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ORIGINAL ARTICLE

The Effect of Hepatosteatosis on the Course of Chest CT Severity Scores in COVID-19 Patients

Hepatosteatozun COVID-19 Hastalarında Göğüs BT Şiddet Skorlarının Seyrine Etkisi

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ABSTRACT

Background/Aims: In the literature, the temporal variation of computed tomography severity score (CT-SS) values on consecutive CTs, which is an indicator of pneumonia severity, was not evaluated according to the presence of hepatosteatosis. We aimed to investigate the effect of hepatosteatosis on the temporal change of CT-SS in COVID-19 patients.
Material and Methods: Our retrospective study included 472 RT-PCR positive COVID-19 patients (≥18 years old) admitted to our hospital between December 2021 and January 2022. Chest CT severity scores ranging from 0 to 5 were assigned to each lobe of the lung and total CT-SS was obtained. For quantitative analysis, if the hepatic/splenic attenuation ratio was <1, hepatosteatosis was defined in the first CT. Wilcoxon test was used to evaluate the temporal changes of CT-SS values relative to the presence of hepatosteatosis.
Results: A total of 472 patients were included in the study and the mean age was 64.04±14.35 years. 255/472 (54%) of the patients were hepatosteatosis positive. There was no significant difference between hepatosteatosis groups and ICU admission and mortality (p=0.269; p=0.429). The median CT-SS values of the first CT scan of patients with hepatosteatosis were significantly higher than patients without hepatosteatosis (p<0.001). There was a significant increase between the 1st and the 2nd CT-SS in both patients with and without hepatosteatosis (both p<0.001). The increase in the second CT-SS was higher in patients with hepatosteatosis than in patients without hepatosteatosis.
Conclusion: Hepatosteatosis is one of the important factors affecting the severity of pulmonary involvement, especially in the early period of COVID-19. Hepatosteatosis may be an indicator of poor prognosis in the temporal change of pneumonia severity in COVID-19 patients.

Keywords: COVID-19, Computed tomography severity score, hepatosteatosis, hepatic-to-splenic attenuation ratio

ÖZ

Amaç: Literatürde pnömoni şiddetinin bir göstergesi olan BT şiddet skoru (BT-ŞS) değerlerinin, ardışık BT' lerde hepatosteatoz varlığına göre zamansal değişimi değerlendirilmemiştir. COVID-19 hastalarında, hepatosteatozun BT-ŞS' nin geçici değişimi üzerindeki etkisini araştırmayı amaçladık.
Materyal ve Metotlar: Retrospektif çalışmamıza Aralık 2021 ile Ocak 2022 tarihleri arasında hastanemize başvuran 472 RT-PCR pozitif COVID-19 hastası (≥18 yaş) dâhil edildi. Akciğerin her lobuna 0 ile 5 arasında değişen toraks BT şiddet skorları atandı ve toplam BT-ŞS elde edildi. Hastanın ilk BT'sinden kantitatif analiz için hepatik/dalak atenüasyon oranı <1 ise, hepatosteatoz tanımlandı. BT-ŞS değerlerinin hepatosteatoz varlığına göre zamansal değişimlerini değerlendirmek için Wilcoxon testi kullanıldı.
Bulgular: Çalışmaya toplam 472 hasta dâhil edildi ve ortalama yaş 64.04±14.35 idi. Hastaların 255/472'si (%54) hepatosteatoz pozitifti. Hepatosteatoz grupları ile YBÜ yatış ve mortalite arasında anlamlı fark yoktu (p=0,269; p=0,429). Hepatosteatozlu hastaların ilk BT taramasına ait medyan BT-ŞS değerleri, hepatosteatozu olmayan hastalara göre anlamlı derecede yüksekti (p<0.001). Hepatosteatozu olan ve olmayan hastalarda 1. ve 2. BT-ŞS arasında anlamlı artış vardı (her ikisi de p<0.001). İkinci BT-ŞS'deki artış hepatosteatozlu hastalarda hepatosteatozsuz hastalara göre daha yüksekti.
Sonuç: Hepatosteatoz özellikle COVID-19 erken döneminde pulmoner tutulum ciddiyetini etkileyen önemli faktörlerdendir. Hepatosteatoz, COVID-19 hastalarında pnömoni şiddetinin geçici değişiminde kötü prognozun bir göstergesi olabilir.

