Quantitative Chest CT Analysis in Relationships between CT Patterns, Virus Load, and Pathophysiological States in SARS-CoV-2 infected Patients: A Cross-Sectional Observational Study

Wang Yan[1], Meng Haining[2], Wang Sumei[1], Jia Chao[1], Lian Zhiyuan[1], Xie Weifeng[1], and Qu Yan[1]

[1]University of Health and Rehabilitation Sciences (Qingdao Municipal Hospital
[2]Medical College of Qingdao University

July 13, 2023

Abstract

CT imaging is often used to confirm COVID-19, playing a crucial role in the diagnosis and assessment due to its high sensitivity. The purpose of this study is to investigate results of quantitative CT analysis for CT patterns in SARS-CoV-2 infected patients, and how these relate to viral load and pathophysiological states. We recruited patients who had confirmed SARS-CoV-2 infection and undergone chest CT within 24 hours of confirmation. By quantitative CT analysis, and collecting clinical data, we explored correlations between those variables. Our research included 253 patients, after screening by exclusion criteria, 171 patients were included in final cohort. The incidence of SARS-CoV-2 associated pneumonia was 74.3%. The ROC test results showed AUCs for leukomonocyte count, and virus genes were 0.703, 0.562, 0.567, and 0.582, respectively. GGO pattern in CT was correlated PaO $_2$/FiO $_2$ ratio. Multiple linear regression results indicated GGO was associated with PaO $_2$/FiO $_2$. Meanwhile, the consolidation was correlated with PaCO $_2$ level. Additionally, consolidation was also associated with neutrophil–lymphocyte ratio. Conclusion: Lymphocyte count may be a potential marker for predicting SARS-CoV-2 pneumonia, independent of virus load. Additionally, GGO is correlated with hypoxia, while consolidation is associated with PaCO $_2$ levels and inflammation, which may affect aeration in the lungs.

Quantitative Chest CT Analysis in Relationships between CT Patterns, Virus Load, and Pathophysiological States in SARS-CoV-2 infected Patients: ACross-Sectional Observational Study

Wang Yan[1*], Meng Haining[2*], Wang Sumei[1], Jia Chao[1], Lian Zhiyuan[1], Xie Weifeng[1], Qu Yan[1#]

1.Department of Intensive Care Unit, Qingdao Hospital, University of Health, and Rehabilitation Sciences (Qingdao Municipal Hospital).

Address: No.5 Zhonghai East Road, Southern District, Qingdao City, Shandong Province, China.

Wang Yan: E-mail*keliven@163.net*

Qu Yan E-mail:*qdquyan@aliyun.com* #Qu Yan is the corresponding author.

2.Department of Emergency Medicine, Medical College of Qingdao University, Qingdao, Shandong, China;

Meng Haining: E-mail*menghaining0307@163.com*

*These authors contributed to the work eqully and should be regarded as co-first authors.

Abstract

CT imaging is often used to confirm COVID-19, playing a crucial role in the diagnosis and assessment due to its high sensitivity. The purpose of this study is to investigate results of quantitative CT analysis for CT patterns in SARS-CoV-2 infected patients, and how these relate to viral load and pathophysiological states. We recruited patients who had confirmed SARS-CoV-2 infection and undergone chest CT within 24 hours of confirmation. By quantitative CT analysis, and collecting clinical data, we explored correlations between those variables. Our research included 253 patients, after screening by exclusion criteria, 171 patients were included in final cohort. The incidence of SARS-CoV-2 associated pneumonia was 74.3%. The ROC test results showed AUCs for leukomonocyte count, and virus genes were 0.703, 0.562, 0.567, and 0.582, respectively. GGO pattern in CT was correlated PaO_2/FiO_2 ratio. Multiple linear regression results indicated GGO was associated with PaO_2/FiO_2. Meanwhile, the consolidation was correlated with $PaCO_2$ level. Additionally, consolidation was also associated with neutrophil–lymphocyte ratio. Conclusion: Lymphocyte count may be a potential marker for predicting SARS-CoV-2 pneumonia, independent of virus load. Additionally, GGO is correlated with hypoxia, while consolidation is associated with $PaCO_2$ levels and inflammation, which may affect aeration in the lungs.

Key words: Quantitative CT analysis, SARS-CoV-2 infection, GGO, consolidation, PaO_2/FiO_2 ratio, consolidation.

Introduction

The World Health Organization (WHO) has report (Available from:*https://covid19.who.int/.*) that pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread to 223 countries with more than 186 million confirmed cases and more than 4 million deaths[1]. This has become a public health issue of international concern until now. The proportion of hospitalized patients diagnosed with severe pneumonia and infected with SARS-CoV-2 who develop ARDS, based on oxygenation criteria, ranges from 20% to 67%[2, 3].

