and clinical laboratory indicators in patients with COVID-19 pneumonia.

Participants

Thirty-one patients with a diagnosis of COVID-19 were collected from January 21, 2020, to February 4, 2020, in Jingmen First People's Hospital, Hubei Province. All patients received a respiratory or blood specimen test via real-time fluorescent quantitative polymerase chain reaction (qRT-PCR), and the results were positive for new coronavirus nucleic acids. Furthermore, the viral gene sequence must be highly homologous to the new coronavirus sequence. All participants underwent a high-resolution CT (HRCT) scan and peripheral blood laboratory testing on the same day without other basic diseases that may affect laboratory observation indicators (such as combined bacterial infection and immunosuppression).

Imaging data acquisition and post-processing

HRCT images were collected in the Department of Radiology, Jingmen First People's Hospital, Hubei Province. A GE MEDCIAL SYSTEMS LightSpeed VCT scanner was used. The patient was supine, and the image was captured after the patient was instructed to hold his (her) breath. The following scanning parameters were employed: slice thickness, 1.25 mm; field of view (FOV), 354.0 mm; tube voltage, 120 kV; tube current, 278 mA; and image zoom, 1.00. The AI analysis software used for image processing was a

deep learning system developed by Shanghai United Imaging Intelligence Co., Ltd. and Shanghai Public Health Clinical Center, Fudan University (New Coronavirus Pneumonia Auxiliary Analysis Software, version number: Full-uAI-Discover-NCP.R001.0.0.15980).

Laboratory inspection data collection

We scrutinized the clinical data of all laboratory confirmed COVID-19 patients in the in-hospital medical records system, including clinical charts, laboratory test results, radiological diagnosis opinions and nursing records, and extracted the clinical laboratory examination indicators of each patient through standardized data collection. After the collection of clinical laboratory inspection indicators, the data were independently reviewed and checked by two researchers to ensure that the relevant values were accurate.

Observation indicators

The original HRCT images of thirty-one patients were extracted from the Picture Archiving and Communication System (PACS), and all patients were randomly numbered for identification (patient 1, patient 2, ..., patient 31). The lungs of each patient were divided into 20 bronchopulmonary segments based on anatomical division by AI, and lesions of the whole lung and each lung lobe were calculated. Specific steps: 1) input the HRCT images into the DL automatic segmentation system; 2) calculate the quantitative metrics that characterize infected regions, including but not limited to the volume of infection (VOI) and the percentage of infection (POI) in the whole lung, lung lobes and bronchopulmonary segments. Figure 1 shows the software interface obtained by inputting the original HRCT images of one patient into the DL automatic segmentation system. Figure 2 shows the CT image segmentation results of typical COVID-19 infection cases at three different infection stages: the early stage, progressive stage, and severe stage. The contour drawn by the deep learning system coincided with the lesion boundary visible in the CT image.

The peripheral blood leukocyte count (WBC), neutrophil percentage (G%), lymphocyte percentage (L%), monocyte percentage (M%), lymphocyte count (LY), and haemoglobin content (HGB) were extracted. Laboratory examination data and HRCT image acquisition of all thirty-one patients were completed on the same day, and two independent researchers verified all the values.

Statistical Analysis

The Shapiro-Wilk test was used to verify the normality of the data. The Kruskal-Wallis test was performed on the POIs of the following five lung lobes: the left upper lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe. The Spearman correlation test was carried out to analyse the correlation between the total pulmonary POI and the peripheral blood WBC, G%, L%, M%, LY, and HGB. SPSS 19.0 statistical software (IBM company, Armonk, NY) was employed.

Results

A total of 31 COVID-19 patients were involved in this study, including 18 males (58.1%) and 13 females (41.9%). The patients were 17 to 80 years old with an average age of 42.61 ± 15.99 years. The status of

pulmonary infection is presented in Table 1. No significant difference was noted among the proportions of pulmonary lobe infection ($P > 0.05$). Correlation analysis found that the total pulmonary POI was negatively corrected with the peripheral blood lymphocyte percentage ($r = -0.633$, $P < 0.0001$, Fig. 3) and the lymphocyte count (r=-0.555, $P = 0.001$, Fig. 4) but positively correlated with the neutrophil percentage ($r = 0.565$, $P = 0.001$, Fig. 5). The peripheral blood leukocyte count, monocyte percentage and haemoglobin content did not significantly correlate with the total POI of the lungs (Table 2).

