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ORIGINAL ARTICLE

Hepatosteatosis Patients with Pseudocontrast Sign in COVID-19: Relationships with Disease Severity and Survival Times

COVID-19 Hastalarında, Psödo-Kontrast Bulgulu Hepatosteatozun Hastalık Şiddeti ve Sağkalım Süreleri ile İlişkisi

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Abstract

Introduction: The aim of the study was to investigate associations between hepatosteatosis (HS) with computed tomography severity score (CT-SS) and survival of coronavirus disease 2019 (COVID-19) patients attending the hospital.

Methods: Our study was a retrospective analysis of 435 reverse transcription polymerase-chain reaction-positive COVID-19 patients (aged ≥ 18 years) who attended our hospital between September and December 2021. The patient's chest CT parenchymal findings and CT-SSs were reported. For quantitative analysis, HS was defined if hepatic-to-splenic attenuation ratio (CTL/S)<1. In very fatty livers, we defined the hyperdense appearance of vascular structures compared to liver parenchyma as "pseudocontrast sign (PCS)." We divided patients into three groups based on the hepatic attenuation comparison of vascular attenuation. Group 1: no HS, Group 2: HS without PCS, and Group 3: HS with PCS.

Results: 210/435 (48.3%) patients were included in Group 1, 184/435 (42.3%) in Group 2, and 41/435 (9.4%) in Group 3. The Mean CTL/S of Group 3 was 0.56±0.14, which was significantly lower than the other two groups (p<0.001). There was a very significant (p<0.001) negative correlation between CT-SS and CTL/S. There was no significant difference between HS groups with intensive care unit (ICU) admission (p=0.27) and mortality (p=0.64). In multivariate Cox regression analysis, HS with PCS was an 11-fold (p<0.001) risk factor for shortening the time from hospital admission to death and 3-fold (p=0.035) for shortening the time from ICU admission to death.

Discussion and Conclusion: In our study, HS with the PCS was significantly associated with CT-SS but not with overall mortality. Consequently, this sign may be an independent indicator of shorter survival times among patients who died. However, multicenter studies are needed in a large patient population.

Keywords: CO-RADS; Computed tomography severity score; Hepatosteatosis; Hepatic-to-splenic attenuation ratio

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The novel coronavirus disease 2019 (COVID-19) was first detected in China and then spread all over the world. Some patients with COVID-19 may need treatment in the intensive care unit (ICU) due to causes such as acute respiratory distress syndrome (ARDS) which may result in death due to multiple organ failures. Real-time reverse transcription polymerase chain reaction (RT-PCR) test from nasal or oropharyngeal samples is the gold standard for diagnosis.[1] However, chest computed tomography (CT) can be applied to patients with clinically suspected COVID-19 whose PCR test is negative.[2] In addition, chest CT can provide information about both the pneumonia CT severity score (CT-SS) and liver and spleen parenchyma in the upper abdomen included in the imaging field.[3]

Hepatosteatosis (HS) causes deterioration in liver functions and increases the inflammatory response, leading to a more severe course of COVID-19 infection.[4,5] In addition, HS and obesity have been associated with recurrent infection and increased mortality due to impaired immune systems.[6] Therefore, it is important to evaluate the patients for the presence of HS. Non-contrast CT has proven to be a noninvasive imaging modality for diagnosing and grading HS.[7] The normal liver parenchyma has a similar or higher density to the spleen, and the liver vascular structures appear hypodense compared to the parenchyma. In HS, vascular structures change from isodense to hyperdense relative to the parenchyma, inversely proportional to the decrease in liver parenchyma density. In very fatty livers, we defined the hyperdense appearance of hepatic and portal veins compared to liver parenchyma as "pseudocontrast sign (PCS)." The attenuation value of the liver is at least 10 Hounsfield Units (HU) lower than the attenuation of the spleen.[8] In addition, the diagnosis can be made by calculating the hepatic-to-splenic attenuation ratio (CTL/S).[9]

In the literature, the effects of obesity and HS on admission CTs, CT-SS and disease severity, frequency of ICU hospitalization, and mortality have been investigated.[4,5,10–13] The diagnosis of HS in these studies is based on the quantitative measurements. However, this method can be difficult and time-consuming for clinicians in busy outpatient conditions. Therefore, rapid evaluation with a visual analysis is needed. In our study, we aimed to compare the CT-SS, mortality, and survival times of COVID-19 patients in the groups formed according to the presence of HS with PCS.

Materials and Methods

Our study was single-center and retrospective and was approved by the Amasya University Ethics Committee (28 July 2021, No: 2021/127). In our study, the rules of the "Helsinki Declaration and Good Clinical Practices" were followed. The ethics committee did not consider it necessary to obtain written informed consent from the patients in our study, which used retrospective and electronic data.

Study Population and Data Collection

The data of 490 patients who attended the emergency department of our hospital between September and December 2021 were analyzed retrospectively. Of all consecutive patients with positive RT-PCR tests, we included patients who had chest CT at the time of admission to the hospital. Patients with CT appearances of cirrhosis, with particularly large/numerous focal lesions that precluded ROI assessment in the liver parenchyma, image artifacts on CT that prevented evaluation, and pediatric patients (aged<18) were excluded from the study. Contrast-enhanced CTs were excluded from the study, as IV contrast agents may increase liver parenchymal density and affect attenuation values in patients. As a result, after excluding 55 patients, 435 patients were included in the study (Appendix 1).

