ORIGINAL RESEARCH

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Association between hepatosteatosis and severity of COVID-19 pneumonia: a CT-based study

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Abstract

Objective: Recent studies show that comorbidities are a risk factor for coronavirus disease 2019 (COVID-19) pneumonia. We aimed to evaluate whether hepatosteatosis (HS) plays a role in predicting the severity of the disease.

Method: We included 505 patients whose real-time polymerase chain reaction tests were positive and who had a thoracic computed tomography (CT) scan. Age, gender, height-weight, and comorbidities of the patients were noted. Three radiologists re-evaluated thoracic CTs, and the severity score (between 20-40 was considered a severe disease) was determined. Liver and spleen densities were measured by standardizing, the liver-spleen density ratio was selected, and steatosis was defined as ≤0.8. We used X^2 and student t-test, logistic regression, and odds ratio with a 95% confidence interval.

Results: In 149 (29.5%) patients, liver/spleen density ratios favored adiposity. The mean tomography severity score of the patients was 16 (±10.5). When we look at the distribution of 192 (38%) patients with a CT severity score of ≥20; the number of patients over 65 years of age and the male gender were higher. We also found a higher rate of HS in this group compared to the group with a lower CT severity score. When the correlation between the patients' liver/spleen density ratios and the severity of pneumonia was examined, we observed that the severity of the disease increased significantly as the liver/spleen density ratio decreased ($p<0.001$).

Conclusion: HS and age were independently related with severe COVID-19 pneumonia. For patients who have viral pneumonia, the liver-spleen density ratio might be measured.

Keywords: Viral pneumonia, liver/spleen density ratio, severity index

INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged towards the end of 2019 and affected the whole world. It has been declared a pandemic in almost all countries. All findings caused by the disease in the body have yet to be clearly defined. While some people have the disease asymptomatically, the clinical results are variable in those who are symptomatic. Pneumonic infiltration is one of the most important COVID-19 sign. The radiological features of COVID-19 pneumonia were characterized immediately after the disease's start, and radiological assessment became critical in detecting the disorder. Thorax computed tomography (CT) is an imaging method that is easily accessible and provides rapid diagnosis of the condition. Primary radiological findings of COVID-19 pneumonia are bilateral peripheral localized ground glass opacities, interlobular septal thickenings, nodules in ground glass density, crazy paving appearance, and reversed halo findings.

The presence of some comorbidities with the onset of the pandemic has shown that the risk of developing complications increases (1). Age, metabolic syndrome, and obesity may affect the severity and can cause an increase in mortality rates (2,3).

Hepatosteatosis (HS), commonly known as fatty liver

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disease, is recognized not only as a metabolic disorder but also as a modulator of immune function and inflammatory responses. Recent clinical and experimental studies have shown a significant correlation between hepatic steatosis and the severity of viral infections, especially with viruses such as hepatitis B and C and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4-6). Steatotic livers may predispose patients to more severe viral disease courses and complications, exhibiting impaired interferon signaling and dysregulated cytokine production. For example, SARS-CoV-2-infected nonalcoholic fatty liver disease patients experience increased hospitalization rates, progression to severe COVID-19, and worse clinical outcomes, likely due to the proinflammatory state associated with steatosis and comorbid metabolic syndrome (6-8). Additionally, fatty infiltration of the liver has been associated with reduced antiviral treatment efficacy in chronic hepatitis C. Understanding the mechanistic interactions between HS and viral pathogenesis is critical for risk stratification, prognosis, and the development of targeted treatment strategies in patients with chronic liver disease (9). HS can be easily diagnosed with imaging methods. CT is a valuable, reliable technique for diagnosing and measuring HS and liver disease severity (10,11). Because in HS, less dense liver parenchyma is measured with Hounsfield Units (HU) than expected, the spleen can be used as a control since it does not contain structural fat. The liver-spleen density ratio showed a good correlation with methods such as liver biopsy (12). Tomography is not reliable in evaluating milder forms of steatosis, but it is a valuable method with high accuracy for severe HS (9,13).

Thorax CT scans help diagnose and evaluate the prognosis of COVID-19 (14). And severity score calculated with thorax computer tomography can be used to measure pulmonary involvement, with 83.3% sensitivity and 94% specificity in diagnosing severe infection (19.5/40) and 96.3% negative predictive value to exclude severe cases. Higher severity scores are linked to the risk of requiring mechanical ventilation, tachypnea, hypoxemia, and inflammatory reaction (15).