Table 1
Lung (lobes) average infection volume and proportion

Anatomical partition	VOI (cm^3)	POI (%)
Whole lung	281.19 ± 421.55	8.91 ± 15.01
Left lung	115.45 ± 191.99	7.81 ± 13.26
Upper lobe	57.02 ± 108.02	7.72 ± 14.92
Lower lobe	58.44 ± 93.80	10.31 ± 20.26
Right lung	165.73 ± 243.46	9.98 ± 17.14
Upper lobe	54.39 ± 89.82	9.50 ± 18.50
Middle lobe	20.44 ± 39.93	8.20 ± 18.54
Lower lobe	90.91 ± 123.99	13.54 ± 22.82
VOI = volume of infection, POI = percentage of infection		

Table 2
Correlation between total lung infection and the clinical laboratory indicators

	POI of whole-lung	
	Correlation coefficient (r)	P-value
Neutrophil percentage	0.565	0.001
Lymphocyte percentage	-0.633	< 0.0001
Lymphocyte count	-0.555	0.001
Leukocyte count	0.070	> 0.05
Monocyte percentage	0.097	> 0.05
Haemoglobin content	-0.193	> 0.05

Of note, several patients in different disease periods showed a dynamic trend of a continuously increased peripheral blood neutrophil percentage and a progressively decreased lymphocyte percentage and lymphocyte count, which correlated with the increase in the pulmonary infection volume (Table 3, Fig. 6).

Table 3
Dynamic changes of the lung infection volume and laboratory indicators in some patients

	Infected lung volume (cm^3)	Neutrophil percentage (%)	Lymphocyte percentage (%)	Lymphocyte count ($\times 10^9$/L)
Patient 18				
Time 1	572.2	52	28.8	1.33
Time 2	957.7	72.5	19.5	1.38
Time 3	1596.4	95.9	1.7	0.31
Patient 22				
Time 1	202.7	57.8	28.6	0.99
Time 2	298.8	60.2	30.3	0.88
Patient 24				
Time 1	157.1	64	23.4	1.25
Time 2	198.3	67.2	18.9	1.08
Patient 27				
Time 1	3.4	51.6	33.3	1.15
Time 2	330.2	70.1	19.8	0.85
Patient 28				
Time 1	852.4	66.3	24.7	0.74
Time 2	1299.7	85	8.5	0.36

Discussion

The COVID-19 pandemic is becoming increasingly severe due its rapid spread, which has raised worldwide concern. COVID-19 mortality is lower but its morbidity is higher compared with SARS and MERS [8, 9]. The lungs are more vulnerable to SARS-CoV-2 than other organs. Pathological studies have shown that the primary changes in the lungs of COVID-19 patients include diffuse alveolar injury, fibrinous protein exudation, and alveolar cell desquamation accompanied by transparent membrane formation and lymphocyte-based inflammatory cell infiltration in the stroma [10], which are the foundation of CT imaging signs of patients with COVID-19. Based on the current diagnostic sensitivity of HRCT, early changes in the lungs of COVID-19 patients are easily detected. Given that the effectiveness of nucleic acid testing,the gold standard for diagnosis, has been unsatisfactory, it may lead to missed diagnoses of many COVID-19 patients, making it difficult to control the epidemic. Therefore, there is an urgent need to focus on the preliminary screening of patients with low-dose CT. To ensure the accuracy of diagnosis, it is necessary to combine CT results with clinical laboratory testing indicators. Changes in the laboratory indicators of COVID-19 are well known by clinicians and radiologists. However, there is a lack of evidence that indicates the exact relationship between COVID-19 progression and laboratory testing indicators. Therefore, our research mainly aimed to explore that potential relationship.

At present, a handful of autopsy reports have demonstrated that COVID-19 is a disease that induces multi-organ and multi-system damage and does not simply affect the lungs [11]. The immune system damage caused by SARS-CoV-2 should not be underestimated. The spleen volume of COVID-19 patients is significantly reduced, and the number of $CD4^+$ T cells and $CD8^+$ T cells in the spleen and peripheral lymph nodes is also reduced; such effects are accompanied by tissue degeneration and necrosis as well as proliferation of macrophages, which are specifically like those noted with SARS-CoV infection [12–14]. Lymphocytopaenia seems to potentially signify that COVID-19 may deplete and disrupt the immune system in some direct or indirect manner, resulting in an AIDS-like response. Studies on SARS indicate that SARS-CoV cannot infect human lymphocytes and monocytes *in vitro* and that attacking lymphocytes and mononuclear cells with infectious SARS-CoV, inactivated virus particles, or receptor protein-binding fragments of the virus is unable to trigger an apoptotic response [15]. In addition, autopsies of COVID-19 patients yielded negative immunohistochemistry and PCR results from spleen, bone marrow, and peripheral lymphoid tissues. The above results suggest that SARS-CoV-2 is unlikely to destroy the human immune system via a direct mechanism. The reason is probably related to the lack of angiotensin-converting enzyme 2 (ACE2) expression in human immune tissues or organs [16, 17].