Anahtar Kelimeler: COVID-19, Bilgisayarlı Tomografi şiddet skoru, hepatosteatoz, hepatik-dalak atenüasyon oranı

Introduction

Since the novel coronavirus disease 2019 (COVID-19) was first detected in China, the direct and indirect effects are still not fully understood in extrapulmonary organs (1). Especially in patients with comorbidities with COVID-19, severe complications such as multiple organ failure and acute respiratory distress syndrome (ARDS) may need treatment in the intensive care unit (ICU) and mortality may develop. Therefore, chest computed tomography (CT), which can be used in the diagnosis and post-treatment follow-up, can provide information about the severity of pneumonia [CT severity score (CT-SS)] as well as information about the heart, kidney, liver, and spleen parenchyma included in the imaging field (2,3). Hepatosteatosis and obesity, which affect approximately 30% of the population, constitute metabolic syndrome (4). Hepatosteatosis leads to a more severe course of COVID-19 infection by causing both an inadequate immune response and an excessive inflammatory response by causing deterioration in liver functions (5–8). Therefore, it is beneficial to detect

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patients with non-contrast CT in terms of the presence of hepatosteatosis, and liver parenchyma density appears hypodense to the spleen in patients with hepatosteatosis (9). Although the definitive diagnosis of hepatosteatosis is made by histopathological examination, it can also be diagnosed non-invasively with non-contrast CT. The attenuation value of the liver is at least 10 Hounsfield Units (HU) lower than the attenuation of the spleen (9). In addition, the diagnosis can be made by calculating the hepatic-to-splenic attenuation ratio (CTL/S) (10–12).

In the literature, the effect of hepatosteatosis, which was evaluated especially on admission CT, on pneumonia severity and the prognosis was investigated (13–15). However, the temporal change of CT-SS values in consecutive CTs, which is an indicator of pneumonia severity, was not evaluated according to the presence of hepatosteatosis.

In this study, we aimed to investigate the effect of hepatosteatosis, which is common in the general population, on the course of pneumonia severity in COVID-19 patients.

Material and Methods

This single-center study was approved by the Ethical Committee of Amasya University Sabuncuoğlu Şerefeddin Education and Research Hospital (8 July 2021, No: 128). This study was conducted according to the Declaration of Helsinki and Good Clinical Practice. Since the study was retrospective, the ethics committee did not consider it necessary to obtain consent from the patients.

Study population and data collection

The data of 557 patients with positive RT-PCR tests and chest CTs admitted to the emergency department of our hospital between December 2021 and January 2022 were analyzed retrospectively. Patients with chronic liver diseases, liver lesions, image artifacts that hinder the evaluation of CT, contrast-enhanced CTs, and pediatric patients (<18 years) were excluded from the study. As a result, after excluding 85 patients, 472 patients were included in the study (Fig. 1).

Clinical and laboratory data

The laboratory results obtained within one day from the initial chest CT date and comorbidities such as diabetes, chronic lung and cardiovascular diseases, admission to the hospital and/or ICU, and the dates of death were scanned from our hospital's electronic medical records. The patient's length of stay in the service and ICU and their survival were recorded.

CT protocol

In all non-contrast chest CT scans, patients were instructed to hold their breath in the supine position. Chest imaging was performed with a 128-slice CT scanner (GE Healthcare Revolution EVO CT) using the routine protocols in our hospital. The mean time interval between the first and second CTs was 14.41±15.53 days and the mean time interval between the second and third CTs was 18.73±20.07 days.

