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Quantitative Evaluation of the Severity Index of Lung Parenchymal Involvement in Covid 19 Disease by Computed Tomography and its Relation to Biochemical Parameters

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Abstract

Introduction: COVID-19 has profoundly impacted global health systems since its emergence in 2019. The association between various biomarkers and COVID-19 has been investigated, with a particular focus on CRP, ferritin, fibrinogen, and D-dimer levels. Although these biomarkers alone are not diagnostic for COVID-19, their elevation is associated with disease severity and prognosis. In recent years, new horizons have opened in radiology with artificial intelligence and computer software that can obtain quantitative or semi-quantitative data. Instead of visually subjective data scales, technological developments that can now provide clearer numerical data are taking place in our lives. Options include lesion detection, determination of morphological characteristics, 3D volumetric imaging, and segmentation. The 3D slicer program is completely open free software that can be used to obtain this data and has many medical patch support programs. This study aimed to quantitatively evaluate lung parenchymal involvement in COVID-19 patients using 3D Slicer software and correlate it with biochemical parameters.

Materials and Methods: In this retrospective analysis of 213 hospitalized patients with COVID-19 pneumonia, this study evaluated CRP, ferritin, and their ratios for disease severity and lung involvement potential. Examining gender differences in biochemical parameters.

Results: According to the study results, the study included 54.5% males and 45.5% females. Mean CRP levels were significantly higher in males (88.74±75.78) than in females (68.26±66.07) ($p=0.034$). Ferritin levels were significantly higher in males than in females ($p<0.001$). CRP, ferritin, and fibrinogen levels were correlated with lung involvement, indicating prognostic potential.

Conclusion: The findings underscore the importance of biochemical markers in assessing disease severity and highlight gender-specific differences in COVID-19 management. However, no significant correlation was found between the ferritin/CRP ratio and lung involvement rates. These insights provide personalized strategies for pandemic control.

Key words: Covid 19; Computerized Tomography; 3D Slicer; Ferritin/CRP; D-dimer/Fibrinogen

Introduction

COVID-19, also known as coronavirus disease 2019, is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, China, and has since spread globally, leading to a pandemic. SARS-CoV-2 is spread primarily through respiratory droplets and close contact with infected people (1). Common symptoms include fever, cough, fatigue and shortness of breath, although some infected individuals may be asymptomatic (1,2).

The global pandemic had a profound impact on society, with significant disruption to travel, trade, education and health systems. In response to the crisis, a range of measures were implemented to control the spread of the disease, including social distancing, mask-wearing and vaccination campaigns (3,4).

CRP: C-reactive protein (CRP) is a biomarker indicative of COVID-19 infection. Patients with COVID-19 exhibit elevated levels of CRP, a protein that increases in response to inflammation and infection. Although elevated CRP levels can be indicative of inflammatory diseases, including COVID-19, they lack specificity and can be elevated due to other infections and inflammatory conditions. In COVID-19 patients, CRP levels can offer valuable information regarding the severity and prognosis of the disease; however, they are not employed for diagnostic or monitoring purposes. Evaluated alongside other clinical findings and test results, CRP can aid in the comprehensive management of the disease (5,6).

Ferritin: COVID-19 infection is associated with ferritin, a protein responsible for iron storage, which may increase during infection and

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inflammation. Although elevated ferritin levels are commonly observed in COVID-19 patients, high ferritin levels are not specific to this condition and can also occur due to other inflammatory conditions and infections. Therefore, ferritin levels alone cannot be relied upon for COVID-19 diagnosis. Although ferritin levels are not used directly in diagnosing or treating COVID-19, they provide valuable insights into disease management when considered alongside other clinical findings and tests. Integrating biomarkers like ferritin with other diagnostic and therapeutic approaches offers a comprehensive strategy for disease management (7,8,9).