Computed tomography (CT) imaging is often used to confirm COVID-19 and plays a crucial role in the diagnosis and treatment assessment of COVID-19 due to its high sensitivity [4, 5]. The main characteristics of COVID-19 observed through CT imaging include bilateral pulmonary ground-glass opacity (GGO), a "crazy paving" pattern, airway changes, and a reversed halo sign. Other manifestations may include consolidation and interlobular septal thickening. GGO is the earliest and most prominent pulmonary abnormality observed, while consolidation appears in the later stages [6, 7]. Furthermore, several studies have indicated that CT features are associated with the level of plasma cytokines [8, 9], and even with the prognosis of pneumonia associated with SARS-CoV-2[6, 10]. Based on these results, we want to make it clear whether a heavy virus load could result in significant alteration in CT manifestation and quantitative CT analysis of different CT patterns can provide more information about patients to help clinicians make better clinical interventions. However, there are a few questions that need to be answered. First, there is limited research available that links the physiological, laboratory [such as arterial blood gas (ABG), complete blood count (CBC), etc.], and imaging features of patients with SARS-CoV-2[2]. Second, the understanding of CT imaging reports is subjective and relies on clinical experience. Therefore, it is necessary to clarify the relationship between CT patterns and pathophysiological states.

The purpose of this study is to investigate the results of quantitative CT analysis for different CT patterns in SARS-CoV-2 infected patients, and how these relate to viral load and pathophysiological states.

Method

Study population

The local ethics board has approved this cross-sectional clinical cohort study. Patients infected with SARS-CoV-2 who were in charge in Qingdao Hospital, University of Health, and Rehabilitation Sciences (Qingdao Municipal Hospital) from Jun. 9^{th} to 15^{th}, 2023 (the initial week of deblocking for isolation in Qingdao region, China) were eligible to participate in this research. SARS-CoV-2 was detected by polymerase chain

reaction (PCR) with a sample of throat swab or sputum specimen and the Cycle threshold (Ct) value below 40 was regarded as positive. Pneumonia was diagnosed according to the American Thoracic Society guidelines for community-acquired pneumonia[11]. The inclusion criteria was adult patients, who had a confirmed SARS-CoV-2 infection and undergone chest CT within 24 hours of admission. Patients with a.) history of pulmonary surgery; b.) thoracocyllosis or rib fracture; c.) pneumothorax with/without drainage; d.) Massive pleural effusion can't be analysis by CT; e.) clinical diagnosed pneumonia without PCR validation; f.) clinical data missing were excluded. According to CT manifestation, patients were divided into SARS-CoV-2 infection without pneumonia and pneumonia associated with SARS-CoV-2. Clinical data were extracted from the hospital information system (HIS), and CT raw data (The digital imaging and communications in medicine, DICOM files) for the final target patients were downloaded from the picture archiving and communication system (PACS) in Qingdao Hospital, University of Health, and Rehabilitation Sciences.

Clinical laboratory data

The medical records were reviewed to record the patient's medical history and interventions upon admission. The virus load was detected by the PCR Ct value of swab or sputum specimens for each patient. To describe the oxygenation situation and inflammatory response of these patients, results for ABG, fraction of inspired oxygen (FiO_2), method of oxygen inhalation, and CBC were recorded. The ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO_2/FiO_2 ratio) was also calculated. All laboratory records were collected within a 12-hour window around the date of the CT test.

CT examination protocol

CT examinations were performed using a multidetector scanner without the use of contrast medium for enhancement. Image raw data were collected by the Somatom Sensation 64 scanner (SIEMENS, Germany). The tube voltage used was 120 KV and the tube current was set to automatic. The pitch was 1.375 and the slice thickness was 5mm. All cases used the classic filtered back projection method with a soft tissue kernel of B20 and a lung kernel of B60. In all patients, a spiral acquisition was obtained from the apex to the bottom of the lungs at the stage of end inspiratory hold breathing. Coronal and sagittal multiplanar reconstructions were also available in all cases. The raw data were concluded into a 250-330 mm field of view and a 512×512 reconstruction matrix. The data were then downloaded, saved as DICOM files, and made available for analysis.