Image analysis

The radiologist (10 years of experience in general radiology) reported the chest CT scans for the pneumonia severity and hepatosteatosis retrospectively, blinded to the clinical data and laboratory indicators. In addition, chest CT-SSs were calculated as; if there is no lung involvement= 0; if < 5% involvement= 1; if 5–25% involvement= 2; if 26–49%= 3; if 50-75% involvement= 4; if there is > 75% involvement= 5. Total CT-SS is obtained by summing 5 lung lobe scores (score range: 0-25) (Fig. 2a, b, c). (16). The study population was divided into two groups based on hepatic attenuation. The radiologist measured the Hounsfield unit (HU) values of the liver and spleen on the first unenhanced chest CT images. For the analysis of liver density, 1.5 cm^2 regions of interest (ROIs) were placed in three different areas (one measurement from the left lobe, and two measurements from the right lobe), separated by hepatic veins. Spleen density was obtained from a single 1.5 cm^2 ROI placed in the parenchyma. CTL/S was calculated by taking the mean HU measurement of the ROIs measured from the three liver segments and dividing it by the spleen HU. For quantitative analysis, hepatosteatosis was defined if the hepatic/splenic attenuation ratio (CTL/S) was less than 1 (12,17). In both organs, ROIs were located in parenchyma areas at least 1 cm from vascular structures, hilum, and high-density (e.g. calcification) areas (Fig. 2d).

Statistical analysis

SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2017. Armonk, NY) was used for statistical analysis. Kolmogorov-Smirnov was used to evaluate the normal distribution. Group comparisons according to the presence of hepatosteatosis were made using the chi-square / Fisher Exact test (Frequency and percentage) and the Student t-test (mean and standard deviation) / Mann-Whitney U test [median, and Q1: first quartile; Q3: third quartile]. Wilcoxon signed-rank test was used to evaluate the temporal changes of median CT-SS values relative to the presence of hepatosteatosis on three consecutive CTs. $p<0.05$ was considered statistically significant.

Results

Of the total 472 patients, 255/472 (54%) were hepatosteatosis positive. The mean age was 64.04±14.35 years. The mean age of patients with hepatosteatosis was not significantly higher than the patients without hepatosteatosis (p= 0.748). There were 273/472 (57.8%) male patients. The frequency of hepatosteatosis was significantly higher in male patients, 167/255 (65.5%) (p<0.001). Of the patients with hepatosteatosis on CT, 241/255 (94.5%) were inpatients (p= 0.04). There was no significant difference between ICU admission and hepatosteatosis groups (p=0.269). 139/472 (29.4%) of our patients died. There was no significant difference between mortality and the presence of hepatosteatosis (p=0.429). There was no significant difference between co-morbidities and hepatosteatosis groups (Table 1).

Table 1: Comparison of the presence of hepatosteatosis with demographic data and comorbidities

		Hepatic steatosis				
		Absent		Present		p value
		n	%	n	%	
Gender	Female	111	51.2	88	34.5	<0.001
	Male	106	48.8	167	65.5	
	Total	217		255		
Survival	Alive	157	72.40	176	69.00	0.429
	Death	60	27.60	79	31.00	
	Total	217		255		
Hospitalization	Outpatient	23	10.60	14	5.50	0.040
	Inpatient	194	89.40	241	94.50	
	Total	217		255		
Inpatient	non-ICU	143	73.70	166	68.90	0.269
	ICU	51	26.30	75	31.10	
	Total	194		241		
Diabetes mellitus	Absent	146	67.30	172	67.50	0.969
	Present	71	32.70	83	32.50	
	Total	217		255		
Hypertension	Absent	112	51.60	122	47.80	0.414
	Present	105	48.40	133	52.20	
	Total	217		255		
Hyperlipidemia	Absent	163	75.10	182	71.40	0.361
	Present	54	24.90	73	28.60	
	Total	217		255		
Chronic pulmonary diseases	Absent	181	83.40	214	83.90	0.881
	Present	36	16.60	41	16.10	
	Total	217		255		
Cardiovascular disease	Absent	160	73.70	194	76.10	0.558
	Present	57	26.30	61	23.90	
	Total	217		255		
Peripheral vascular diseases	Absent	205	94.50	237	92.90	0.497
	Present	12	5.50	18	7.10	
	Total	217		255		
Chronic kidney diseases*	Absent	212	97.70	251	98.40	0.738
	Present	5	2.30	4	1.60	
	Total	217		255		

Chi-square or (*) Fisher tests were used to compare categorical variables according to hepatic steatosis groups.