Fibrinogen: COVID-19 infection is associated with fibrinogen, a protein essential for blood clotting that may increase during infection and inflammation. Elevated fibrinogen levels are often observed in COVID-19 patients, which could help assess the severity and prognosis of the disease (9,10). However, high fibrinogen levels are not exclusive to COVID-19 infection, as other inflammatory conditions and infections can also lead to elevated levels. Therefore, fibrinogen levels alone cannot serve as a definitive diagnostic marker for COVID-19 infection (9,10). Although fibrinogen levels do not directly contribute to the diagnosis or treatment of COVID-19, they can aid in disease management when considered alongside other clinical findings and test results.

D-dimer: The correlation between COVID-19 infection and D-dimer has been established. D-dimer, a byproduct of fibrin breakdown, tends to increase during infections and inflammations. Elevated D-dimer levels are often observed in COVID-19 patients, indicating disease severity and prognosis. However, elevated D-dimer levels are not specific to COVID-19; other inflammatory conditions and infections can also result in increased levels. Therefore, D-dimer alone cannot definitively diagnose COVID-19. Although not employed for diagnosis or treatment, D-dimer assessment alongside other clinical findings and tests can inform disease management. Integrating D-dimer with other biomarkers and diagnostic methods enhances our comprehensive understanding and facilitates disease management. (11,12).

Thrombosis: The thrombosis triggered in COVID-19 patients is distinct from that in individuals without the disease. This is primarily due to the hyperinflammatory response and hypercoagulable state caused by direct viral infection of the vascular endothelium (13,14). This predisposes patients to thrombosis and coagulation disorders, leading to fatigue (15). However, there are limited biochemical markers that reflect COVID-19-related coagulation issues (16).

Ferritin/CRP ratio: The ratio of CRP to albumin, known as the CRP/albumin ratio, serves as a biomarker in inflammatory and infectious diseases, particularly in acute inflammatory conditions such as COVID-19 (17,18,19). Albumin is a protein that the body utilizes to combat infections, and low levels of it can indicate inflammation and infection. Conversely, CRP is a protein that rises during infection and inflammation (17,18,19). The CRP/albumin ratio is utilized as a more sensitive biomarker in inflammatory and infectious conditions, with high ratios indicating more severe conditions, while low ratios may suggest milder conditions or normal health (17,18,19). In COVID-19 patients, the CRP/albumin ratio is used to assess the severity and prognosis of the condition, but it should not be solely relied upon for a definitive diagnosis. Instead, it should be considered alongside other clinical findings and test results (17,18,19). The ferritin/CRP ratio could act as a more sensitive biomarker in cases of inflammation and infection. Elevated ferritin/CRP ratios indicate more severe infection and inflammation, whereas lower ratios may suggest milder infection and inflammation or normal health status (17,18,19). Likewise, the ferritin/CRP ratio has been utilized as an indicator of infection severity and prognosis, especially in COVID-19 patients. However, its interpretation should consider other clinical findings and test results (17,18,19).

3D Slicer: 3D Slicer is a free and open source software package used for medical image analysis and visualisation. It was developed by the National Alliance for Medical Image Computing (NA-MIC) and is distributed under a BSD-style open source licence. The software is designed to support a variety of medical imaging modalities, including CT, MRI, ultrasound and microscopy (20,21,22). The name "3D Slicer" comes from its ability to take volumetric data from medical images and "slice" it into two-dimensional images. The software allows users to interactively segment and label regions of interest in the images, generate 3D surface models and perform quantitative analysis (20,21,22). One of the key features of 3D Slicer is its ability to integrate with other software packages and extensions, allowing users to customise the software to meet their specific needs. There are numerous extensions available for 3D Slicer, including tools for image registration, diffusion tensor image analysis and image-guided surgery (20,21,22). 3D Slicer has