Clinical and Laboratory Data

Initial chest CT images, laboratory results (within the first 24 h after hospital admission), and demographic data were obtained from our hospital's electronic medical records.

CT Protocol

Non-contrast chest CT scans were performed using a multidetector CT scanner, (128-slice GE Healthcare Revolution EVO CT), the protocol routinely applied in our hospital.

Image Analysis

The radiologist (9 years of experience in general radiology) reported the first chest CT scan that was performed within 24 h after admission to the hospital for the presence of COVID-19 pneumonia and HS retrospectively, blinded to the clinical data and laboratory indicators. Chest CTs were classified as CO-RADS in the range of 1–5 (1=very low and 5=very high) based on the suspicions of COVID-19 lung involvement.[14] In addition, chest CT-SSs were calculated based on the percentages of parenchymal involvement for each lobe using a predefined visual method on a total scale of 25 points (0=0%, 1=1–5%, 2=6–25%, 3=26–50%, 4=51–75%, and 5≥75%). Then, the scores of each 5 lobes were

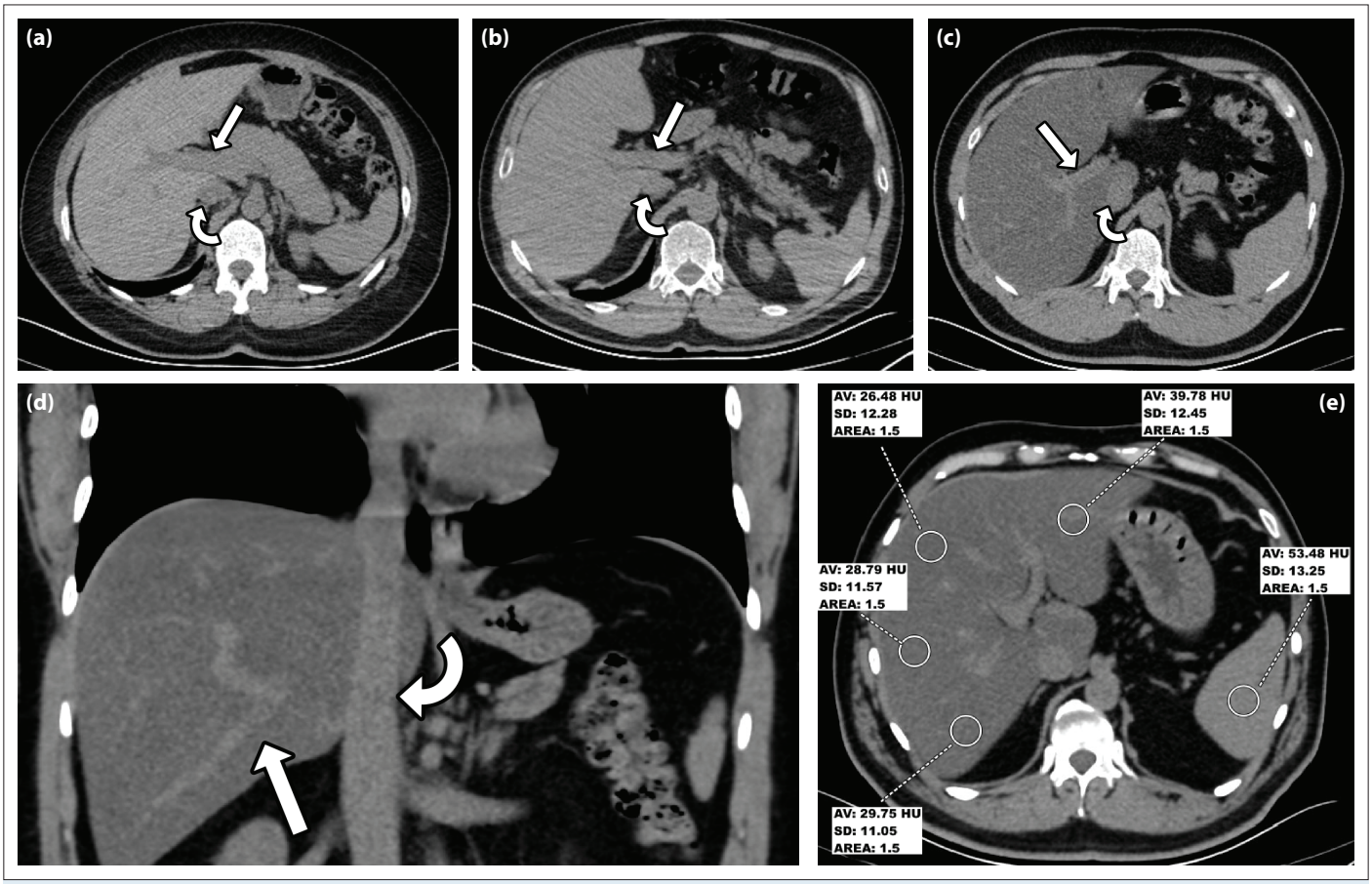

Figure 1. 47-year-old man was admitted to our hospital with complaints of fever, cough, and sore throat. His RT-PCR test was positive and non-contrast chest CT was consistent with CO-RADS 1, CT-SS=0 (Appendix 2). His treatment was started as an outpatient. However, as the patient's complaints increased on the 9th day, he applied to our hospital again and the second chest CT was performed. Due to CT CO-RADS 5 and CT-SS= 16, he was hospitalized and treated in the service for 5 days; then, he was discharged with full recovery. Based on the qualitative analysis of liver density, we divided the study population into 3 groups. Straight arrows show the portal vein and oblique arrows show the inferior vena cava. **(a)** In group 1 (no hepatosteatosis [CTL/S≥1]), the vascular structures are hypodense compared to normal liver parenchyma. **(b)** In Group 2 (HS without PCS), the vascular structures are isodense with minimal fatty liver parenchyma. **(c, d)** In Group 3 (HS with PCS), the vascular structures are relatively hyperdense compared to the liver parenchyma, due to the loss of density of the advanced fatty liver parenchyma. **(e)** In the axial upper abdomen sections included in the non-contrast chest CT image, we measured the hepatic attenuation (HU) values by placing 1.5 cm^2 ROIs in 4 different segments in both lobes of the liver. Furthermore, a 1.5 cm^2 ROI was placed in the spleen the attenuation value was measured as HU. CTL/S value was obtained by dividing the mean of 4 HU values in the liver by the spleen HU values.