The mean liver density of all patients was 52.89±10.37 HU (9.55-77.64). The mean liver density of patients with hepatosteatosis was significantly lower than the patients without hepatosteatosis (p<0.001). The mean CTL/S of patients with hepatosteatosis was significantly lower than the patients without hepatosteatosis (p<0.001). Among laboratory parameters, GGT (p<0.001), LDH (p<0.001), total bilirubin (p= 0.007), direct bilirubin (p= 0.014), CRP (p<0.001) and ferritin (p<0.001) were statistically significantly higher in patients with hepatosteatosis (Table 2).

In patients with hepatosteatosis, median CT-SS values were statistically significantly higher in the first CT (12; Q1-Q3: 6-18; p<0.001) and the second CT (17; Q1-Q3: 14-24; p= 0.010) compared to patients without hepatosteatosis. In patients with hepatosteatosis, the third median CT-SS value (18; Q1-Q3: 14-24; p= 0.114) was statistically insignificantly higher than in patients without hepatosteatosis (Table 2).

Table 2: Comparison of HS presence with laboratory data and CT-SS values

	HS	N	Mean/ Median	SD	Min./Q1	Max./Q3	p value
Age	A	217	63.81	15.05	24.00	93.00	0.748
	P	255	64.24	13.75	26.00	94.00	
	T	472	64.04	14.35	24.00	94.00	
Liver density (HU)	A	217	58.86	6.43	40.87	75.76	<0.001
	P	255	47.70	9.86	9.55	67.79	
	T	472	52.83	10.12	9.55	75.76	
CTL/S	A	217	1.17	0.15	1.00	1.79	<0.001
	P	255	0.81	0.16	0.13	0.99	
	T	472	0.98	0.24	0.13	1.79	
First CT-SS*	A	217	7.00		1.00	15.00	<0.001
	P	255	12.00		6.00	18.00	
	T	472	10.00		3.00	17.00	
Second CT-SS*	A	117	15.00		7.00	21.00	0.010
	P	119	17.00		12.00	24.00	
	T	236	17.00		9.00	22.00	
Third CT-SS*	A	53	15.00		10.00	21.00	0.114
	P	43	18.00		14.00	24.00	
	T	96	15.50	7.73	0.00	25.00	
AST (0-40; U/L)	A	217	31.44	50.77	7.00	694.00	0.347
	P	255	34.76	22.66	9.00	207.00	
	T	472	33.24	38.23	7.00	694.00	
ALT (0-41; U/L)	A	217	29.21	64.45	4.00	917.00	0.409
	P	255	32.88	27.33	3.00	189.00	
	T	472	31.19	48.07	3.00	917.00	
ALP (40-125; U/L)	A	196	77.21	34.52	18.00	309.00	0.466
	P	232	74.82	33.08	14.00	245.00	
	T	428	75.91	33.73	14.00	309.00	
GGT (10-71; U/L)	A	217	30.42	33.74	5.00	345.00	<0.001
	P	254	49.85	63.29	6.00	661.00	
	T	471	40.90	52.66	5.00	661.00	
LDH (135-225; U/L)	A	215	296.70	139.84	154.00	1422.00	<0.001
	P	255	338.21	146.57	121.00	1167.00	
	T	470	319.22	144.87	121.00	1422.00	
Total bilirubin. (0-1.2; mg/dl)	A	216	0.45	0.33	0.06	3.19	0.007
	P	254	0.53	0.30	0.12	2.26	
	T	470	0.49	0.32	0.06	3.19	
Direct bilirubin. (0-0.4; mg/dl)	A	216	0.18	0.17	0.01	1.82	0.014
	P	254	0.22	0.16	0.01	1.25	
	T	470	0.20	0.16	0.01	1.82	
CRP (0-5; mg/L)	A	217	45.19	54.75	0.06	291.83	<0.001
	P	255	65.74	61.54	1.22	347.00	
	T	472	56.29	59.35	0.06	347.00	
Ferritin (22-322; ug/L)	A	213	249.05	398.31	5.20	3500.00	<0.001
	P	254	463.16	953.94	5.50	12021.70	
	T	467	365.50	760.02	5.20	12021.70	
WBC (3.39–8.86; 10□/l)	A	217	7.70	5.43	1.42	63.34	0.648
	P	255	7.51	3.91	2.91	27.20	
	T	472	7.60	4.67	1.42	63.34	
Neutrophil count (1.65-4.97; 10□/l)	A	217	5.50	4.06	0.34	33.32	0.488
	P	255	5.81	5.43	1.53	69.00	
	T	472	5.67	4.84	0.34	69.00	
Lymphocyte count (1.17-3.17; 10□/l)	A	217	1.40	0.77	0.16	4.52	0.274
	P	255	1.33	0.71	0.14	5.60	
	T	472	1.36	0.74	0.14	5.60	
INR (0.88-1.3)	A	206	1.07	0.30	0.09	4.73	0.814
	P	246	1.07	0.24	0.87	4.23	
	T	452	1.07	0.27	0.09	4.73	
D-dimer (0-0.5; µg/mL)	A	214	1.17	2.68	0.02	32.00	0.398
	P	253	1.43	3.71	0.03	46.60	
	T	467	1.31	3.27	0.02	46.60	
Triglycerides (0-200; mg/dl)	A	202	140.84	90.34	3.00	881.00	0.393
	P	247	148.28	92.69	35.00	822.00	
	T	449	144.93	91.62	3.00	881.00	
Cholesterol (0-200; mg/dl)	A	189	151.12	42.71	57.00	297.00	0.201
	P	228	145.86	40.91	67.00	278.00	
	T	417	148.24	41.77	57.00	297.00	
HDL (35-55; md/dl)	A	183	40.84	13.04	12.00	84.00	0.011
	P	224	37.42	13.84	9.00	139.00	
	T	407	38.96	13.58	9.00	139.00	
LDL (0-130; md/dl)	A	184	95.32	36.77	13.00	215.00	0.072
	P	223	88.84	35.54	23.00	210.00	
	T	407	91.77	36.20	13.00	215.00	