been widely adopted by the medical imaging research community and has been used in a variety of applications including neuroimaging, cardiology and radiotherapy planning. It has also been used in the development of medical devices and surgical planning (20,21,22). Overall, 3D Slicer is a powerful and flexible tool for medical image analysis and visualisation, with a wide range of capabilities and a large community of users and developers supporting its ongoing development and improvement (20,21,22). In our study, we investigated whether the ferritin/CRP ratio could be used to grade inflammation in the same way as the CRP/albumin ratio. In our study, thoracic segmentation is performed using the Chest Imaging Platform with semi-automated segmentation methods using the 3D Slicer, and areas of parenchymal involvement, including infiltrated areas and normal aerated parenchymal areas, are determined and calculated using the Hounsfield threshold. In addition, we investigated whether there was a relationship between the ratios obtained and the percentage of lung parenchyma involvement.

Materials and Methods

This study, conducted between January 2020 and December 2022 in a tertiary care hospital, was a retrospective analysis of 213 patients aged 18-95 years who were selected randomly from those with Covid pneumonia and received inpatient treatment with PCR (+). In this study, non-contrast thoracic computed tomography (CT) was examined with 5 mm thick sections and images obtained in the lung parenchyma and mediastinal windows after 2.5 mm reconstructions. Biochemical parameters such as CRP, ferritin, fibrinogen, D-dimer, ferritin/CRP ratio were also obtained. Thorax CT examinations were evaluated simultaneously with the patient's biochemistry data and with the examinations performed within a maximum of 2 days. Thoracic CT examinations were performed using the 3D Slicer program version 5.0.2, with lung parenchyma images obtained through the application of the Lung CT Segmenter and Lung CT Analyzer on the Chest Imaging Platform. The lung CT Segmenter can be obtained through either the placement of a few markups on the lung or the utilization of a deep-learning lung and lobe segmentation algorithm. This tool also supports sensitive and manually assisted airway segmentation. The segmentation of the air lumens of the right and left lung parenchyma, trachea, both main bronchi, and segmental-subsegmental bronchi was achieved through this process.

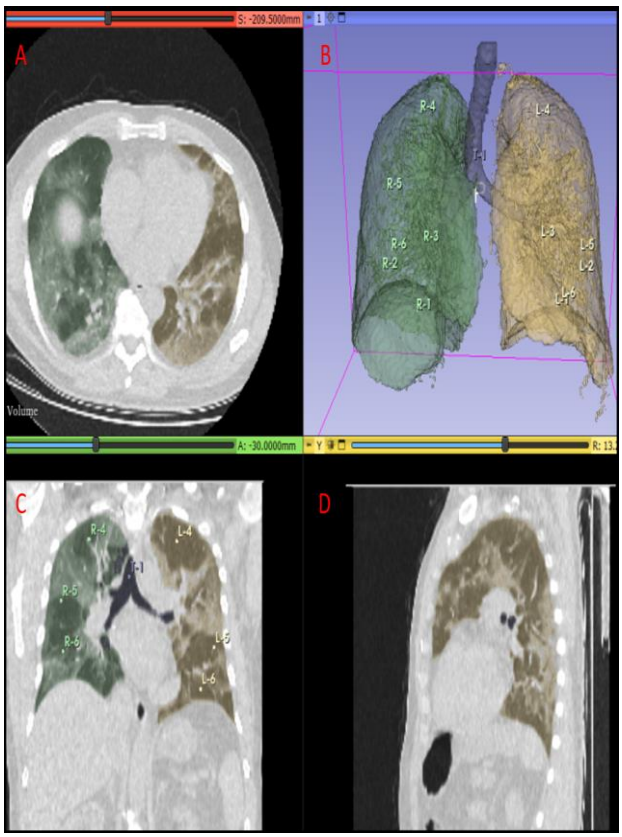

Figure 1: Both lung parenchyma segmentation and 3D volume. **A:** Axial CT scan section of the lungs showing two regions with green and brown tones. **B:** 3D reconstruction of the lungs with color-coded segmentation. **C:** Coronal CT scan section of the lungs showing two regions with green and brown tones and also showing the markups. **D:** Sagittal CT scan section of the lungs showing two regions with green and brown tones.