Imaging analysis

The CT scan data were analyzed by 3D slicer software[12] (version 5.0.3, *http://www.slicer.org/*) to estimate the affected lung area (GGO + consolidation + other patterns). The DICOM files were imported into a dedicated medical imaging software that includes a semi-automated segmentation algorithm for lung segmentation. Two senior doctors reviewed the results independently, without access to patients' clinical information such as therapy or primary disease. In case of discrepancies, consensus was reached after consulting to another senior radiologist, and the results were saved as regions of interest (ROI) for quantitative analysis. Chest CT scans measured the density of the pulmonary voxel within ROI in Hounsfield units (HUs). Depending on the range of HU, ROI was divided into ground-glass opacity (GGO) regions (-500HU to -100HU), consolidations (-100HU to 100HU), and others (aerated lung: <-500HU, *etc.*). Volumetric analysis and/or visualization in 3D Slicer via the Lung CT Analyzer project (*https://github.com/rbumm/SlicerLungCTAnalyzer/*) were performed. The total lung and affected volumes were estimated by reconstructing each marked slice using Lung CT Analyzer, a plug-in integrated into 3D Slicer[13]. (Data processing procedure was shown in Fig. 1).

(Fig. 1 Set here)

Statistics

CT data was analyzed by 3D Slicer software. GGO, consolidation, and the total lung volume were estimated. And the ratio for corresponding pattern to total lung volume were calculated. Statistics and graphing

were performed using R software (version 4.13,*https://www.r-project.org*) and extension packages. Continuous variables compared using the Mann-Whitney U test or t test. Continuous variables with Gaussian distribution were expressed as mean value ± standard deviation (mean ± *SD*), and skewed distribution as median (interquartile range, *IQR*). Categorical variables were expressed as a percentage (%). The Spearman correlation test was used for correlations between quantitative CT features versus laboratory findings. Receiver operating characteristic curve (ROC) were used to detect sensitivity and specificity for virus load to predict incidence of pneumonia events. The relationship between CT patterns and oxygenation, $PaCO_2$ level and inflammatory response were explored by using multiple linear regression. All statistical tests were two sided.$p<0{\cdot}05$ was considered statistically significant and analyses were done without any imputation for missing data.

Results

During the initial week of deblocking for isolation in Qingdao region, China, there were 253 patients admitted to Qingdao Hospital, University of Health, and Rehabilitation Sciences due to SARS-CoV-2 infection. According to exclusion criteria, there were 171 patients included in final cohort (The research flow chart was shown in Fig. 2).

(Fig. 2 set here)

A total of 3654 slice of CT pictures have been reviewed. The pneumonia event incidence was 74.3%. The FiO_2 was 0.6 (0.21–0.6), the PaO_2/FiO_2ratio 160mmHg (50–237mmHg), and the $PaCO_2$ was 38.6mmHg (21.7–41.8mmHg). Neutrophil counting was 7.52×10^9/L (1.19–10.44×10^9/L), leukomonocyte was 0.77×10^9/L (0.1–1.26×10^9/L), mononuclear macrophage counting was 0.48×10^9/L (0.08–0.68×10^9/L), and the C reaction protein was 19.56mg/L (0.59–47.60mg/L), among these patients. The clinical baseline data were listed in Table 1.

(Table 1 set here)

The PCR results contains nucleocapsid protein (N) gene and open reading frame (ORF) gene. N gene Ct value was 30 (18–34), and ORF gene was 33 (20–36).The median of total lung volume was 3088ml (1055–3809ml), GGO pattern was 833ml (392–1047ml) and its corresponding ratio to total lung was 30.3% (8.1%–40.3%); while the consolidation pattern was 186ml (63–316ml), the ratio was 7.2% (1.7%–11.4%); the affected lung was 1045ml (482–1359ml), and the ratio was 39% (10%–55%). ROC test results showed the area under the curve (AUC) for N gene, ORF gene, leukomonocyte count, N gene + leukomonocyte count, and ORF gene + leukomonocyte count were 0.562, 0.567, 0.703, and 0.582, respectively when adjusted with age, gender, and C reaction protein level ($p<0.05$ results are shown in Fig. 3).

(Fig. 3 set here)

In the pneumonia associated with SARS-CoV-2 group (n = 127), we found that the GGO ratio was correlated with FiO_2, PaO_2/FiO_2 ratio (r= 0.59, -0.58; $p<0.01$, respectively). Although the consolidation ratio associated with FiO_2, PaO_2/FiO_2 ratio (r = 0.32, -0.39;$p<0.01$, respectively), the strength of correlation was weaker when compared with GGO. Multiple linear regression result indicated that GGO ratio was associated with PaO_2/FiO_2(β= -3.0, $p<0.01$; R^2 = 0.4,$p_{\text{for model}}<0.01$) when adjusted with consolidation ratio (β= -0.85, $p=0.25$), Age (β = -0.98, $p=0.08$), Gender (β = 4.10, $p=0.73$), hemoglobin level (β = 0.15, $p=0.54$), and D-Dimer level (β = 0.03,$p=0.58$); while the consolidation ratio was correlated with $PaCO_2$ level (β = 0.43, $p<0.01$;R^2 = 0.28, $p_{\text{for model}}<0.01$) when adjusted with GGO ratio (β = -0.1, $p=0.98$), Age (β = -0.037, $p=0.57$), Gender (β = -3.5, $p=0.01$), hemoglobin level (β = 0.008, $p=0.77$), and D-Dimer level (β = -0.001, $p=0.80$). Additionally, the consolidation ratio (β = 0.692, $p<0.01$)) also associated with neutrophil–lymphocyte ratio (NLR) when adjusted with GGO ratio (β = 0.003, $p=0.99$) (The results of multiple linear regression were demonstrated in Fig.4.)

