Is Fatty Liver Associated with Increased Mortality and Morbidity in Coronavirus Disease 2019 (COVID-19) Pneumonia?

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Background: **Fatty liver has been shown to be associated with severe COVID-19 disease without any impact on mortality. This is based on heterogenous criteria for defining both fatty liver as well as the severity parameters. This study aimed to study the impact of fatty liver on the mortality and severity of disease in patients with COVID-19 pneumonia.** ***Methods:*** **In a case control study design, patients with COVID-19 pneumonia (COVID-19 computed tomography severity index [CTSI] on high-resolution computed tomography chest of ≥1) with fatty liver (defined as liver to spleen attenuation index ≤5 on noncontrast computed tomography cuts of upper abdomen) were compared with those without fatty liver. The primary outcome measure was in-hospital mortality, and the secondary outcome measures were CTSI score, need for intensive care unit (ICU) care, need for ventilatory support, duration of ICU stay, and duration of hospital stay.** ***Results:*** **Of 446 patients with COVID-19 pneumonia, 289 (64.7%)admitted to Max Hospital, Saket, India, between January 1, 2021, and October 30, 2021, had fatty liver. Fifty-nine of 446 patients died during the index admission. In-hospital mortality was not different between patients with fatty liver (38 [13.24%]) or without fatty liver (21 [13.81%]). COVID-19 CTSI score was found to be significantly higher among patients who had fatty liver (13.40 [5.16] vs 11.81 [5.50]; *P* = 0.003). There was no difference in the requirement of ICU (94 [32%] vs 62 [39.49%]; *P* = 0.752), requirement of ventilatory support (27 [9.34%] vs 14 [8.91%]; *P* = 0.385), duration of ICU stay (8.29 [6.87] vs 7.07 [5.71] days; *P* = 0.208), and duration of hospital stay (10.10 [7.14] vs 10.69 [8.13] days; *P* = 0.430) between the groups with fatty liver or no fatty liver. Similarly, no difference was found in primary or secondary outcomes measure between the group with severe fatty liver vs mild/moderate or no fatty liver. High total leucocyte count and Fibrosis-4 (FIB-4) index were independently associated with mortality.** ***Conclusions:*** **Fatty liver may not be associated with increased mortality or clinical morbidity in patients who have COVID-19 pneumonia.** **(J Clin Exp Hepatol 2022;12:1320–1327)**

The pandemic of coronavirus disease 2019 (COVID-19) has led to significant morbidity and mortality across the world since the early part of 2020. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory system, and most deaths are related to the severe viral pneumonia and respiratory failure. However, other organ systems also seem to get affected to a variable degree. Patients who have underlying comorbidity seem to be more predisposed to worst outcomes. Almost one-third to three-fourth of patients with COVID-19 have been reported to have some degree of liver injury at the time of presentation.[1,2] Because of this, patients with pre-existing liver disease, especially those with cirrhosis, have been reported to develop decompensation and even death when they acquire infection with SARS-CoV-2.[3] The risk is higher in patients who have more advanced liver disease at the time of getting infected.[4,5] A number of earlier studies have presented data suggesting that the COVID-19 disease is either severe[6–9] or progressive[10] in the presence of underlying fatty liver. None of these studies have demonstrated any impact of fatty liver on mortality in the COVID-19 patients. Different definitions were used to detect the presence of fatty liver in these studies (the new MAFLD [metabolic-associated fatty liver disease] criteria[11] or radiological criteria or past history of the presence of NAFLD [nonalcoholic fatty liver disease] or hepatic steatosis index[12]), which makes the results difficult to compare. Even the stage of COVID-19 was not

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Abbreviations: CTSI: computed tomography severity index; HRCT: high-resolution computed tomography; ICU: intensive care unit; LAI: liver attenuation index; MAFLD: metabolic (dysfunction) associated fatty liver disease; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PACS: picture archiving and communication system
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clearly defined, and they included patients ranging from mild to severe disease. In some studies, the presence of noninvasively measured advanced liver fibrosis was found to be more strongly associated with adverse outcomes.[13]

So, we carried out a study comparing the outcomes in clearly defined cases of fatty liver with COVID-19 pneumonia (the most severe form of COVID-19 illness).