summed, and the total CT-SS was calculated (Appendix 2).[15] The study population was divided into 3 groups based on the hepatic attenuation comparison of vascular attenuation. Group 1 (no HS): the vascular structures are hypodense compared to the normal liver parenchyma; Group 2 (HS without PCS): the vascular structures are isodense with minimal fatty liver parenchyma, and Group 3 (HS with PCS): the vascular structures are seen as relatively hyperdense compared to the liver parenchyma due to the density loss of the advanced fatty liver parenchyma (Fig. 1a–d). The radiologist measured the Hounsfield unit (HU) values of the liver and spleen on the unenhanced chest CT images. For analysis of liver density, 1.5 cm^2 regions of interest (ROI) were placed in four different segments of both lobes 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 four liver segments and dividing it by the spleen HU. HS was defined if the hepatic-to-splenic attenuation ratio (CTL/S)<1.[9] 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. 1e).

Statistical Analysis

SPSS Statistics program (Version 25.0) was used for the statistical analysis. The Kolmogorov–Smirnov test was used for normal distribution. Mean values and standard deviation were used for normally distributed variables.

Table 1. Comparison of demographic data and comorbidities according to HS groups

	Hepatosteatosis (HS) groups						Total	p[a]	Sig. diff.[b]
	HS negative		HS positive						
	Group 1		Group 2		Group 3				
	n	%	n	%	n	%			
Age (years)									
<60	75	47.2	61	38.4	23	14.5	159	**0.014**	**1–3**
≥60	135	48.9	123	44.6	18	6.5	276	**0.006**	**2–3**
Gender									
Male	104	40.9	118	46.5	32	12.6	254	**0.004**	**1–2**
Female	106	58.6	66	36.5	9	5	181	**0.001**	**1–3**
Survival								0.64	
Alive	146	48	123	40.5	35	11.5	304		
Death	64	48.9	61	46.6	6	4.6	131		
Outpatient	17	63	8	29.6	2	7.4	27		
Inpatient								0.27	
Non-ICU	139	48.8	116	40.7	30	1.5	285		
ICU	54	43.9	60	48.8	9	7.3	123		
CO-RADS 5									
Absent	75	69.4	30	27.8	3	2.8	108	<**0.001**	**1–2**
Present	135	41.3	154	47.1	38	11.6	327	<**0.001**	**1–3***
CO-RADS 5–3								<**0.001**	**1–2**
Absent	44	77.2	10	17.5	3	5.3	57		
Present	166	43.9	174	46	38	10.1	378		
Diabetes mellitus								0.671	
Absent	143	49	124	42.5	25	8.6	292		
Present	67	46.9	60	42	16	11.2	143		
Hypertension								0.597	
Absent	105	49.3	91	42.7	17	8	213		
Present	105	47.3	93	41.9	24	10.8	222		
Cardiovascular diseases								0.362	
Absent	146	46.9	132	42.4	33	10.6	311		
Present	64	51.6	52	41.9	8	6.5	124		
Pulmonary diseases								0.355	
Absent	171	47.9	149	41.7	37	10.4	357		
Present	39	50	35	44.9	4	5.1	78		
Neurological diseases								0.20	
Absent	193	46.7	180	43.6	40	9.7	413		
Present	17	77.3	4	18.2	1	4.5	22		
Kidney diseases								0.607	
Absent	205	48	182	42.6	40	9.4	427		
Present	5	62.5	2	25	1	12.5	8		

n: Number; Sig. diff.: Significant differences between groups; a: The difference in frequencies between the groups was analyzed with the Pearson Chi-Square test. In the comparison of *post hoc* paired groups, p<0.017 was considered statistically significant; b: Groups with a significant difference in pairwise comparisons; *: Fisher tests were used to compare Group 1 and Group 3; ICU: Intensive care unit; CO-RADS: COVID-19 reporting and data system.