(Fig. 4 set here)

Discussion

We included a total of 171 patients with SARS-CoV-2 infection in this retrospective study. The incidence of pneumonia associated with SARS-CoV-2 was 71.8%. Our findings suggested that lymphocyte count was a more reliable indicator for predicting pneumonia in patients infected with SARS-CoV-2, compared to viral load. Additionally, CT analysis of pneumonia patients showed that the percentage of ground-glass opacity (GGO) pattern in CT scans strongly correlated with the hypoxia level of patients, while consolidation pattern was associated with $PaCO_2$ level.

Although the lymphocyte was proved to be a strong indicator for severity of SARS-CoV-2 infection in medical fundamental studies, our findings confirm that it is the lymphopenia (lymphocyte count $<1.0*10^9$/L) of the patients is the potential predictor and associated with the developing into pneumonia, instead of viral load from the aspect of clinic. Cytotoxic lymphocytes, such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, are essential for controlling viral infections. The functional exhaustion of cytotoxic lymphocytes is correlated with disease progression[14].*Zheng* [15] *et al.* found that patients with SARS-CoV-2 infection had a significantly decreased total number of NK and $CD8^+$ T cells. Additionally, the function of NK and $CD8^+$ T cells was found to be exhausted, with increased expression of NKG2A in COVID-19 patients. However, during the convalescence period, the number of NK and $CD8^+$ T cells was restored, which suggests that the functional exhaustion of cytotoxic lymphocytes is associated with SARS-CoV-2 infection. Results of *Qiong et al.* research[16] indicated compared to mild infected patients, the blood counts of patients in the severe group showed lymphopenia (lymphocyte count $<1.0\times10^9$/L). Moreover, the enriched annotations of differential genes that were incrementally downregulated from the healthy control group to severe group were mostly related to T cell functions. These functions include T cell receptor signaling and antigen receptor-mediated signaling pathways. Consist with results above, our findings indicated lymphopenia could be a strong predictor of SARS-CoV-2 pneumonia dependently from virus load. In some cases, and certain serial reports [17, 18], the findings of CT and RT-PCR may be incongruous, which can corroborate our results to some extent.

Furthermore, in the pneumonia cohort, CT patterns appear to be associated with different pathophysiological changes. Up to now, there are bench of studies to discuss the diagnostic potential of CT score or quotative CT analysis for Covid-19 pneumonia[6, 17, 18]. To our limited knowledge, there has been negligible research investigating the relationship between CT patterns and pathophysiological changes. Our research indicates that GGO patterns are associated with the degree of hypoxia, while consolidation patterns are related to high levels of $PaCO_2$. GGO pattern are the most common initial findings in COVID-19 pneumonia[7, 19]. GGOs are a type of abnormality seen on a chest imaging test like a CT scan or an X-ray. They are characterized by a hazy area of increased density in the lung tissue, which looks like ground glass[19]. In COVID-19 pneumonia, these GGOs can appear in both lungs and are usually located in the peripheral regions.*Damiano Caruso et al.* [6] included 136 Covid-19 patients and analysis their CT, finding that GGO alterations on chest CT scans could help identify patients with COVID-19 (AUC 0.661, cutoff 0.39 L, 68% sensitivity and 59% specificity,$p < 0.001$). Our data proved that GGO pattern ratio was strongly associated with hypoxia when adjusted with consolidation pattern ratio, a possible explanation could be that pulmonary edema and hyaline membrane formation are considered potential pathological driving forces behind GGO, which has been confirmed by postmortem biopsy of a COVID-19 patient[20]. On the contrary, the resolution of GGOs may indicate an improvement in the patient's condition[21, 22]. Another study showed that patients who exhibited GGO had significantly higher levels of IL-2, IL-4, and INF-γ compared to those who did not exhibit GGO[9]. Additionally, we found that the consolidation ratio was positively corelated with $PaCO_2$ level though take GGO ratio into consideration. As COVID-19 progresses, GGOs may increase in size and merge with other GGOs, eventually evolving into fibrous streaks and solid nodules, which contributed the consolidation ratio. Recently studies showed that consolidation also common pattern in the late stage of COVID-19[20, 21]. Consolidation was one of mechanism of "baby lung" for ARDS, which could result in decreasing of lung volume, also affect ventilation[23, 24]. Hypercapnia was common symptom in late ARDS stage no matter cased by SARS-CoV-2 infection or classic pythons[25, 26].