While the CT scan region generally encompasses the upper abdomen, the liver and spleen can be examined without further imaging in individuals experiencing COVID-19-related pneumonia.

Since HS is highly prevalent globally and related to several factors that increase the possibility of COVID-19 risk, we propose that tomographic hepatosteatosis could represent an independent risk factor for severe SARS-CoV-2 infection in terms of CT severity.

METHOD

After the draft of the study was determined, approval numbered 107/03 was given by Diskapi Yildirim Beyazit Research and Training Hospital Clinical Research Ethics Committee on March 22, 2021. The study was conducted between 01.04.2021 and 30.06.2021. Nasopharyngeal and oropharyngeal swabs were collected. Inclusion criteria comprised individuals aged 18 years and older with a positive result on real-time polymerase chain reaction (RT-PCR) testing, as well as the availability of liver and spleen sections alongside a thoracic CT scan. Five hundred-five patients with no known malignancy and no mass were included. The study did not include patients waiting more than four days between RT-PCR positivity and CT scan. The clinical records of these patients were reviewed. The patients' details were noted, including their age, gender, body mass index (obesity), and comorbidities such as type 2 diabetes mellitus (T2DM), hypertension (HT), cardiac, pulmonary, and renal disease.

CT technique

The CT scans were conducted with patients lying in a supine position while holding their breath during the inspiration phase, and they were performed without the use of contrast. All imaging procedures were carried out utilizing the same scanning protocol on a 16-slice Toshiba Alexion CT scanner. This particular device is commonly employed for patients suspected of having COVID-19. In all cases, a lung scan was conducted from the apex to the diaphragm. Radiologists standardized tube parameters. Tube flow modulation was 00-250 mAs, tube voltage was 90-120 kV, slice thickness was 3 mm, pitch factor was 0.8, rotation time was 75 s, the field of view was 250–300 mm, and the matrix was 512×512.

CT evaluation

The images were analyzed on the workstation (GE Medical Systems AW 4,7) by three radiologists (ESG, SO, YA) with at least ten years of experience. Incompatibilities were discussed, and a consensus was formed. For CT evaluation, the window center was used as -500 HU and the window width as 1500 HU.

Lung involvement

In the interpretation of CT, the presence of patchy ground glass opacities and interlobular septal thickenings, typical findings of COVID-19 pneumonia, were noted. Consolidation, including air bronchogram, enlargement of mediastinal lymph nodes, tree nodules with buds, and pleural effusion, was also noted. According to the Radiological Society of North America Expert Consensus criteria, CT findings were divided into five groups, and CT findings are classified in this method from average to typical signs of COVID-19 pneumonia. (16).

The degree of pulmonary involvement was determined by calculating the thorax CT severity index from Yang et al.'s study (17). According to this, ten segments are in the right lung and

ten in the left lung. When calculating the CT severity index per segment, a score of 0 was given for negative findings, one if less than 50% of the segment had abnormal findings, and two if more than 50% had abnormal results. The total CT severity index varied from 0 (no involvement) to 40 (more than 50% involvement in all twenty segments) and was calculated by adding the segment scores (Figure 1). A CT severity index of ≥20 points indicated severe disease.

Liver/spleen density ratio

To determine liver density, the mean of the HU within a 3 cm² region of interest (ROI) in three different areas of both lobes is divided by hepatic veins.. The mean of three measurements was accepted as liver parenchymal density in HU. Spleen density was obtained from 3 cm2 parenchymal ROI (Figure 2). CT liver-spleen density ratio (CT L/S) was calculated, and steatosis was determined if the CT L/S index was less than or equal to 0.8 (18-20).