Median values and interquartile range (IQR) were used for non-normally distributed variables. One-way ANOVA test was used to compare normally distributed continuous variables according to HS groups. LSD test and Tamhane T2 test were used according to whether the variables that differed significantly between the groups

Table 2. Comparison of continuous variables according to HS groups

	n	Mean/Median	SD	Min./25th	Max./75th	p	Sig. diff.
Age (years)							
Group 1	210	66		52	76.25	0.843	1–2
Group 2	184	66		57	75	**0.003**	**1–3**
Group 3	41	57		47	64.5	**0.002**	**2–3**
Total	435	66		54	75		
Liver density (HU)							
Group 1	210	59.24	6.57	4.87	77.64	<**0.001**	**1–2**
Group 2	184	50.2	6.52	28.65	65.52	<**0.001**	**1–3**
Group 3	41	32.4	8.47	9.55	57.4	<**0.001**	**2–3**
Total	435	52.89	1.37	9.55	77.64		
CTL/S*							
Group 1	210	1.17	0.15	1	1.79	<**0.001**	**1–2**
Group 2	184	0.86	0.11	0.5	0.99	<**0.001**	**1–3**
Group 3	41	0.56	0.14	0.13	0.91	<**0.001**	**2–3**
Total	435	0.98	0.24	0.13	1.79		
CT severity score							
Group 1	210	9		2	15	<**0.001**	**1–2**
Group 2	184	11.5		7.25	18	**0.008**	**1–3**
Group 3	41	11		8.5	20	0.990	2–3
Total	435	10		5	16		
Length of hospital stay (day)							
Group 1	193	12		8	18	0.147	1–2
Group 2	176	13		9	20	0.037	1–3
Group 3	39	10		7	13	**0.003**	**2–3**
Total	408	12		8	18		
Length of stay in ICU (day)							
Group 1	54	10		6	2.25	0.71	
Group 2	60	11		7	18.75		
Group 3	9	8		4	21.5		
Total	123	10		6	19		
Time from hospital admission to death (day)							
Group 1	64	21		15.25	3.75	0.436	1–2
Group 2	61	20		13.5	29.5	**0.001**	**1–3**
Group 3	6	8		3.75	12.25	**0.001**	**2–3**
Total	131	20		13	0.30		
Time from ICU admission to death (day)							
Group 1	49	10		6	18.5	0.74	
Group 2	47	9		6	18		
Group 3	4	4.5		1.5	6.75		
Total	100	9		6	17.75		
WBC (3.39–8.86; 10^9/L)[a]							
Group 1	210	6.24		4.84	9.01	0.99	
Group 2	184	6.21		4.94	8.18		
Group 3	41	6.36		4.96	8.49		
Total	435	6.29		4.87	8.47		
CRP (0–5; mg/L)[a]							
Group 1	210	15.78		7.05	67.48	<**0.001**	**1–2**

Table 2 (cont). Comparison of continuous variables according to HS groups

	n	Mean/Median	SD	Min./25th	Max./75th	p	Sig. diff.
Group 2	184	51.83		17.65	98.36	0.050	1–3
Group 3	41	3.6		12.61	85.74	0.146	2–3
Total	435	31.65		1.16	89.65		
Ferritin (22–322; ug/L)a							
Group 1	207	117.9		46.20	303.4	<**0.001**	**1–2**
Group 2	182	226.6		102.85	502.28	<**0.001**	**1–3**
Group 3	40	281.3		132.20	635	0.236	2–3
Total	429	184.4		69.05	383.45		

SD: Standard deviation; Min: Minimum; Max: Maximum; 25th: 25th percentile; 75th: 75th percentile; Sig. diff: Significant differences between groups, In the comparison of continuous variables according to HS groups; One-way ANOVA for those with a normal distribution (LSD test for homogeneous variances in pairwise *post hoc* comparison, [*] Tamhane T2 test for non-homogeneous), for those not normally distributed (a) Kruskal–Wallis test (Mann–Whitney U test for pairwise *post hoc* comparison test) was used.

Table 3. Cox regression model of risk variables for hospital survival times

	Univariate Cox regression analysis				Multivariate Cox regression analysis			
	p	HR	95% CI for HR		p	HR	95% CI for HR	
			Lower	Upper			Lower	Upper
Gender	0.664	1.081	0.761	1.537				
Age	0.046	1.019	1.0004	1.0385	**0.001**	**1.035**	**1.014**	**1.056**
ICU	0.125	0.727	0.484	1.092				
HS_Group 2–1	0.23	1.245	0.871	1.779	0.773	1.059	0.717	1.563
HS_ Group 3–1	<0.001	1.618	4.240	26.594	<**0.001**	**10.99**	**3.97**	**3.423**
CT severity score	0.007	1.032	1.009	1.056	0.525	1.009	0.981	1.039
Diabetes mellitus	0.426	0.859	0.590	1.249				
Hypertension	0.308	1.210	0.839	1.746				
Cardiovascular diseases	0.457	1.146	0.800	1.640				
Pulmonary diseases	0.954	1.013	0.652	1.574				
Neurological diseases	0.313	1.348	0.755	2.406				
Kidney diseases	0.422	0.664	0.244	1.805				
WBC	0.026	1.042	1.005	1.080	0.373	1.020	0.977	1.064
Triglycerides	0.037	1.002	1.0001	1.0043	0.115	1.002	1.0001	1.0044
Elevated liver enzymes	0.04	1.524	1.019	2.28	0.524	1.179	0.710	1.959
LDH	0.004	1.001	1.0004	1.0021	0.548	1.000	0.998	1.001
CRP	0.002	1.004	1.002	1.007	0.534	1.001	0.997	1.005
Ferritin	<0.001	1.001	1.0004	1.001	**0.004**	**1.001**	**1.0002**	**1.0011**
Fibrinogen	0.008	1.002	1.0005	1.003	0.038	1.002	1.0009	1.0032