Furthermore, our research observed a correlation between consolidation and NLR. NLR reflects the balance between two aspects of the immune response: (i) the innate response, primarily mediated by neutrophils,

and (ii) adaptive immunity, supported by lymphocytes. It has been reported that an elevated NLR is often observed in conditions that involve tissue damage and activate the systemic inflammatory response, such as bacterial and fungal infections, sepsis, acute stroke, atherosclerosis, myocardial infarction, severe trauma, and cancer[27, 28]. Recently, studies revealed that NLR can predict clinical outcomes and plays as an easy-to-obtain biomarker to evaluate severity for Covid-19 patients[29, 30]. A multicenter retrospective cohort study from France investigated the prognostic value of the NLR for disease severity and mortality in 1035 COVID-19 patients[31]. The NLR at admission to the emergency department was found to have a predictive ability for disease severity (area under the curve (AUC), 0.59; cut-off value, 6.88; sensitivity, 48%; specificity, 66%) and disease mortality (AUC, 0.62; cut-off value, 8.23; sensitivity, 47%; specificity, 72%). Consolidation pattern always emerge in the late stage of illness progress and could be regarded as the evolving form for GGO[4, 22]. That could be a potential explanation for our finding.

Analysis is affected by skill and experience of radiologist and clinical physician in image interpretation, whereas quantitative evaluation is a reproducible and comparable technique. With this information, we can begin to hypothesize that as the illness progresses, the GGO evolves into a consolidation pattern, and hypoxia develops into hypercapnia, and clinical outcome may getting worsen. The appearance of consolidation patterns could be a sign of worsening lung function. By understanding the relationship between CT patterns, oxygenation, and inflammation, we can gain more insight into the disease process and develop better strategies for diagnosis and treatment, especially for intubating and ventilation timing, strength of anti-inflammation *etc.*

However, our study has several limitations. Firstly, we did not discuss the relationship between CT patterns and clinical outcomes. The present study focuses on the immediate associations between CT patterns and oxygenation, as well as the PCR test for SARS-CoV-2, to reveal the potential clinical significance of CT patterns. We aim to address this in our future studies. Secondly, the mechanics of ventilation were not involved in the present research. Some patients recruited in the cohort applied high-flow oxygen or non-invasive ventilation, and it was impossible for us to collect this data. Thirdly, although the sample size evaluation was performed, a larger sample size would make the present findings more convincing.

Conclusion

In conclusion, the present study suggests that lymphocyte count may be a potential marker for predicting SARS-CoV-2 pneumonia, independent of virus load. Additionally, ground-glass opacity (GGO) manifested in CT scans is correlated with hypoxia, while consolidation is associated with PaCO2 levels and inflammation, which may affect aeration in the lungs.

List of abbreviations

GGO: ground glass opacity, CT: computed tomography, PCR: polymerase chain reaction, WHO: According to World Health Organization, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, ABG: arterial blood gas, CBC: complete blood count.

Data availability statement

Data and materials supporting the findings of this manuscript are available from the corresponding authors upon request.

Funding statement

This research received no external funding.

Conflict of interest disclosure

The author confirms that the work described has not been published before; it is not under consideration elsewhere; the publication has been approved by all co-authors and all co-authors agreed to publication in this journal. All the authors declare no conflict of interest and agree to publication.

Ethics approval statement

The studies involving human participants were reviewed and approved by the Ethics Review Form for Medical Research and Clinical Technology Application and Ethics Committee of Qingdao Hospital, University of Health, and Rehabilitation Sciences.

Patient consent statement

The patients/participants provided their written informed consent to participate in this study. All the associated materials involved in the present research are in accordance with the Declaration of Helsinki.

Permission to reproduce material from other sources.

Not Applicable

Author contributions

QY and WY conceived, designed, and supervised the study, and WY, MHN wrote the drafts of the manuscript. WSM participated in the data recording, JC, LZY and XWF finalized the analysis. All the authors read and approved the final manuscript, and the authors contributed to the article and approved the submitted version.

Acknowledgments

This study was supported by Xu Zhipeng, radiologist from the Radiography Department of Qingdao Hospital, University of Health, and Rehabilitation Sciences (Qingdao Municipal Hospital).