PATIENTS AND METHODS

Study Design

It was a retrospective observational case–control study.

Inclusion Criteria

Admitted patients who were positive for SARS-CoV-2 nasopharyngeal swab reverse transcription polymerase chain reaction (rt-PCR) with the availability of upper abdominal cuts on the high-resolution computed tomography (HRCT) chest and a COVID-19 computed tomography severity index (CTSI) score of ≥1.

Exclusion Criteria

Patients with known history of underlying cirrhosis, liver cancer, and congestive cardiac failure and those with a CTSI score of <1 were excluded.

Data Collection

HRCT chest of patients done, between January 1, 2021, and October 30, 2021, with a suspected diagnosis of COVID-19 pneumonia, SARS-CoV-2 infection, and viral pneumonia were retrieved from the picture archiving and communication system (PACS) of Max Smart Super Speciality Hospital and Max Super Speciality Hospital, Saket.

Data of COVID-19 CTSI score and the CT attenuation difference between the liver and spleen on noncontrast upper abdominal cuts of the CT scan were recorded.

Demographic data and laboratory data, including complete blood count, liver function test, renal function test, lipid profile, serum Lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, serum ferritin, Hepatitis B surface antigen (HBsAg), and anti-HCV, were recorded from the electronic health records.

Noninvasive assessment of liver fibrosis was done using the FIB-4 index, which was calculated as per the standard formula incorporating the values of age, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and platelets.[14]

Definitions

Fatty liver was defined as the liver attenuation index (LAI) of ≤5, in the nonenhanced scans of the upper abdomen (retrieved as part of the HRCT chest). LAI was calculated as the attenuation difference between the liver and spleen on a noncontrast-enhanced CT scan of upper abdomen.[15] Patients were further subgrouped into mild to moderate fatty liver (LAI: minus10 to plus5) and severe fatty liver (LAI: less than minus10).

Primary Outcome Measure

The primary outcome was mortality rates of patients with COVID-19 pneumonia with underlying fatty liver.

Secondary Outcome Measures

The secondary outcome was the severity of patients with COVID-19 pneumonia with underlying fatty liver. Parameters studied for severity were COVID-19 CTSI, need for intensive care unit (ICU) admission, need for ventilatory support, length of ICU stay, and length of hospital stay.

Endpoints

Patients were followed up till discharge from the hospital or till death during the index hospital admission.

Statistical Analysis

A sample size of 240 in each group was calculated to detect a difference in mortality of 10% at 5% significance level and 80% power based on the reported mortality in the groups with and without steatosis $\pi 1 = 0.226$ and $\pi 2 = 0.152$.[16]

The results are presented as mean (standard deviation) for normally distributed and median (range) for skewed continuous data and proportions for categorical data. The cases with fatty liver were compared with the controls without fatty liver by Student *t*-test for quantitative characteristics and by chi-square test for qualitative characteristics. For the variables with highly skewed distribution, Mann–Whitney test was used. The significance level was fixed at 5%, and SPSS, version 21, was used for calculations.

The study was reviewed and approved by the Institutional Ethics Committee, and a waiver of consent was granted by the Institute ethics committee in the view of retrospective analysis of deidentified data for patients admitted during the COVID-19 pandemic (Ref no: BHR/RS/MSSSH/GMHRCMS/MHEC/GASTRO/21–8; dated January 3, 2022).

RESULTS

Between January 1 , 2021, and October 30, 2021, 459 patients with COVID-19 admitted to Max Hospital, Saket, had HRCT chest available on PACS. Of these, 13 had a COVID-19 CTSI score of 0 and were therefore excluded. Of the 446 patients with COVID-19 pneumonia, 289 (64.79%) had fatty liver as per the definition used, and 157 did not have fatty liver.