However, the mechanism underlying lymphopaenia in peripheral blood of COVID-19 patients remains unclear. There are three possible explanations: a) The inflammatory storm gives rise to the destruction and consumption of lymphocytes. Studies have shown that the strong type I interferon (IFN) response caused by viral infection and the high levels of glucocorticoids caused by normal stress responses can induce T cell apoptosis [18, 19]. In addition, the intense cytokine storm itself experienced by SARS patients can induce lymphocyte apoptosis [15, 20], suggesting that lymphocyte apoptosis might exist in COVID-19 patients. b) Reduced lymphocyte production. Any debilitating disease inevitably activates the stress response mediated by the hypothalamic-pituitary-adrenal axis (HPA) and increases cortisol

secretion. Steroid levels in the blood can significantly affect the number and biological behaviour of lymphocytes in the circulatory system. Robertson *et al*. reported that glucocorticoids can induce human lymphoblast apoptosis; even under physiological conditions, the number of lymphocytes also has a significant negative correlation with the circadian rhythm of the cortisol content [21–23]. After viral infection, the body exhibits a stress reaction, and the HPA axis is activated to produce more steroids, thus inhibiting the level of lymphocytes in the circulatory system. Of course, the possibility that the lymphocyte levels also change after patients receive an exogenous cortisol treatment cannot be excluded. However, many COVID-19 patients have exhibited a decreasing trend in lymphocytes in peripheral blood before receiving a clinical intervention. At present, controversy exists regarding whether glucocorticoids should be used to relieve the symptoms of patients with severe viral pneumonia [7, 24–26]. Therefore, the application of glucocorticoids in the treatment of COVID-19 should be considered dialectically. In addition, whether glucocorticoids can cause immunosuppression in SARS-CoV-2-infected patients and the relationship between the dosage of glucocorticoids and the prognosis of patients still require further research. c) Abnormal distribution of lymphocytes in the body. The immune response of the respiratory tract to invasive pathogens is initiated by airway epithelial cells. After airway epithelial cell infection, resident respiratory dendritic cells (rDCs) are activated by pathogens or antigens to process antigens and simultaneously migrate to peripheral lymphoid organs. After arriving at peripheral lymphoid organs, rDCs present the processed antigens to immature T lymphocytes in the form of the major histocompatibility complex (MHC)-peptide complex. After binding to the MHC-peptide complex, T cells are activated to proliferate and migrate to the infected site [27, 28]. This process will inevitably lead to the redistribution of lymphocytes in the lesion and other areas. It is worth noting that the effect of COVID-19 on the immune system does not simply involve reducing the number of lymphocytes via a specific mechanism, which is quite likely attributed to a combination of the above three reasons. The exact mechanism of this change needs to be confirmed by relevant cellular and molecular pathology research. In addition, our study also demonstrated that the number and percentage of lymphocytes decreased progressively as COVID-19 progressed, suggesting that the level of lymphocytes in the blood might be a biomarker to predict the prognosis of COVID-19 patients.

Our study also found a significant positive correlation between the percentage of neutrophils in peripheral blood and the volume of pulmonary infection. Neutrophils are differentiated from hematopoietic stem cells in bone marrow and exhibit active chemotaxis, phagocytosis and bactericidal effects. As the most abundant leukocytes in the circulatory system, neutrophils play a central role in the natural immune system and participate in the regulation of adaptive immune responses. Generally, neutrophil activation is more sensitive to bacterial infection, but research on SARS has shown that cytokines and complement activation play an important role in the progression of SARS, which is related to neutrophil activation and aggregation [29, 30]. Based on this finding, it is hypothesised that the increased proportion of neutrophils in peripheral blood of patients with COVID-19 may also be related to the production of multiple cytokines (such as IFN-γ) and the activation of the complement system after infection with the virus. Moreover, if the patient is infected with bacteria in the late stage of the disease, the percentage of neutrophils would also increase. A retrospective study involving 1,312 patients with SARS reported that the neutrophil count

is a highly reliable prognostic indicator of fatality in SARS-CoV-infected patients, predicting relatively high mortality [31]. Evidence also suggests that when people are infected with some severe respiratory viruses (such as SARS-CoV, H5N1), neutrophil infiltration into the lungs will produce high levels of chemokines, such as CXCL10, which can induce fulminant pneumonia and aggravate the ARDS [32]. Based on the above reasons, we suggest that the neutrophil level in peripheral blood should be an area of focus during the treatment of COVID-19 patients. Once the neutrophil level in peripheral blood becomes abnormal, certain interventions and related supportive treatment should be administered in time to improve the prognosis and reduce the fatality rate.