Omnibus tests of overall model coefficients p<0.001; CI: Confidence interval; HR: Hazard ratio Elevated liver enzymes: AST and ALT; If the lower and upper confidence intervals included "1 value" that variable was not included in the model; WBC: White blood cell; ICU: Intensive care unit; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

in paired *post hoc* comparisons were homogeneous or heterogeneous, respectively. The Kruskal–Wallis test was used to compare the non-normally distributed continuous variables according to the HS groups. Mann–Whitney U test was used for pairwise *post hoc* comparison of variables with significant differences between the groups. The correlation coefficient and statistical significance for the relations between normally distributed CTL/S and non-normally distributed CT-SS variables were calculated by Spearman's test. For Group 3, liver parenchyma attenuation value (HU) and for CTL/S, threshold values were determined by ROC analysis. Pearson's Chi-square or Fisher tests were used to compare categorical variables according to HS groups. Bonferroni correction was

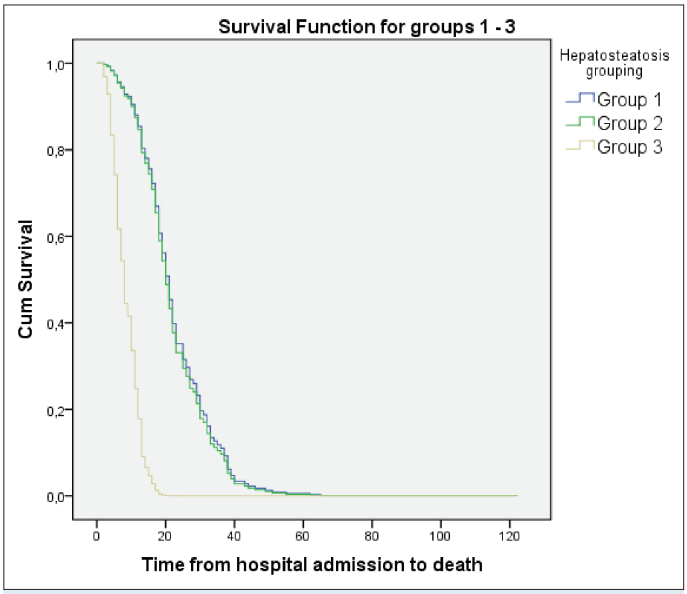

Figure 2. Cox regression curves for hospital survival times by HS groups.

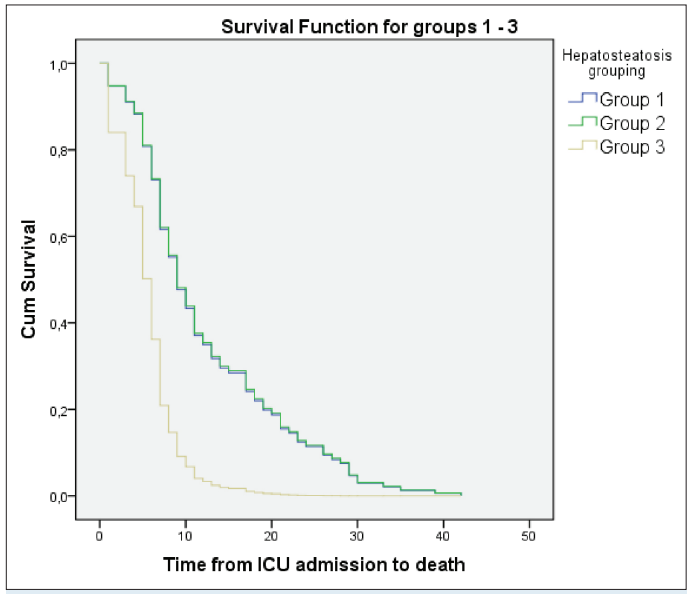

Figure 3. Cox regression curves for ICU survival times by HS groups.

used after pairwise comparisons of continuous and categorical variables with or without normal distribution, and p<0.017 was considered statistically significant. Cox regression analysis was used to identify risk factors affecting time from hospitalization to death and from ICU admission to time of death. The main factors related to mortality were evaluated by univariate and multivariate Cox regression analysis. Explanatory variables with a p<0.25 in the univariate analysis were included in the multivariate Cox regression analysis.[16] p<0.05 was considered statistically significant.

Results

Of the total 435 patients, 225/435 (51.7%) were HS-positive (Groups 2 and 3) (Fig. 1). There were 254/435 (58.4%) male patients. The median age was 66 years (IQR, 54-75). 225/408 (55.15%) of inpatients, had HS on their CT images. There was no significant difference between ICU admission and HS groups (p=0.27). 131/435 (30.1%) of our patients died. There was no significant difference in mortality between the groups (p=0.64). There was a significant difference between Group 1 and Groups 2 and 3 in patients with at least CO-RADS 5 on CT (Group 1–2 p<0.001; Group 1–3 p<0.001). There was no significant difference between comorbidities and HS groups (Table 1).