HS: Hepatic steatosis; A: Absent; P: Present; T: Total; CT-SS: CT severity score; CTL/S: Hepatic-to-splenic attenuation ratio; SD: Standard deviation; Min: Minimum; Max: Maximum; Q1: first quartile; Q3: third quartile
In the comparison of continuous variables according to HS groups. the Student's t-test was used for those with normal distribution and the Mann-Whitney U test for those who were not normally distributed (*).

Table 3: Temporal change of consecutive CT-SSs in patients with and without hepatosteatosis

Hepatic steatosis			N	Mean Rank	Sum of Ranks	p value
Absent	Second CT-SS - First CT-SS	Negative Ranks	9[a]	32.50	292.50	<0.001
		Positive Ranks	96[b]	54.92	5272.50	
		Ties	12[c]			
		Total	117			
	Third CT-SS - Second CT-SS	Negative Ranks	18[d]	21.67	390.00	0.042
		Positive Ranks	30[e]	26.20	786.00	
		Ties	5[f]			
		Total	53			
Present	Second CT-SS - First CT-SS	Negative Ranks	17[a]	41.38	703.50	<0.001
		Positive Ranks	96[b]	59.77	5737.50	
		Ties	6[c]			
		Total	119			
	Third CT-SS - Second CT-SS	Negative Ranks	19[d]	17.50	332.50	0.774
		Positive Ranks	16[e]	18.59	297.50	
		Ties	8[f]			
		Total	43			

Wilcoxon Signed Ranks Test was used. p<0.05 was considered statistically significant.

a. Second CT-SS < First CT-SS
b. Second CT-SS > First CT-SS
c. Second CT-SS = First CT-SS
d. Third CT-SS < Second CT-SS
e. Third CT-SS > Second CT-SS
f. Third CT-SS = Second CT-SS