The total ventilation volume of the lung parenchyma was determined using this method (Figure 1). The Lung CT Analyzer is a software extension of the 3D Slicer platform, specifically designed for the analysis of lung CT scans. This tool provides visual assessment of the extent of pulmonary infiltration, ground-glass opacity, consolidation, and emphysema. However, the inability to quantify abnormalities in numbers or milliliters makes it challenging to compare results objectively. The ongoing COVID-19 pandemic has resulted in a high number of patients with severe lung infiltrations, necessitating careful monitoring over time. On the volumetric sections obtained, threshold intervals were created according to HU values, and the areas showing involvement with different HU values in the lung parenchyma were reprocessed and coded with different color tones in the total parenchyma.

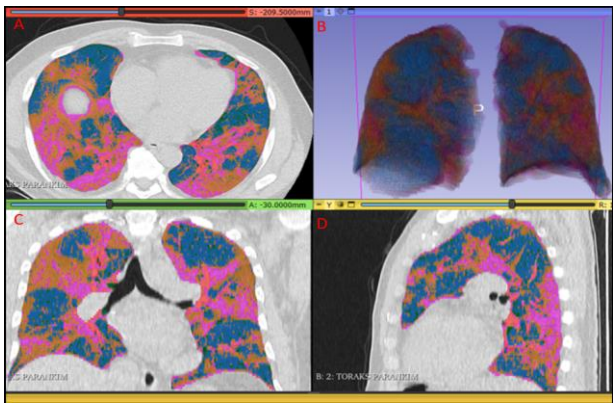

Figure 2: Regional colour coding and volumetric analysis of lung parenchyma according to HU values. **A:** Axial CT scan presenting the lungs with color-coded regions that indicate the distribution of varying HU values within the lung parenchyma, offering insight into the extent and pattern of involvement. **B:** 3D volumetric rendering of the lungs with the entire parenchyma color-coded according to the HU values, giving a comprehensive view of the distribution of different tissue densities. **C-D:** Coronal and sagittal CT scan of the lungs with multiple regions color-coded based on different HU values, highlighting variations in tissue density across the lung parenchyma

Figure 2) Threshold adjustments, Bulla/emphysema - 1050>x>-990 HU, inflated areas -990>x>-650 HU, infiltrated areas -650>x>-400 HU, collapsed areas -400>x>0 HU ranges were determined and 3D slicer programme standards were accepted (Figure 3).

Ethical consent: The study was approved by the ethics committee with protocol number SÜKAEK-2022/2/5.

Statistical analysis: SPSS (version 22.0, SPSS Inc.) was utilized for the statistical analysis of the data. The Kolmogorov-Smirnov test was applied to determine if the data followed a normal distribution. Continuous variables that followed a normal distribution were expressed as mean ± standard deviation, while continuous variables that did not follow a normal distribution were expressed as median (IQR, Q1-Q3), and categorical variables were expressed as number (n) and percentage (%). The Mann-Whitney U test was used to compare two independent groups that did not follow a normal distribution, and the Kruskal-Wallis test was used to compare more than two groups. The Spearman correlation test was used for correlation analysis, and the chi-square test was used to compare categorical variables. A statistical significance level was considered as %5.