The mean liver density of all patients was 52.89±10.37 HU (9.55–77.64). The mean liver density of Group 3 was significantly lower than the other two groups (Group 1–3 p=<0.001; Group 2–3 p<0.001). The mean CTL/S of all patients was 0.98±0.24 (0.13–1.79). The mean CTL/S of Group 3 was significantly lower than the other two groups (Group 1–3 p<0.001; Group 2–3 p<0.001). The liver density threshold value for Group 3 was 37.89 HU (AUC=0.960; 95% CI: 0.923–0.997, p<0.001), providing 90% sensitivity and 99.98% specificity. The threshold value for the CTL/S ratio for Group 3 was 0.75 (AUC=0.973; 95% CI: 0.956–0.990, p<0.001), providing 95% sensitivity and 99.11% specificity. There was a low (correlation coefficient [r] = -0.275), but very significant (p<0.001) negative correlation between CT-SS and CTL/S. The median CT-SS value of Group 3 was 11 (IQR, 8.5–20), which was higher than Group 1 (p=0.008) (Table 2).

The median days from hospital admission to death were 8 in Group 3 (IQR, 3.75–12.25), which was shorter than in Groups 1 and 2 (p=0.001, p=0.001). In multivariate Cox regression analysis, age 1-fold (hazard ratio [HR]: 1.035; 95% CI: 1.014–1.056, p=0.001), HS with pseudocontrast 11-fold (HR: 10.99; 95% CI: 3.97–30.423, p<0.001), and ferritin 1-fold (HR: 1.001; 95% CI: 1.001–1.0002, p=0.004) were risk factors that shorten this time (Table 3 and Fig. 2).

The median days from ICU admission to death were 4.5 in Group 3 (IQR, 1.5–6.75), which was shorter than in Groups 1 and 2, and there was no significant difference (p=0.74). In multivariate Cox regression analysis, only HS with PCS 3-fold was a risk factor that shortens this time (HR: 3.237; 95% CI: 1.084–9.668, p=0.035) (Table 4 and Fig. 3).

Table 4. Cox regression model of risk variables for ICU survival times

	Univariate Cox regression analysis				Multivariate Cox regression analysis			
	p	HR	95% CI for HR		p	HR	95% CI for HR	
			Lower	Upper			Lower	Upper
Gender	0.184	1.316	0.878	1.972				
Age	0.273	1.011	0.991	1.032				
HS_Group 2–1	0.962	0.990	0.662	1.482	0.95	0.987	0.644	1.51
HS_Group 3–1	0.006	4.465	1.550	12.866	**0.035**	**3.237**	**1.084**	**9.668**
CT severity score	0.34	1.012	0.987	1.038				
Diabetes mellitus	0.167	0.733	0.472	1.139				
Hypertension	0.324	1.228	0.817	1.848				
Cardiovascular diseases	0.619	1.112	0.731	1.691				
Pulmonary diseases	0.925	1.025	0.612	1.716				
Neurological diseases	0.055	1.932	0.987	3.782				
Kidney diseases	0.67	1.286	0.405	4.083				
WBC	0.056	1.045	0.999	1.093				
Triglycerides	0.005	1.003	1.001	1.006	0.097	1.003	1.001	1.006
Elevated liver enzymes	0.521	1.166	0.730	1.863				
LDH	0.026	1.001	1.0002	1.0026	0.488	1.001	0.999	1.002
CRP	0.165	1.002	0.999	1.005				
Ferritin	0.027	1.001	1.0001	1.0011	0.322	1.000	1.0001	1.0009
Fibrinogen	0.212	1.001	1.0001	1.0022	0.873	1.000	0.999	1.002

Omnibus tests of overall model coefficients p=0.007; CI: Confidence interval; HR: Hazard ratio; Elevated liver enzymes: AST and ALT; If the lower and upper confidence intervals included "1 value" that variable was not included in the model; WBC: White blood cell; ICU: Intensive care unit; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

Discussion

In our study, we investigated the association of HS on chest CT severity score (CT-SS) and survival times by evaluating the presence of HS on CT quantitatively and qualitatively in COVID-19 patients. To our knowledge, this is the first study to investigate the severity of the disease and the time from hospitalization to death using HS groups. We found that HS-positive Group 2 (HS without PCS) and Group 3 (HS with PCS) had higher CT-SS on admission CT scan compared to Group 1 (no HS). There was no statistically significant relationship between these groups and mortality and ICU admission rates. However, in Cox regression modeling, the variable that most affected survival times was Group 3. We found that the time from hospitalization to death in Group 3 was shorter than in Group 1. Age and ferritin were the other factors affecting survival times. CRP, one of the inflammatory markers, did not affect these times and was not associated with Group 3. The median value of ferritin was significantly higher in Group 3 compared to the other two groups. Although there was no significant difference between the groups for the time from ICU hospitalization to death, Group 3 was the variable that most affected this time in Cox regression modeling. Only in Group 3, the frequency of patients under 60 years of age was higher. The frequency of HS was higher in males. However, there was no relationship between gender and survival time.