Our research has the following limitations. First, the sample size is small, and the data are not normally distributed. Thus, the information obtained may exhibit deviations. Subsequent research with a larger sample is needed to further reveal the specific relationship between these two factors. Second, the inconsistency in the treatment options of the patients included is also another limitation. Although it has been confirmed that the lymphocyte count in COVID-19 patients is reduced before they receive treatment, it cannot be excluded that different treatment options administered during hospitalization could bias the results.

Conclusions

In this study, AI was used to explore the distribution of lung infection in COVID-19 patients, and no significant difference in the severity of each lung lobe infection was observed. The correlation between overall lung lesions and related clinical laboratory tests was analysed, revealing that the reduction in the peripheral blood lymphocyte level caused by COVID-19 and the increase in the neutrophil level were significantly related to the degree of lung lesions. Accordingly, the dynamic changes in the relevant test indicators after SARS-CoV-2 infection could play a role in guiding the choice of treatment options for patients.

Declarations

Acknowledgements

Not applicable.

Authors' Contributions

WXR completed the data integration and statistical analysis and was a major contributor to manuscript writing. CQL was responsible for extracting the imaging data and collecting the laboratory examination data. JXX and LHR completed the CT image inspection to ensure the quality of the data. MXY, ZL, JRR, BWX and TLJ finished the examination and verification of the laboratory examination results of patients. GYJ finalized the study design and provided technical support. All the authors read and approved the final manuscript.

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Availability of data and materials

The datasets collected and analysed during the current study are included in this published article and its supplementary information files. More detail information on the datasets and materials used in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee of Jingmen First People's Hospital. Due to the infectiousness of the disease and the regulations of nosocomial infection prevention and control, we failed to directly contact COVID-19 patients. However, with clinician assistance, verbal informed consent was obtained from patients or their family members. All patients' data were anonymised before use.