Lung Area	Total lung volume (ml)	Inflated (ml)	Inflated (%)	Emphysema (ml)	Emphysema (%)	Infiltrated (ml)	Infiltrated (%)	Collapsed (ml)	Collapsed (%)	Affected (ml)	Affected (%)
Total lung	3564	1117	31	183	5.1	1439	40.4	825	23.1	2264	64
Right lung	1855	615	33	90	4.9	803	43.3	437	23.6	1240	67
Left lung	1709	682	40	93	5.4	636	37.2	388	22.7	1024	60

Figure 3: The results of the example for the quantitative assessment of the lung parenchyma

Table 1: Biochemical parameters and calculated lung involvement rate

Variables	Mean ± SD	Median (Q1-Q3)
Age (year)	58.63±16.02 (18-95)	60(46-72)
CRP (mg/dl)	79.41±72.09 (1-405)	62(19.7-114)
Ferritin/CRP (mg/dl)	21.36±86.07 (0.29-1184)	6.68(31.17-16.05)
Ferritin (mg/dl)	498.83±444.1 (8-2000)	380(167-694)
Fibrinogen (mg/dl)	451.1±114.44 (31-757)	463(378-534)
D-dimer (mg/dl)	1.64±4.06 (0.1-35.2)	0.6(0.37-1.2)
Right lung covid infiltration (%)	34.1±18.01 (6-86)	31(19-46)
Left lung covid infiltration (%)	34.45±18.79 (6-89)	31(20-45)
Total lung covid infiltration (%)	34.15±17.77 (6-85)	31(20-46)

Results

The study included 213 patients, comprising 116 men (54.5%) and 97 women (45.5%), all of whom were hospitalised with confirmed cases of COVID-19 (+) pneumonia. The mean age of the patients was 58 years, with no statistically significant age difference between the genders (p=0.626). The mean and median values of the biochemical parameters assessed, as well as the calculated lung involvement rates, are presented in Table 1. Upon gender-based evaluation, the mean

Table 2: Biochemical parameters and calculated lung involvement rates by gender

	Male Mean ± SD	Female Mean ± SD	p
Age (Year)	59.12±16.37	58.05±15.67	0.626
CRP(mg/dl)	88.74±75.78	68.26±66.07	0.034
Ferritin/CRP (mg/dl)	28.18±113.3	13.19±29.27	0.206
Ferritin (mg/dl)	640.23±473.26	329.72±337.91	0.001
Fibrinogen (mg/dl)	464.36±105.91	435.24±122.55	0.064
D-dimer (mg/dl)	1.92±4.66	1.32±3.21	0.284
Right lung covid infiltration (%)	33.54±17.85	34.77±18.27	0.621
Left lung covid infiltration (%)	33.35±17.87	35.77±18.79	0.337
Total lung covid infiltration (%)	33.32±17.45	35.13±18.18	0.461

Tablo 3: Lung parenchymal involvement rates divided into 4 sections

	% 5.00-24.99 (n=77) Mean ± SD	%25.0-49.99 (n=95) Mean ± SD	% 50.0-74.99 (n=35) Mean ± SD	%75.0-100.0 (n=6) Mean ± SD	p
CRP (mg/dl)	48.82±58.24	84.74±68.42	120.44±72.01	148.43±114.19	0.001
Ferritin (mg/dl)	387.70±391.14	502.37±436.99	618.33±405.57	1171.33±703.84	0.001
Ferritin/CRP	35.47±137.3	12.9±29.62	10.75±17.3	35.97±59.63	0.298
Fibrinogen (mg/dl)	390.89±113.87	475.28±98.39	505.88±106.62	521.33±71.23	0.001
D-Dimer (mg/dl)	1.60±4.34	1.72±4.52	1.52±2.11	1.74±0.75	0.994

CRP level in males was found to be significantly higher than in females (p=0.034). Furthermore, the mean ferritin level in males was found to be significantly elevated in comparison to that in females (p<0.001). Nevertheless, no significant differences were observed between the sexes in the mean values of other variables, including the CRP/ferritin ratio, D-dimer, fibrinogen, and the percentage of lung parenchymal involvement (Table 2). Furthermore, no significant differences were observed in the biochemical data concerning CRP, ferritin, the ferritin/CRP ratio, D-dimer, fibrinogen, and the percentage of lung parenchymal involvement. Nevertheless, when the extent of lung parenchymal involvement was categorised into four classes (mild-moderate-severe) (0-24.99%, 25-49.99%, 50-74.99%, and 75-100%), the mean values of CRP, ferritin, and fibrinogen were found to be significantly higher in patients with severe lung involvement (75-100%) (p<0.001). No significant differences were observed in the remaining parameters and ratios (Table 3).