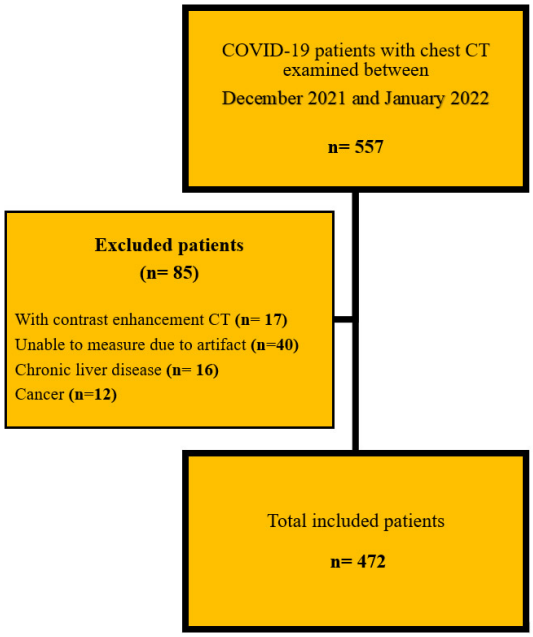

Fig. 1 Study flowchart for the inclusion and exclusion criteria of the patient sample.

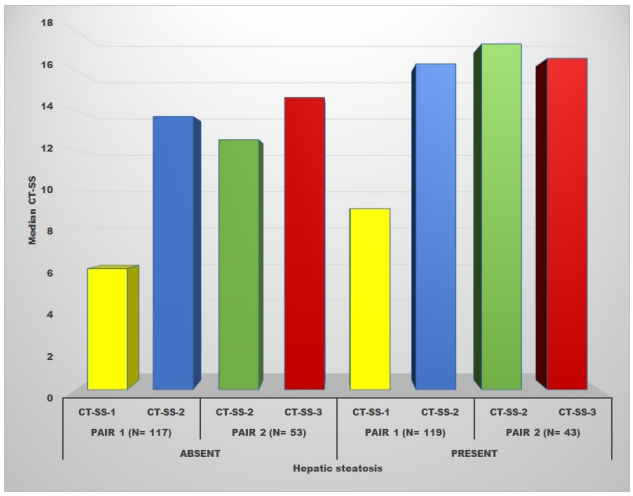

Fig. 3 Graph of temporal change of chest CT-SSs according to hepatosteatosis

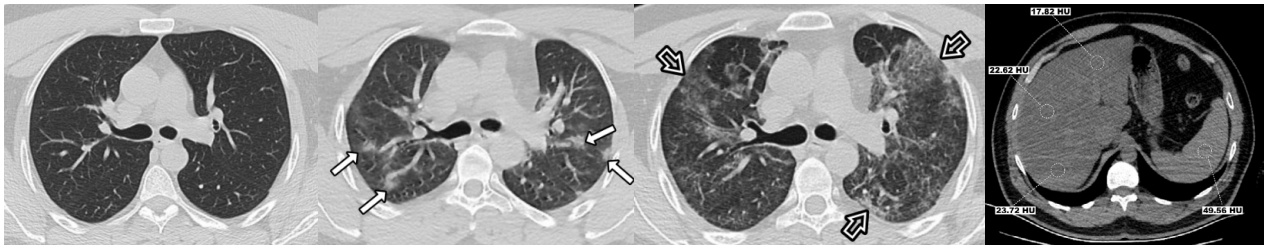

Fig. 2 A 43-year-old male patient was admitted to our hospital with complaints of fever, cough, and sore throat. RT-PCR test was positive. **a)** Unenhanced chest CT at admission was normal (CT-SS=0). His treatment was started as an inpatient. However, when the patient's complaints increased, follow-up CTs were performed and he was admitted to the ICU. **b)** On the second CT, areas of peripheral weighted ground glass density (GGO) (white arrows) were observed in both lungs (CT-SS= 8). **c)** On the third CT, there was an increase in GGOs and transformation into areas of crazy paving patterns (open arrows) in both lungs. The patient who was treated was discharged with recovery. **d)** Quantitative analysis of liver (mean 21.39 HU) and spleen (49.56 HU) density was performed (CTL/S= 0.43). The liver was hypodense relative to the spleen

When we compared the CT-SSs course according to the hepatosteatosis groups, there was a statistically significant increase between the first and second CT-SSs values in both patients with and without hepatosteatosis (respectively; p<0.001; p<0.001). However, this increase was higher in patients with hepatosteatosis than in patients without hepatosteatosis (Fig. 3) (Table 3).