References

1. Yazdi NA, Ghadery AH, SeyedAlinaghi S, Jafari F, Jafari S, Hasannezad M, Koochak HE, Salehi M, Manshadi SAD, Meidani M *et al* : Predictors of the chest CT score in COVID-19 patients: a cross-sectional study. *Virol J* 2021, 18(1):225.

2. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, Laffey J, Carrafiello G, Carsana L, Rizzuto C *et al* : Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* 2020, 8(12):1201-1208.

3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al* : Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.*Jama* 2020, 323(11):1061-1069.

4. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L: Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020, 296(2):E32-e40.

5. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J: Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020, 296(2):E41-e45.

6. Caruso D, Polici M, Zerunian M, Pucciarelli F, Polidori T, Guido G, Rucci C, Bracci B, Muscogiuri E, De Dominicis C *et al* : Quantitative Chest CT analysis in discriminating COVID-19 from non-COVID-19 patients. *Radiol Med* 2021, 126(2):243-249.

7. Ye Z, Zhang Y, Wang Y, Huang Z, Song B: Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* 2020, 30(8):4381-4389.

8. Carbonell G, Del Valle DM, Gonzalez-Kozlova E, Marinelli B, Klein E, El Homsi M, Stocker D, Chung M, Bernheim A, Simons NW *et al* : Quantitative chest computed tomography combined with plasma cytokines predict outcomes in COVID-19 patients. *Heliyon* 2022, 8(8):e10166.

9. Wu Z, Liu X, Liu J, Zhu F, Liu Y, Liu Y, Peng H: Correlation between ground-glass opacity on pulmonary CT and the levels of inflammatory cytokines in patients with moderate-to-severe COVID-19 pneumonia.*Int J Med Sci* 2021, 18(11):2394-2400.

10. Oi Y, Ogawa F, Yamashiro T, Matsushita S, Oguri A, Utada S, Misawa N, Honzawa H, Abe T, Takeuchi I: Prediction of prognosis in patients with severe COVID-19 pneumonia using CT score by emergency physicians: a single-center retrospective study. *Sci Rep* 2023, 13(1):4045.

11. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA *et al* : Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*2019, 200(7):e45-e67.

12. Lanza E, Muglia R, Bolengo I, Santonocito OG, Lisi C, Angelotti G, Morandini P, Savevski V, Politi LS, Balzarini L: Quantitative chest CT analysis in COVID-19 to predict the need for oxygenation support and intubation. *Eur Radiol* 2020, 30(12):6770-6778.

13. Hofmanninger J, Prayer F, Pan J, Röhrich S, Prosch H, Langs G: Automatic lung segmentation in routine imaging is primarily a data diversity problem, not a methodology problem. *Eur Radiol Exp*2020, 4(1):50.

14. Zhang C, Wang XM, Li SR, Twelkmeyer T, Wang WH, Zhang SY, Wang SF, Chen JZ, Jin X, Wu YZ *et al* : NKG2A is a NK cell exhaustion checkpoint for HCV persistence. *Nat Commun* 2019, 10(1):1507.

15. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z: Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020, 17(5):533-535.

16. Zhang Q, Meng Y, Wang K, Zhang X, Chen W, Sheng J, Qiu Y, Diao H, Li L: Inflammation and Antiviral Immune Response Associated With Severe Progression of COVID-19. *Front Immunol* 2021, 12:631226.

17. Caruso D, Pucciarelli F, Zerunian M, Ganeshan B, De Santis D, Polici M, Rucci C, Polidori T, Guido G, Bracci B *et al* : Chest CT texture-based radiomics analysis in differentiating COVID-19 from other interstitial pneumonia. *Radiol Med* 2021, 126(11):1415-1424.

18. Caruso D, Zerunian M, Polici M, Pucciarelli F, Guido G, Polidori T, Rucci C, Bracci B, Tremamunno G, Laghi A: Diagnostic performance of CT lung severity score and quantitative chest CT for stratification of COVID-19 patients. *Radiol Med* 2022, 127(3):309-317.

19. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA *et al* : CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020, 295(1):202-207.

20. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L *et al* : Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020, 8(4):420-422.

21. Duan YN, Qin J: Pre- and Posttreatment Chest CT Findings: 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020, 295(1):21.

22. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, Hu Q, Xia L: Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol* 2020, 30(6):3306-3309.

23. Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L: The "baby lung" became an adult. *Intensive Care Med* 2016, 42(5):663-673.

24. Gattinoni L, Pesenti A: The concept of "baby lung". *Intensive Care Med* 2005, 31(6):776-784.

25. Ding X, Chen H, Zhao H, Zhang H, He H, Cheng W, Wang C, Jiang W, Ma J, Qin Y *et al* : ECCO(2)R in 12 COVID-19 ARDS Patients With Extremely Low Compliance and Refractory Hypercapnia. *Front Med (Lausanne)* 2021, 8:654658.