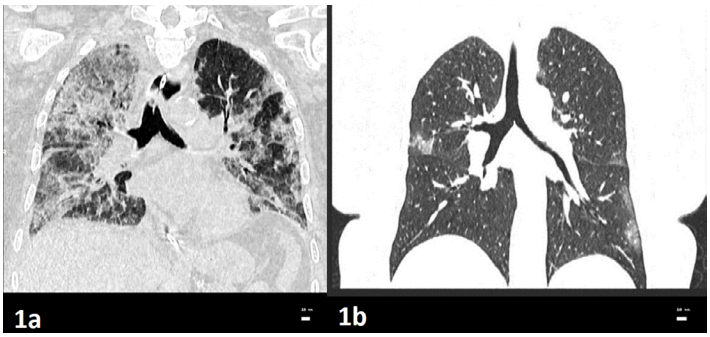


Figure 1. (a) Coronal CT section of a 75-year-old patient with a positive COVID-19 PCR test, widespread involvement of both lungs, the CT severity index was calculated as 34. (b) Coronal CT section of a 61-year-old patient with a positive COVID-19 PCR test, limited-focal involvement in both lungs, the CT severity index was calculated as 8.

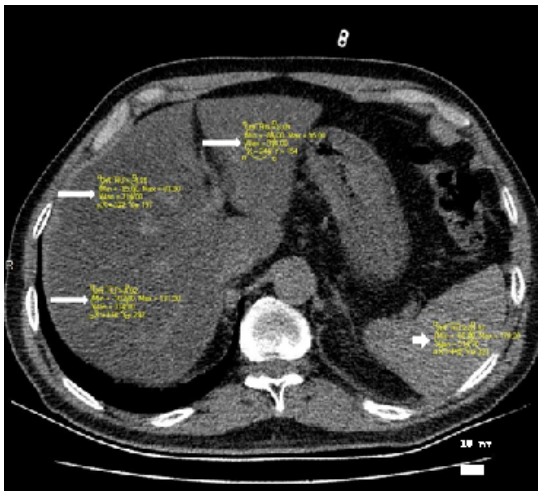


Figure 2. Region of interest (ROI) positioning and measuring in three different areas of the liver showing with log arrow, each separated by hepatic vessels with an area of approximately 3 cm². Spleen density was obtained from 3 cm² parenchymal ROI showing with short arrow.

Statistical Analysis

Quantitative data were expressed as mean and standard deviation, while qualitative data were expressed as percentages. The student's t-test was applied to the continuous variables, and the chi-square test was applied to the categorical variables. Then, logistic regression analysis was performed, and the results including odds ratios (OR) and 95% confidence interval (CI) were accepted. A significance level of $p < 0.05$ was used to ensure statistical significance in the analysis. Statistical analyses were performed using SPSS version 25 for MAC (IBM, New York, NY, USA).

RESULTS

The basic characteristics of the 505 patients included in the study are shown in Table 1. The mean age was 55.49 (±17.08). Two hundred and sixty-nine (53%) patients were male, and 236 (47%) were female. One hundred and eighty-one (35.8%) of the patients had at least one comorbidity. Forty-seven patients (9%) had obesity, 104 (20%) had HT and cardiovascular disease, and 55 (10%) had T2DM (Table 1).

Table 1. Demographic data of 505 patients with COVID-19 pneumonia

Parameter		Value (n=505)
Sex		
	Male	269 (53%)
	Female	236 (47%)
Age (year)*		55.4±17)
Comorbidities		
	HT-CVS	104(20%)
	T2DM	55 (10%)
	Obesity	47 (9%)
Tomographic fatty liver disease (CT L/S index ≤0.8)		149 (29.5%)
CT findings		
	Ground glass opacity	388 (77%)
	Crazy-paving pattern	45 (9%)
	Consolidation	116 (23%)

*: Mean±Standard Deviation, HT-CVS: Hypertension-cardiovascular, T2DM: Type 2 diabetes mellitus, CT L/S index: Computerized tomography liver-spleen density ratio)

We observed tomographic fatty liver disease (CT L/S index ≤0.8) in 149 patients (29.5%). In addition, when the thorax CT findings of the patients were examined, ground glass opacity was found in 388 (77%) patients, the crazy-paving pattern in 45 (%9) patients, and consolidation in 116 (%23) patients.

The mean severity score of the patients was calculated as 16 (±10.5). It was observed that 192 (38%) patients (CT severity score≥20) had severe disease. When the group with severe tomographic disease (CT score ≥20) and the group without

severe pneumonia were compared, it was seen that the first group was older, mainly consisted of males (101 vs. 52%), and the presence of HS (CT L/S index ≤0.8) (103 vs. 69%) was higher. There was a significant difference between the two groups regarding age and HS, with a p-value less than 0.05. Table 2 shows the distribution of obesity (31.5% vs. 19.2%, p=0.005), HT (43.3% vs. 15.2%, p=0.001), and T2DM (25.1% vs. 16.3%, p=0.02) among the groups, while other comorbidities were similar between the groups.