The early phase of COVID-19 infection is directly related to the pathogenic effect of the virus and the late phase is due to excessive cytokine release.[2] The receptor of the SARS-CoV-2 virus is angiotensin-converting enzyme 2. Since this receptor is found mostly in cholangiocytes (60%) and less in endothelial and hepatocyte cells in the liver, it can directly infect liver cells.[2] In addition, the virus was detected in liver biopsies independent of viral load, and changes related to apoptosis of liver cells were observed.[17] In addition, lipid metabolism dysfunction occurs due to the direct effect of the virus and causes changes consistent with hepatic steatosis, mild lobular, portal inflammation, and apoptosis in histopathological examination.[18] Pro-inflammatory cytokines increase due to liver damage caused by the virus. On the other hand, in addition to deterioration in liver functions, HS related to obesity increases the inflammatory response and causes a weakened immune system.[4,5,19,20] Since only positive patients were included in our study, the

frequency of HS was not calculated, and in other studies, they reported that the probability of HS is higher in positive groups compared to COVID-19-negative control groups.[5,11] Palomar-Lever et al.[4] and Çoraplı et al., who included only COVID-19-positive patients in their study, found that CT-SS was higher in patients with COVID-19 who had HS, like us.[13] As in the study of Tahtabasi et al., a significant negative correlation was found between CT-SS and CT/S in our study.[5,11] Forlano et al.[21] found that CRP values were significantly higher in the HS group, but they found that there was no significant difference in ferritin values. In our study, although CRP and ferritin levels were significantly higher in groups with HS, no significant difference was found in neutrophil and lymphocyte counts. We thought that the high CT-SS in patients with HS with PCS was due to the direct effect of the virus and increased inflammation secondary to HS.

Singh et al.[22] and Hegyi et al.[23] reported in their review that the presence of HS did not make a difference in terms of the frequency of COVID-19 mortality, but there was an increased risk of serious infection. However, in terms of ICU admission frequency, Singh et al.[22] reported a significant increase in the group with HS, but Hegyi et al.[23] reported no significant difference. Forlano et al.[21] and Portincasa et al.[24] reported that there was no difference in mortality and ICU hospitalization rates between the group with and without HS, which was consistent with our study. While the prevalence of HS in the Turkish population was 45.5%, the rate of HS in inpatients in our study was 55.15%, and there was no relationship between the risk of hospitalization (inpatient) and HS groups.[25] Therefore, the presence of HS may not result in an increased risk of hospitalization and ICU admission in patients with COVID-19. In another study conducted in our country, Çoraplı et al.[13] found that there was no relationship between the presence of HS and length of stay in the hospital and ICU. In our study, the length of hospital stay was significantly shorter in HS with PCS, but there was no significant difference in ICU length of stay. However, unlike Çoraplı et al.,[13] in our study, we evaluated the hospital and ICU survival times in COVID-19 patients compared to the HS groups by including comorbidities, and we found it to be shorter in HS with PCS. Both the direct damage of the virus and the presence of HS may explain the shorter survival times and high CT-SS by increasing the risk of infection severity and mortality, causing a more severe course of COVID-19 infection.

In the study of Zhou et al.,[26] they observed 4 times more severe COVID-19 infection in COVID-19 patients with HS under 60 years of age compared to those without. In our study, the median age of group HS with PCS, which had more severe disease, was lower than other groups. In a previous study conducted in our country, non-alcoholic fatty liver disease was most frequently seen in 3rd and 4th decade age groups.[27] This may explain the lower age rate in the group HS with PCS compared to other groups.

To our knowledge, our study is the first to investigate the effect of HS groups on the survival of patients with COVID-19. Although the presence of HS did not cause an increase in mortality and the frequency of ICU hospitalization, we found that it was an important variable in decreasing the survival time by increasing the disease severity, especially in HS with the PCS group. Visually diagnosing HS patients with PCS can aid in prognosis, especially in times of a severe pandemic.

Our study had several limitations. First, the results of our analysis cannot be generalized because it is a single-center study. Hence, there is a need for multicenter large-scale studies. Second, the diagnosis of HS could not be confirmed by histopathology diagnosis due to pandemic conditions. Third, we did not investigate the effect of HS on the frequency of hospitalization, as the number of outpatients was not sufficient. Finally, the effect of HS on CT-SS in COVID-19 could not be investigated, as assessments were made on the chest CT images at admission.

Conclusion

A statistically significant relationship was found in terms of severe COVID-19 pneumonia and shorter survival times in patients with HS with PCSs in the liver on the upper abdominal sections of non-contrast chest CT scans, in our study. However, multicenter studies are needed in a large patient population. The PCS can provide an easy and quick visual diagnosis of hepatic steatosis on CT. When evaluating chest CT scans of patients with COVID-19 pneumonia, evaluation of the liver for HS and PCS in the included upper abdominal CT scan can provide useful information on the estimation of disease severity.

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Conflict of Interest: None declared.