Consent to publish

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

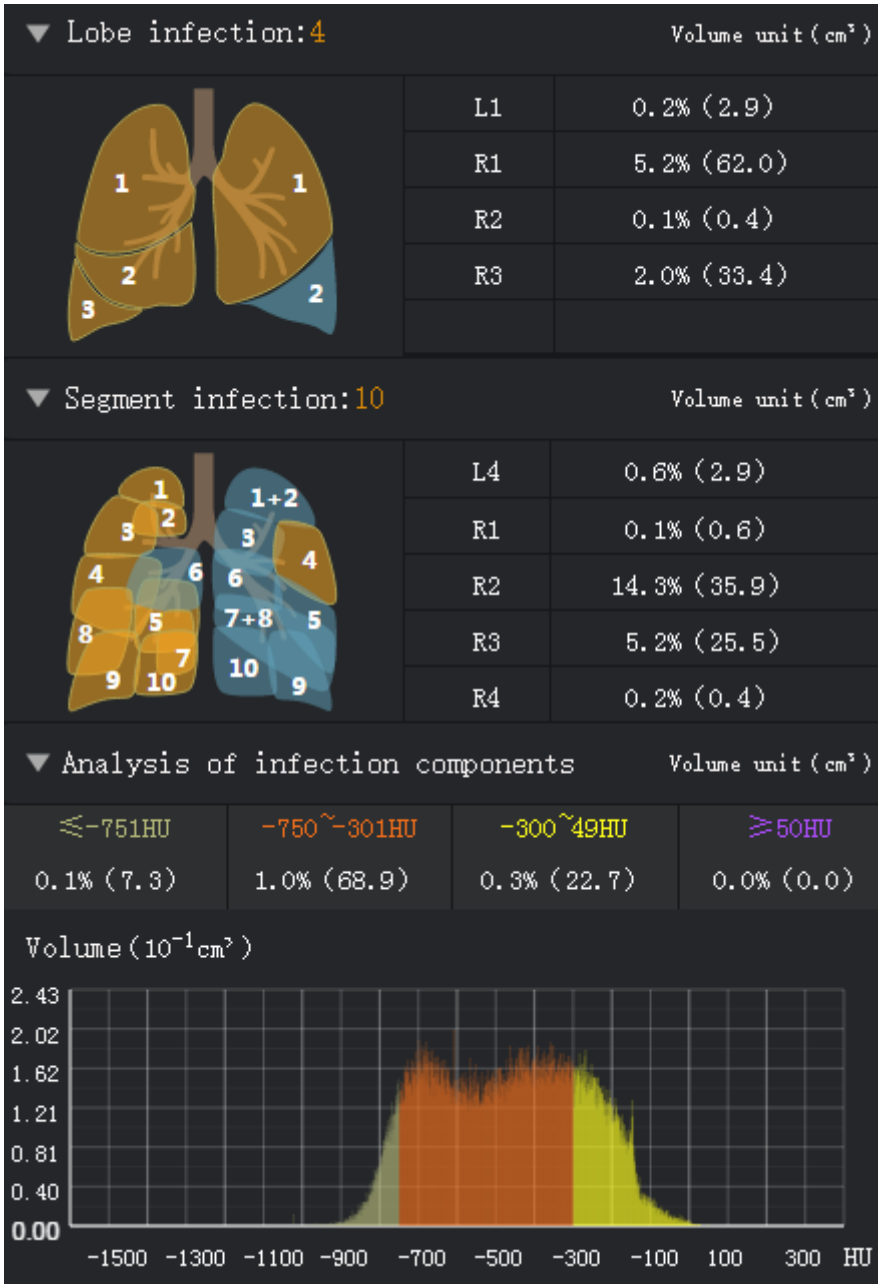

Figure 1

Software interface obtained by inputting the original HRCT images of one patient into the DL automatic segmentation system. The volumes of infection (VOIs) and percentages of infection (POIs) in the lung lobes and bronchopulmonary segments are presented.

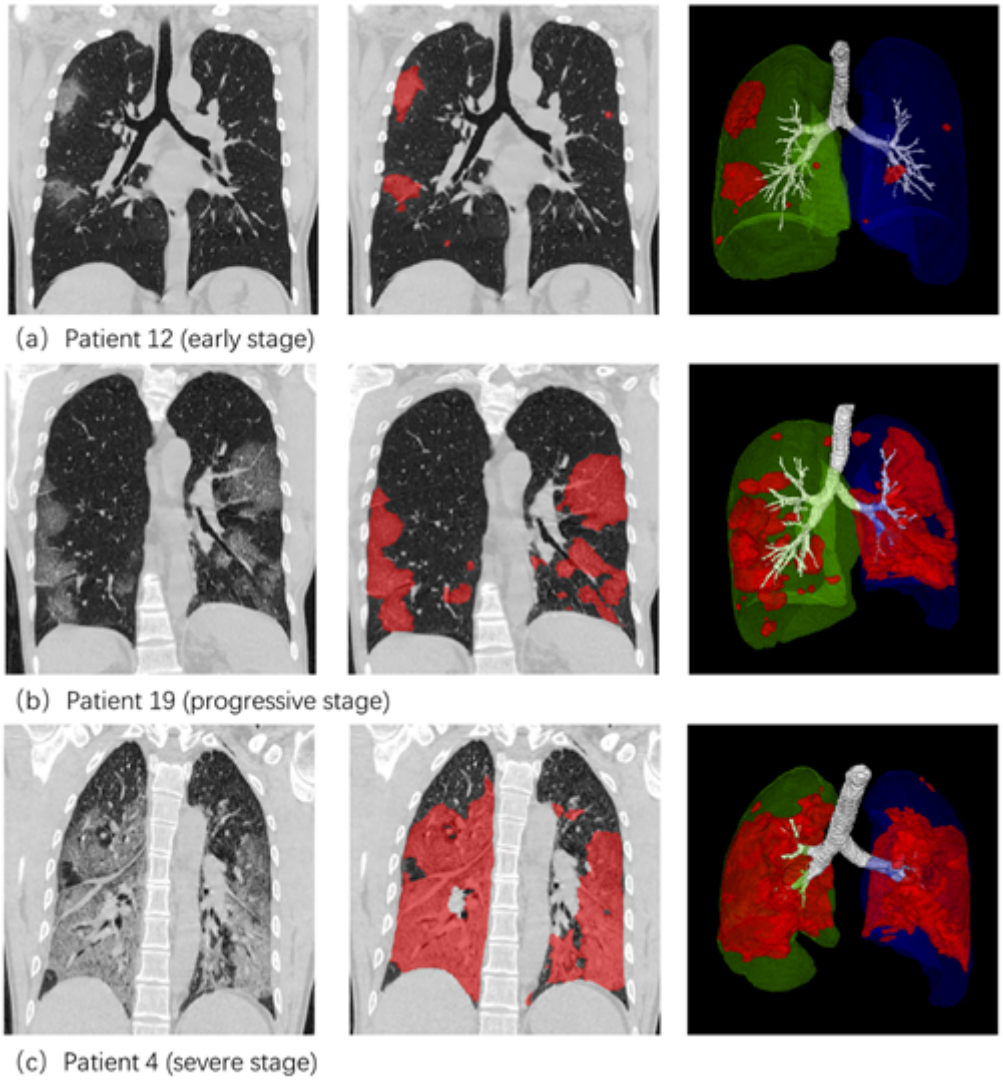

Figure 2

Lesion segmentation results of three COVID-19 cases at different stages of lung infection displayed using the software post-processing platform. Rows 1-3: early, progressive and severe stages, respectively. Columns 1-3: CT image, CT images overlaid with segmentation, and 3D surface rendering of segmented infections, respectively.