Table 2. Comparison of demographic and clinical characteristics according to CT severity score (≥20 vs <20)

Parameter	CT Severity Score≥20 n=192 (38%)	CT Severity Score<20 n=313 (62%)	p-value
Sex	n=101 (52%)	n=148 (47%)	
Mean age*	56.5 (Year)	52.4 (Year)	0.03
CT L/S index ≤0.8	n=103 (69%)	n=46 (31%)	0.04
HT	n=83 (43.3%)	n=47 (15.2%)	0.001
Obesity	n=60 (31.5%)	n=60 (19.2%)	0.005
T2DM	n=48 (25.1%)	n=51 (16.3%)	0.02

CT L/S index: Computed tomography liver-spleen density ratio, HT-CVS: HT: Hypertensi-on-cardiovascular, T2DM: Type 2 diabetes mellitus

When the correlation between the L/S density ratio and the severity of the disease was examined, we observed that the severity of the disease increased statistically as the L/S density ratio decreased (Spearman's rho = −0.523, $p < 0.001$), indicating a moderate negative correlation (Figure 3). The logistic regression analysis identified two variables that were significantly related to CT L/S ≥20/40: HS (OR 3.8, 95% confidence interval [CI] 1.9–8.9, $p < 0.0001$) and age (OR 1.169, 95% CI 1.04–1.31, $p < 0.0001$). Patients with HS had 3.8 times higher odds of having CT L/S ≥20/40 than those without HS, and for each additional year of age, there was a 16.9% increase in odds of CT L/S ≥20/40, all else equal. Both associations were statistically significant.

DISCUSSION

COVID-19 can lead to viral pneumonia, an inflammation of the lung tissue caused by a viral infection. Several factors are related to the severity of COVID-19 pneumonia, and the severity of the disorder varies greatly; with some people experiencing only minor symptoms and others developing serious diseases, including pneumonia. According to the World Health Organization, patients at higher risk of severe disease include older adults and people with comorbidities such as cardiac disease, T2DM, or chronic respiratory disease (21) .

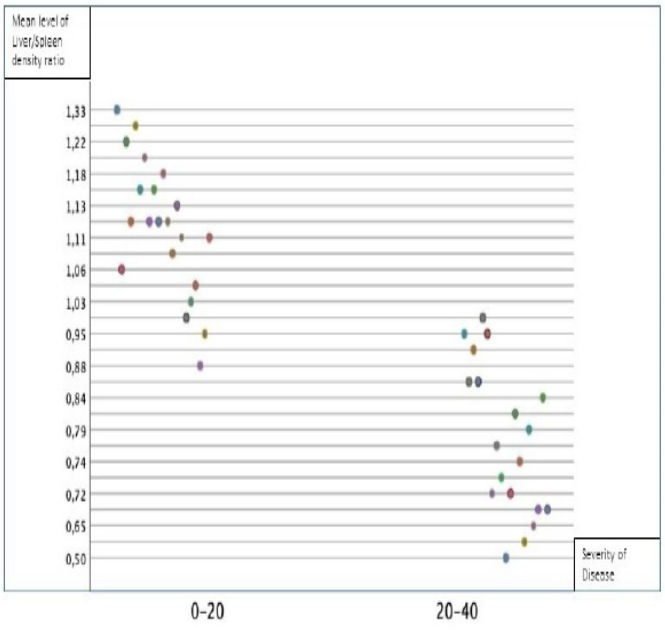


Figure 3. Correlation between the Liver/Spleen density ratio and the severity of COVID-19 pneumonia

One study, which followed patients admitted with COVID-19 in Wuhan, China, showed that among patients with pneumonia, those with underlying illnesses, and older patients were at higher risk of severe disease and mortality. (22) Another research published in JAMA analyzed data from more than 44,000 patients hospitalized with COVID-19 and found that age, male sex, and comorbidities such as obesity, HT, and diabetes were independently related with a higher risk of severe disease and mortality. (23) Obesity is recognized as an independent risk factor for severe illness and mortality in COVID-19 pneumonia. (24) Patients hospitalized with COVID-19 in the United States, those with a body mass index higher than 30 have an increased risk of severe disease and death. (25) The most critical factor affecting the prognosis and mortality of COVID-19 is the presence and severity of viral pneumonia.