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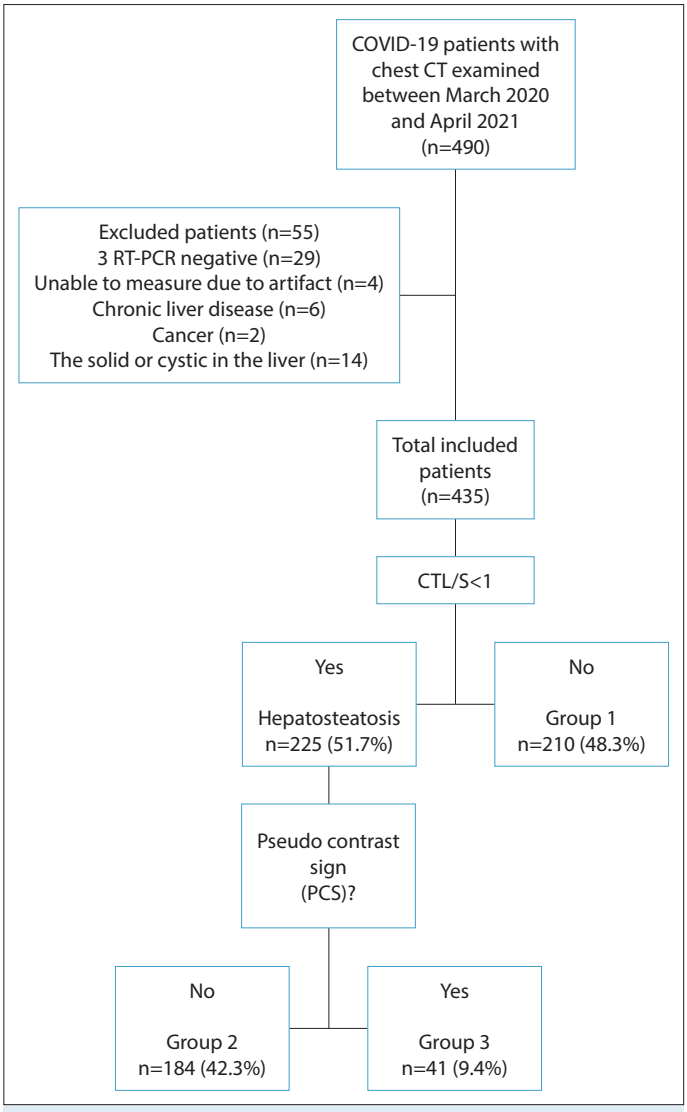
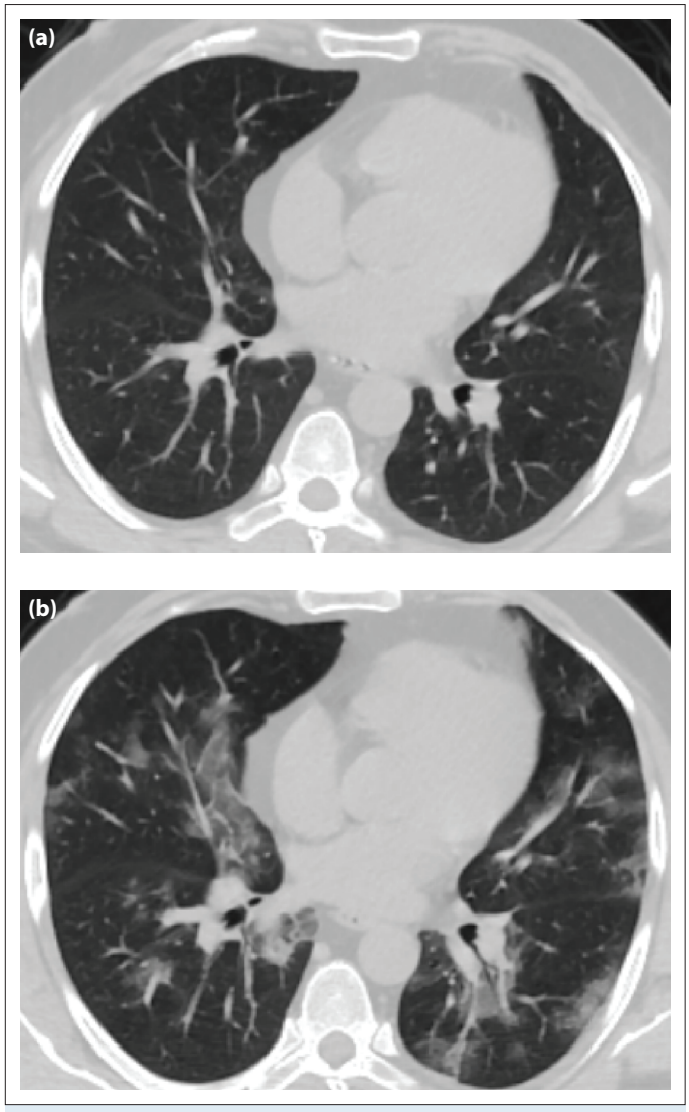
Appendices



Appendix 1. Study flowchart for the inclusion and exclusion criteria of the patient sample. COVID-19: Coronavirus disease; 2019; CT: Computed tomography; RT-PCR: Reverse transcription-polymerase chain reaction; CTL/S: Hepatic-to-splenic attenuation ratio.



Appendix 2. 47-year-old man was admitted to our hospital with complaints of fever, cough, and sore throat. His RT-PCR test was positive and non-contrast chest CT was consistent with CO-RADS 1, CT-SS=0. His treatment was started as an outpatient. However, as the patient's complaints increased on the 9th day, he applied to our hospital again and the second chest CT was performed. Due to CT CO-RADS 5 and CT-SS= 16, he was hospitalized and treated in the service for 5 days, then he was discharged with full recovery. (a) Axial lung window of initial chest CT image shows no pulmonary involvement, CO-RADS 1, CT-SS=0. (b) Axial lung window of second chest CT image shows ground-glass opacities in both lung lobes, mostly peripherally located, CO-RADS 5 and CT-SS=16.