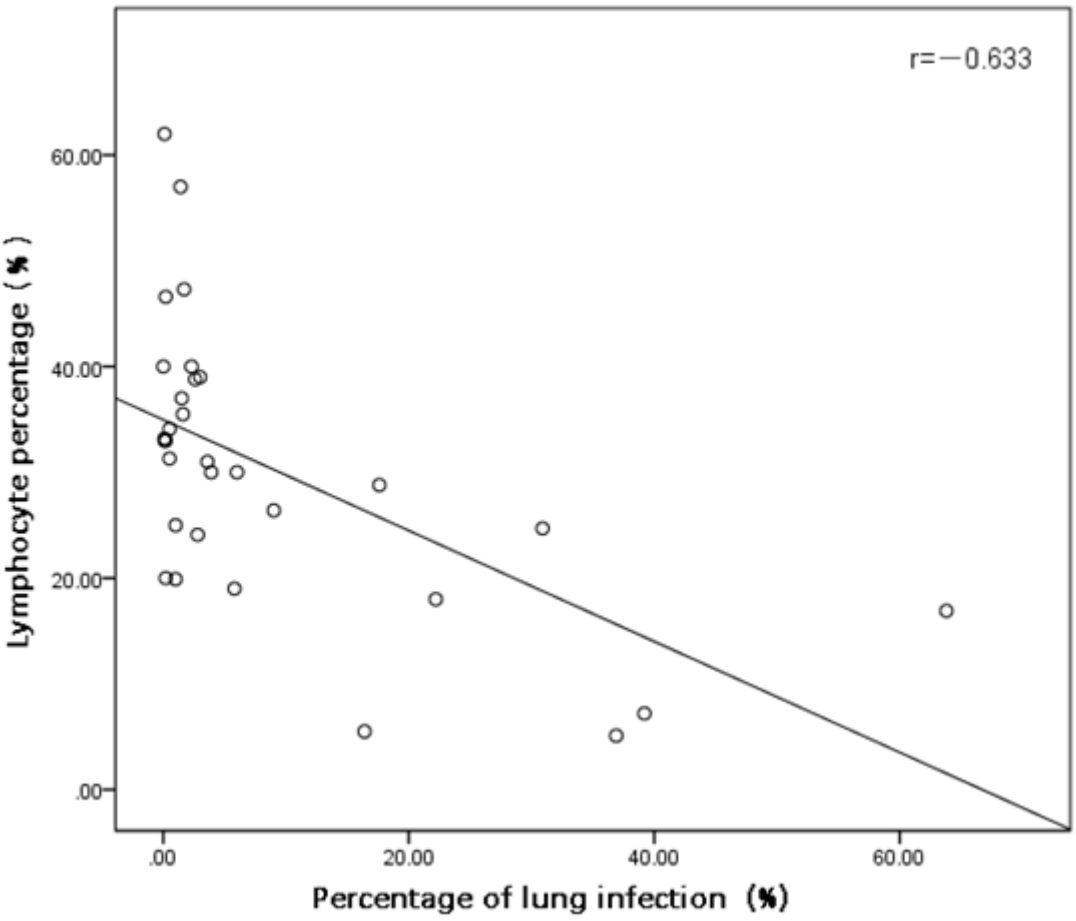

Figure 3

The percentage of infection (POI) of the total lung was negatively correlated with the peripheral blood lymphocyte percentage (L%) (r = -0.633, P < 0.0001).