In this study, patients with a CT severity index above 20, which was considered as severe disease, had a CT L/S ratio of less than 0.8. We found a significant relationship between the CT severity index and the CT L/S density index. Similarly, Lever et al. showed that CT L/S indices of 0.9 and below were associated with severe pneumonia. (26) This is consistent with previous studies reporting an association between hepatic steatosis and worse outcomes in COVID-19 patients (27).

This findings highlight the growing recognition of HS not merely as a metabolic liver condition but as a critical factor

influencing the course and severity of viral infections. This is particularly evident in the context of systemic viral illnesses such as COVID-19, where patients with underlying fatty liver disease exhibit an increased risk of severe clinical outcomes, including acute respiratory distress syndrome, multi-organ dysfunction, and death (28). The pathophysiological mechanisms are multifactorial and appear to involve impaired antiviral immunity, chronic low-grade inflammation, and metabolic dysregulation, all of which compromise host defense and facilitate viral propagation. The bidirectional relationship between HS and viral infections suggests that the liver acts as both a target and a modulator of systemic viral disease. Emerging data support the hypothesis that steatotic liver has an altered immune landscape, characterized by increased intrahepatic expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1ß, and reduced interferon responsiveness, which are key determinants of viral pathogenesis and disease severity.

HS has also been shown to impair the efficacy of antiviral therapies, particularly in chronic hepatitis C virus (HCV) infections, where steatosis is associated with reduced sustained virological response (SVR) rates and faster progression of hepatic fibrosis (9). These findings are clinically relevant as they necessitate more aggressive management and closer monitoring of patients with fatty liver disease who contract viral infections. Moreover, metabolic-associated fatty liver disease often coexists with obesity, T2DM, and cardiovascular disease, compounding the systemic inflammatory burden and further increasing the risk of adverse outcomes (8).

Limitations of the study

According to the logistic regression study, HS and age are essential predictors of CT L/S. However, it is crucial to say as a limitation of our study that some detailed features of the patients which may be associated with CT L/S ≥20/40 were not included in this study.

The other limitation of our study is; the images were obtained from the thorax CT, so the entire liver was not included in the sections. The extent of steatosis in the entire liver could not be assessed. We could not evaluate the entire liver, but our study was designed to meet the L/S density ratio measurement criteria in the literature. For standardized L/S density ratio measurements, ROIs are placed in at least three separate regions in the right lobe (e.g., segments V, VI, VII). Vessels, bile ducts, and lesions should be avoided. Each ROI should generally be 1–3 cm^2 in diameter (small circular areas). All patients in the study were evaluated according to these criteria. Patients who did not meet the measurement criteria, were not included in the study. Thus, although we could not evaluate the entire liver, we used the standard measurement in the literature.

CONCLUSION

Older age, male gender, and the presence of HS were related with a higher risk of severe COVID-19 pneumonia, as reflected in the higher CT severity score. Our results show that the L/S density ratio can be a valuable marker for predicting the severity of COVID-19 pneumonia. This article is not significant for only today in the context of COVID-19, but also for tomorrow it might be of importance in another viral outbreak. For such viral diseases, it is critical that a person's immune response is timely and adequate. Thus, obesity and fatty liver may be important predictors in forecasting this response. Moreover, long COVID has affected and continues to affect millions of people worldwide. Where the outcomes of long COVID will lead is still unknown. Long COVID is typically seen in cases that had severe COVID disease. This is not just a model for COVID; these groups may respond similarly to new viral diseases that may emerge in the future. Even though the COVID-19 pandemic may be over, the disease persists, and monitoring its long-term outcomes will provide guidance in preventing and preparing for future viral diseases.

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Athorship Contributions: Concept: ESG, SÖ, YA,IS, BH, Design: ES, SÖ, BH,YA, IS, Supervising: ES, SÖ, YA, BH, IS, Data collection and entry: ES, SÖ, YA, IS, BH, Analysis and interpretation: ES, IS, BH, YA, SÖ, Literature search: ES,SÖ, YA, Writing: ES,SÖ, YA, BH Critical review: SÖ, BH, IS

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