Discussion

In our study, we investigated the effect of the presence of hepatosteatosis on chest CT scans of COVID-19 patients on the temporal change of CT severity score (CT-SS) which is an indicator of pneumonia severity. In our results, while the first and second CT-SS values were significantly higher in patients with hepatosteatosis, we found an insignificant increase in the third CT-SS value. While admission to the hospital was significantly higher in patients with hepatosteatosis, there was no statistically significant relationship between mortality and intensive care admission rates. When we examined the temporal changes in CT-SS values in both patients with and without hepatosteatosis, we found that there was an increase in CT-SS values in both groups although it was higher in patients with hepatosteatosis.

COVID-19 has two phases of infection, first affected by direct virus damage and then by excessive cytokine release (18). Since angiotensin-converting enzyme 2 (ACE2), the receptor of the SARS-CoV-2 virus, is primarily found in cholangiocytes (60%), endothelial and hepatocyte cells in the liver, the virus can enter different cells in the liver (18). In histopathological examinations of the liver, the virus was detected intracellularly, and findings of hepatic steatosis, periportal inflammation, and apoptosis due to lipid metabolism dysfunction were shown (19,20). While hepatosteatosis that develops due to direct damage to the virus increases proinflammatory cytokines, hepatosteatosis that existed before the disease also responds to both an excessive inflammatory response and a weakened immune response (8,21–23). Like our study, studies that included only COVID-19-positive patients in their population reported higher CT-SS values in patients with hepatosteatosis (5,15). As stated in our study and the literature, the high CT-SS in patients with hepatosteatosis may be due to the excessive inflammatory response as a result of the direct and indirect effects of the virus (7,14). Although there was an increase in CT-SS values in the group with and without hepatosteatosis in our study, higher increase in patients with hepatosteatosis is consistent with the studies in the literature reporting that hepatosteatosis negatively affects the severity of the disease.

Studies reported that the presence of hepatosteatosis did not make a difference in the incidence of COVID-19 mortality, but reported different results in the frequency of hospitalization in the intensive care unit. In terms of the frequency of intensive care hospitalization, Singh A. et al. reported a significant increase in the group with hepatosteatosis, but Hegyi PJ et al, Forlano et al. and Portincasa et al. did not report a significant difference as in our study (24–28). In our study, the frequency of inpatients increased significantly in patients with hepatosteatosis, but there was no significant increase in the frequency of admission to the ICU. Our result showing that hepatosteatosis did not affect mortality was consistent with the literature.

To our knowledge, this is the first study to evaluate the effect of hepatosteatosis on temporal changes in CT-SS on consecutive CT imaging in COVID-19 patients. We tried to emphasize the importance of hepatosteatosis by showing the effect of hepatosteatosis on the prognosis of the disease, especially in epidemics related to SARS-Cov-1 and SARS-Cov-2 viruses from the Coronavirus family that may occur in the future.

Our study had several limitations. First, the results of our analysis cannot be generalized because it is a single-center study. Second, the diagnosis of hepatosteatosis could not be confirmed by histopathology diagnosis due to pandemic conditions. Finally, we could not perform an equal number of CTs on each patient due to patient-related and other reasons.

Conclusion

In conclusion, low attenuation associated with hepatosteatosis in the liver parenchyma in NECT may be an indication that pneumonia severity may increase in COVID-19 patients. Therefore, when evaluating chest CT scans of COVID-19 patients, examination of the liver parenchyma for hepatosteatosis may provide useful information in terms of disease prognosis.

Declarations

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Ethics approval: This retrospective and the single-center study was approved by the Ethical Committee of Amasya University Sabuncuoğlu Şerefeddin Education and Research Hospital (8 July 2021, No:2021/128). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author.

Authors' Contributions

Conceptualization: Ahmet Turan Kaya; Methodology: Ahmet Turan Kaya, Burcu Akman, Veysel Kaya, Şirin Çetin; Formal analysis and investigation: Ahmet Turan Kaya, Şirin Çetin; Writing - original draft preparation: Ahmet Turan Kaya, Burcu Akman; Writing - review and editing: Burcu Akman; Supervision: Ahmet Turan Kaya, Burcu Akman, Veysel Kaya

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