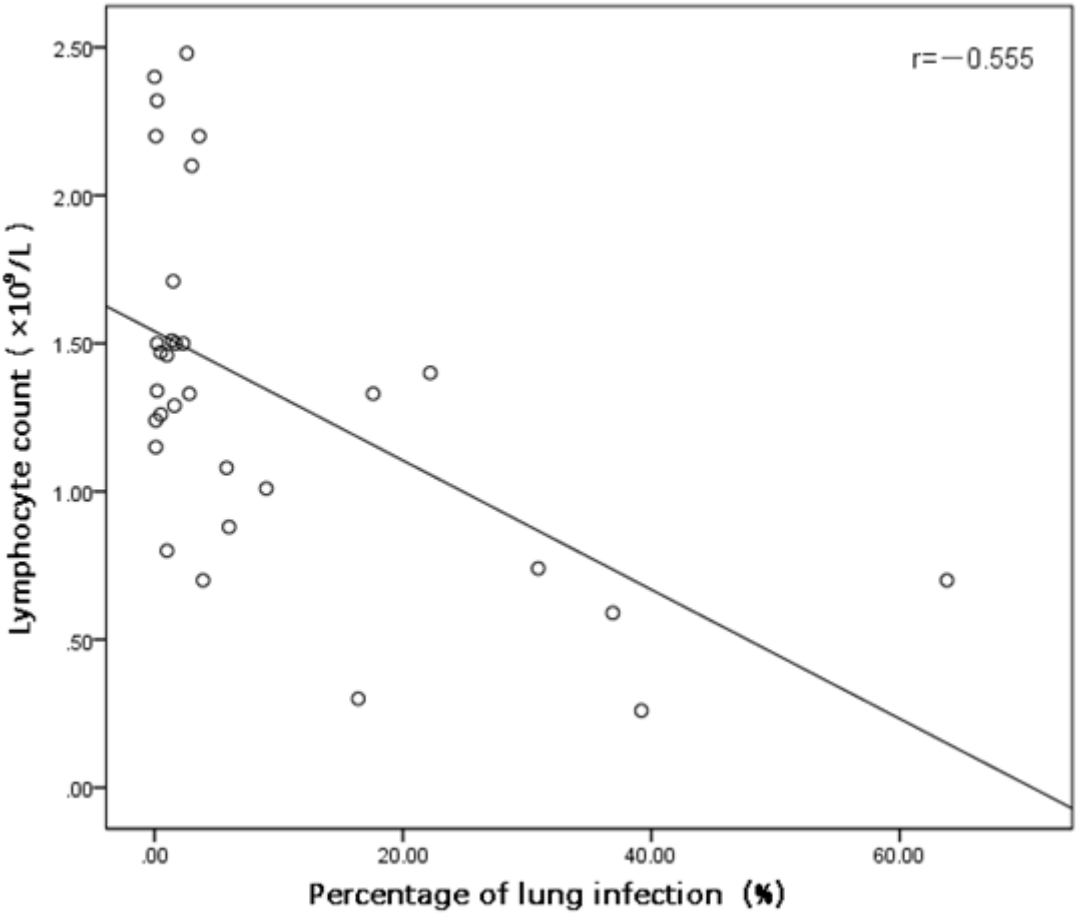

Figure 4

The percentage of infection (POI) of the total lung was negatively correlated with the peripheral blood lymphocyte count (LY) (r = -0.555, P = 0.001).