26. Gendreau S, Geri G, Pham T, Vieillard-Baron A, Mekontso Dessap A: The role of acute hypercapnia on mortality and short-term physiology in patients mechanically ventilated for ARDS: a systematic review and meta-analysis. *Intensive Care Med* 2022, 48(5):517-534.

27. Buonacera A, Stancanelli B, Colaci M, Malatino L: Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. *Int J Mol Sci* 2022, 23(7).

28. Parosanu AI, Pirlog CF, Slavu CO, Stanciu IM, Cotan HT, Vrabie RC, Popa AM, Olaru M, Iaciu C, Bratu LI *et al* : The Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Patients with Metastatic Renal Cell Carcinoma. *Curr Oncol* 2023, 30(2):2457-2464.

29. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, Pelosi P, Rocco PRM: Laboratory Biomarkers for Diagnosis and Prognosis in COVID-19.*Front Immunol* 2022, 13:857573.

30. Piovani D, Tsantes AG, Bonovas S: Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Patients with COVID-19. *J Clin Med* 2022, 11(16).

31. Abensur Vuillaume L, Le Borgne P, Alamé K, Lefebvre F, Bérard L, Delmas N, Cipolat L, Gennai S, Bilbault P, Lavoignet CE *et al* : Neutrophil-to-Lymphocyte Ratio and Early Variation of NLR to Predict In-Hospital Mortality and Severity in ED Patients with SARS-CoV-2 Infection. *J Clin Med* 2021, 10(12).

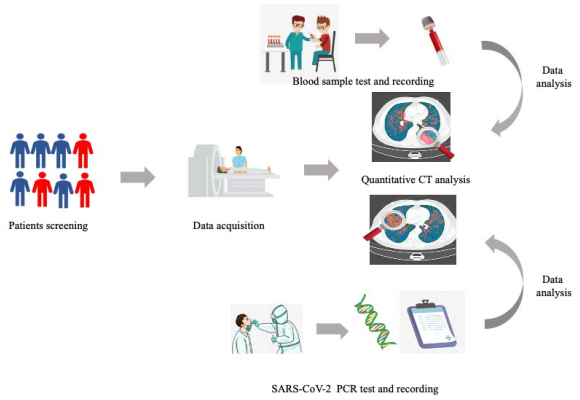

Fig.1 Data processing flow.

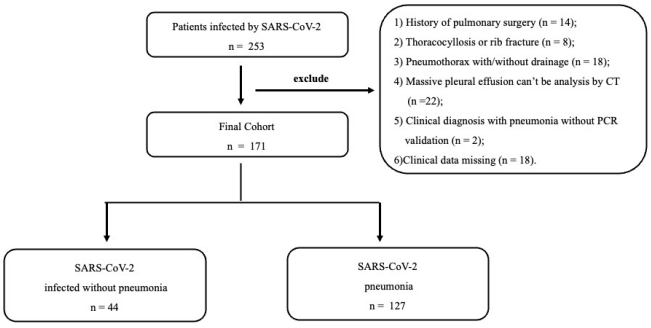

Fig.2 Patients screening flow chart.

Table 1 The baseline data of the final cohort

	SARS-CoV-2 infection n = 171	SARS-CoV-2 pneumonia n = 127
Age, year	80 (72–86)	80 (72–85)
Gender, male (%)	112 (65.5)	77 (60.6)
Laboratory test		
N gene Ct value	30 (27–34)	30 (26–33)
ORF gene Ct value	33 (29–36)	33 (28–36)
	7.5 (5.4–10.4)	7.9 (5.5–10.8)
Neutrophil, $\times 10^9$/L		
Lymphocyte, $\times 10^9$/L	0.8 (0.5–1.0)	0.7 (0.4–1.2)
NLR	9.9 (5.1–18.4)	10.9 (5.9–19.8)
Hemoglobin,g/L	112 (92–129)	109 (92–129)
Thrombocyte, $\times 10^9$/L	177 (138–256)	177 (121–256)
CRP, mg/dL	19.7 (0.6–47.6)	26 (5.8–48.4)
D-Dimer, mg/L	2.2 (0.6–6.0)	2.5 (0.8–6.8)
FiO_2	0.8 (0.4–1.0)	0.6 (0.6–1.0)
PaO_2, mmHg	88 (70.7–103.1)	90 (69.6–103)
PF ratio, mmHg	158 (122.7–253.9)	146.7 (112.7–176.6)
$PaCO_2$, mmHg	38.6 (34.5–56.1)	39 (33–52.7)
Quantitative CT analysis		
Total lung volume, ml	3088 (2287-3808)	2874 (2274–3644)
GGO volume, ml	833 (654.5–10)	1480 (907.5–2280)
GGO ratio (%)	30.3 (21.1–40.3)	54 (40–63.5)
Consolidation volume, ml	186 (128.5–315.5)	236 (154–349)
Consolidation ratio (%)	7.2 (3.8–9.7)	8.8 (4.5–14.5)