Discussion

This study aimed to investigate how the disease manifests differently in men and women and its relationship with biochemical variables by analyzing the demographic characteristics, biochemical parameters, and lung parenchymal involvement rates of 213 patients hospitalized

with COVID-19-positive pneumonia. Firstly, there was no significant difference in mean age between the sex groups, indicating that age is not a determining factor in the onset or progression of the disease and that gender-related variables may play a role. Interestingly, male patients had significantly higher levels of CRP, a marker of inflammation, than female patients. This finding suggests that men may have a stronger inflammatory response to infection, and CRP levels may indicate the severity of the disease according to gender, In the study conducted by Lau ES et all, which included 453 male and 328 female hospitalized patients, CRP levels were significantly higher in male patients, consistent with the findings of our study (23). Ferritin levels also differed between the sexes, with male patients having significantly higher levels than female patients. Ferritin is an indicator of iron storage in the body and can be associated with inflammation. This study implies that iron metabolism may differ between genders or that gender may influence inflammatory responses. In the study by Biole et al on 1752 patients, CRP, troponin, transaminase, and ferritin levels were higher in male patients with severe COVID-19 infection, and lymphocytopenia and thrombocytopenia were more common in men, Similarly, in the study conducted by Sykes et al., it was observed that ferritin levels were significantly higher in males. However, the same study did not find any statistically significant differences in CRP levels between genders (24, 25). The parenchymal involvement rate was found to be significantly correlated with CRP, ferritin, and fibrinogen levels in patients with Covid pneumonia. These parameters increased as the parenchymal involvement rate increased, suggesting that they may play a crucial role in determining the severity of the disease. In the study by Chen et al, an increase in the rate of lung parenchymal involvement was observed as the CRP rate increased, consistent with our study (26). Similarly, a positive correlation was found between the rates of lung parenchymal involvement and ferritin rate. Ferritin levels were found to be higher in hospitalized patients in the study by Shakaroun et al. However, no significant correlation was observed between ferritin/CRP ratio and lung parenchymal involvement rates (27). In the literature, there is no other study investigating the ferritin/CRP ratio for COVID-19 pneumonia. Titov et al. suggested that the ferritin/CRP ratio, being a novel ratio, might play a role in differentiating between hemophagocytic syndrome and sepsis. However, in our study, it was found that this ratio is not significant in patients with COVID-19 pneumonia. Nevertheless, the simultaneous elevation of both inflammatory markers could result in a mathematically insignificant ratio. Additionally, the lack of a control group consisting of pneumonia patients without COVID-19 in our study might have led to statistically insignificant results (28).

Study limitations: Patients with significant movement or breath holding during the CT scan, conditions that may affect HU assessment such as implants, pacemaker electrodes, foreign bodies that may cause metallic artefacts, oncology patients with primary lung cancer or metastases forming a mass in the lung, patients with unilateral or bilateral pleural effusions were excluded from the study because they may cause a decrease in total lung parenchymal area and may overestimate the relatively affected lung parenchymal area.

Conclusion

This study highlights the impact of gender on certain biochemical parameters in COVID-19 positive pneumonia patients and demonstrates that parameters associated with the severity of lung involvement can be determined. These findings may contribute to future research on the management and treatment of the disease. Understanding sex-related biochemical differences is crucial for developing personalized treatment strategies for the disease. Furthermore, the use of these biochemical parameters for evaluating lung involvement may aid in early diagnosis and treatment of patients.

Ethical approval: The study was approved by the ethics committee with protocol number SÜKAEK-2022/2/5
Conflict of interest: The authors did not declare any conflict of interest
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