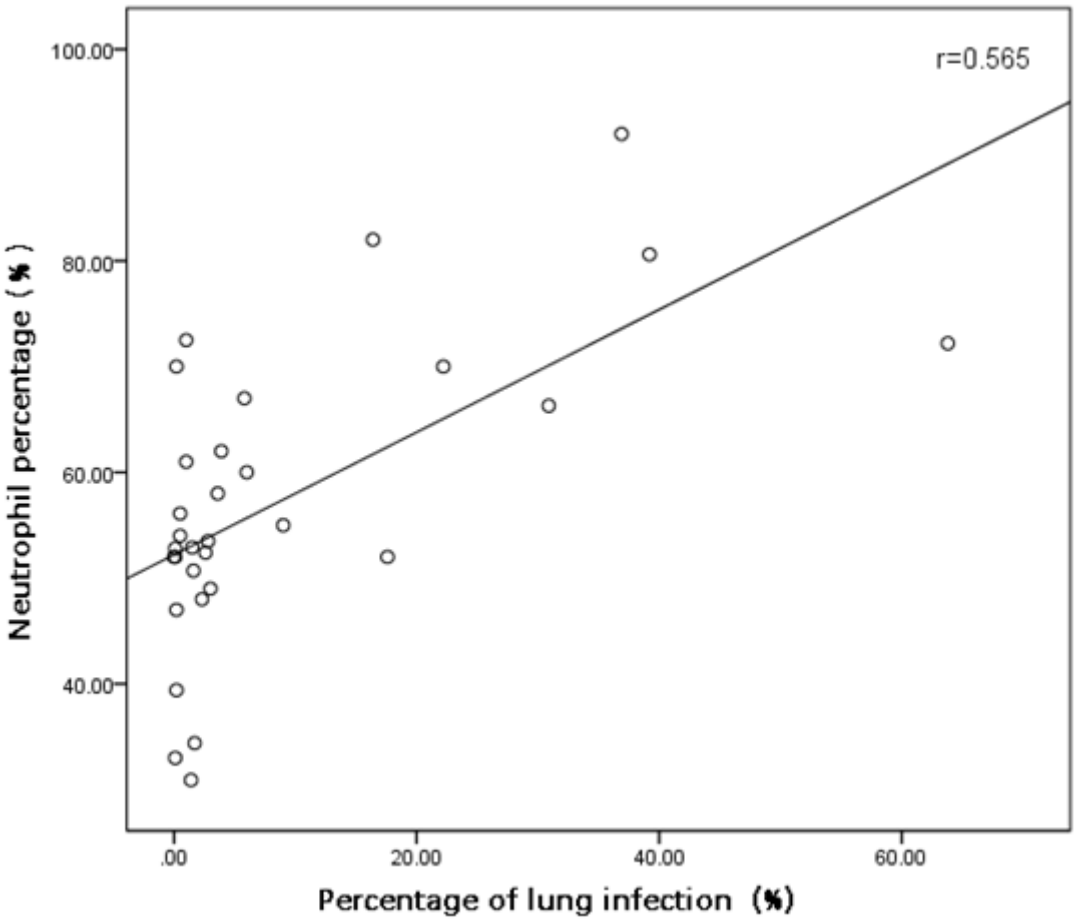

Figure 5

The percentage of infection (POI) of the total lung was positively correlated with the peripheral blood neutrophil percentage (G%) (r = 0.565, P = 0.001).

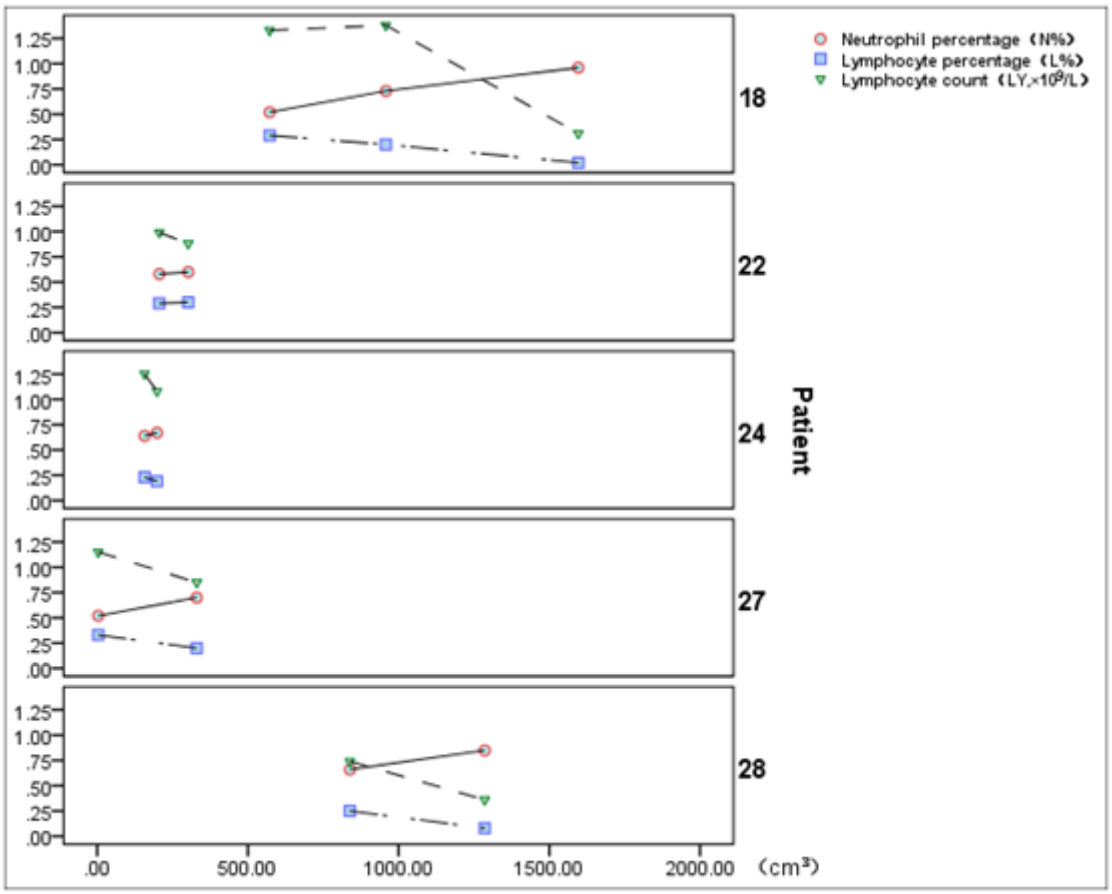

Figure 6

Several patients showed a dynamic trend of a continuously increased peripheral blood neutrophil percentage (G%) and a progressively decreased lymphocyte percentage (L%) and lymphocyte count (LY) as the pulmonary infection volume increased.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistINFDS2001437.docx
- Additionalfile1.docx
- Additionalfile2.docx