N gene: nucleocapsid protein gene, ORF gene: open reading frame gene, NLR: Neutrophil to Lymphocyte ratio, PF ratio: PaO_2/FiO_2 ratio, GGO: ground glass opacity

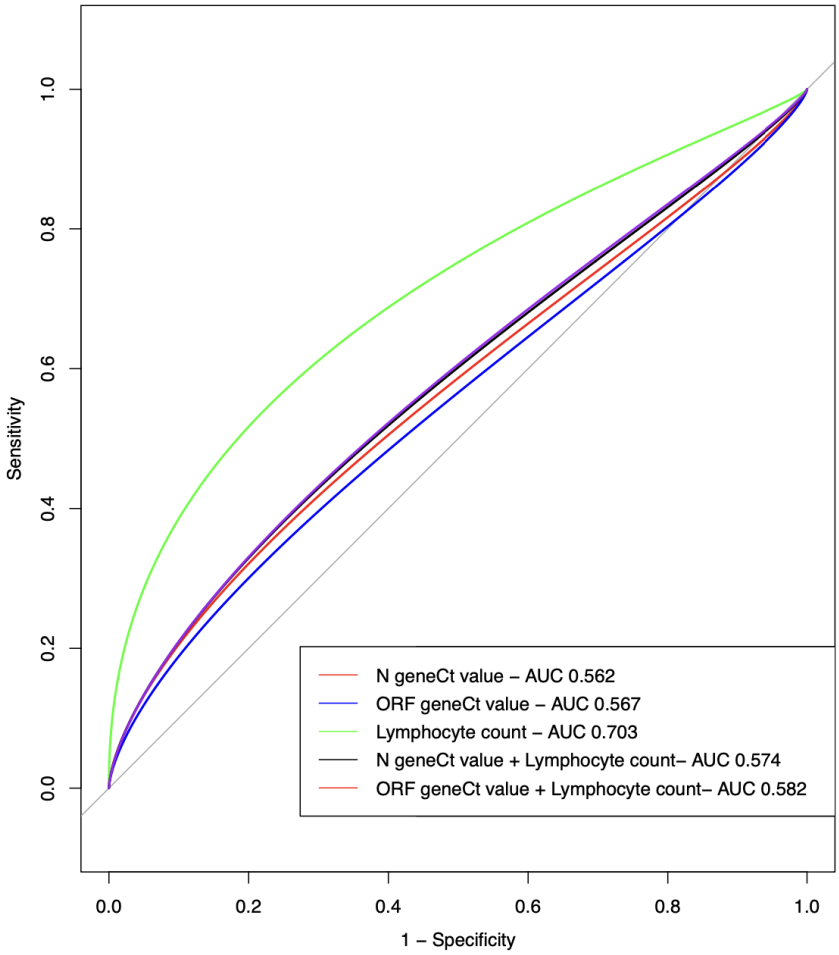

Fig.3 ROC of virus load, lymphocyte count and both combining for predicting pneumonia event.

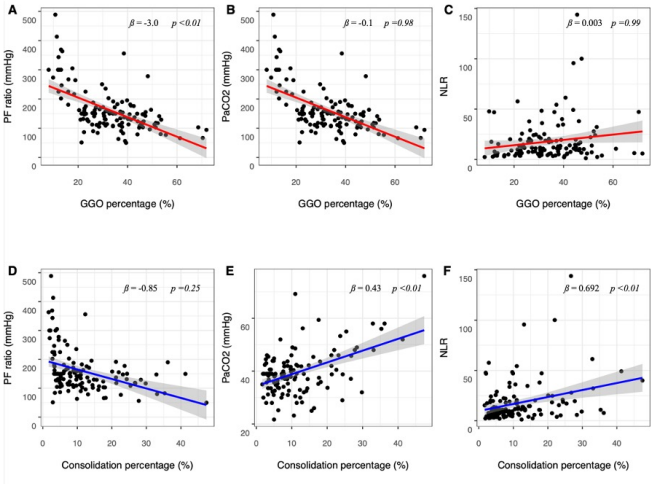

Fig.4 The results of multiple linear regression between PF ratio (PaO_2/FiO_2), $PaCO_2$, neutrophil–lymphocyte ratio (NLR) and GGO, consolidation patterns, adjusted by age, gender, hemoglobin, D-Dimer.