Fatty Liver and COVID-19 Pneumonia

There was no difference in the baseline demographic and laboratory parameters between the group with fatty liver or no fatty liver (Table 1) except for a higher median serum

Table 1 Demographic and Laboratory Parameters in Patients of COVID-19 Pneumonia with Fatty Liver.

Parameters	Fatty liver (n = 289)	No fatty liver (n = 157)	*P* value
Age (years), mean (SD)	56.35 (14.33)	58.29 (17.13)	0.229
Sex (Males), n (%)	195 (67.47)	93 (59.23)	0.082
BMI (kg/m^2), mean (SD)	26.60 (5.23)	25.94 (4.81)	0.459
Hb (gm%), mean (SD)	12.52 (1.96)	12.43 (1.85)	0.650
TLC ($\times 10^3$/cumm), mean (SD)	10.26 (5.73)	11.16 (6.78)	0.136
Platelets (10^9/L), mean (SD)	241.51 (99.31)	242.51 (93.32)	0.918
Bilirubin (mg%), mean (SD)	0.62 (0.36)	0.57 (0.27)	0.137
AST (IU/L), median (range)	46.8 (11–190)	44 (10–1021)	0.248
ALT (IU/L), median (range)	48 (7–262)	49 (7–416)	0.350
SAP (IU/L), median (range)	73 (25–408)	72 (25–224)	0.921
GGT (IU/L), median (range)	62 (8–823)	55 (8–450)	0.174
Albumin (gm%), mean (SD)	3.48 (0.46)	3.40 (0.42)	0.073
Diabetes, n (%)	129 (44.63%)	68 (43.33%)	0.788
HT, n (%)	116 (40.13%)	74 (47.13%)	0.154
LDH (IU/L), median (range)	349.5 (169–706)	364 (132–802)	0.655
D-Dimer (μg/mL), median (range)	0.76 (0.14–22.34)	0.76 (0.20–20.56)	0.916
CRP (mg/L), median (range)	50.87 (0.52–305.53)	52.7 (0.52–283.9)	0.800
Ferritin (ng/ml), median (range)	252.10 (0.00–6260)	56 (0.00–2772.60)	0.001
FIB-4, median (range)	1.69 (0.31–8.02)	1.56 (0.32–25.30)	0.984

BMI, body mass index; Hb, hemoglobin, TLC, Total leucocyte count; AST, Aspartate aminotransferase; CRP, C-reactive protein; SAP, Serum alkaline phosphatase; GGT, Gamma-glutamyl transferase; HT, Hypertension; LDH, Lactate dehydrogenase; FIB, Fibrosis-4.

ferritin level in patients with fatty liver (252.10 [0.00–6260] vs 56 [0.00–2772.60]; P = 0.001). The primary outcome (in-hospital mortality) was not different between patients with fatty liver (38 [13.24%] died) or without fatty liver (21 [13.81%] died); P = 0.866. Among the secondary outcome measures, only the mean COVID-19 CTSI score was found to be significantly higher among patients who had fatty liver (13.40 [5.16] vs 11.81 [5.50]; P = 0.003). There was no difference in the requirement of ICU (94 [32%] vs 62 [39.49%]; P = 0.752), requirement of ventilatory support (27 [9.34%] vs 14 [8.91%]; P = 0.385), mean duration of ICU stay (8.29 [6.87)] vs 7.07 [5.71] days; P = 0.208), and mean duration of hospital stay (10.10 [7.14] vs 10.69 [8.13] days; P = 0.430) between the groups with fatty liver or no fatty liver (Table 2).

Severe Fatty Liver and COVID-19 Pneumonia

In a sensitivity analysis, patients with COVID-19 pneumonia with severe fatty liver (n = 78) were compared with the group with mild fatty liver or no fatty liver (n = 368). The patients with severe fatty liver were younger, less likely to be hypertensive, and they had significantly more liver injury as seen by higher median AST levels (53.50 [11–190] vs 49 [10–102] IU/L; P = 0.017), median ALT levels (54.50 [13–195] vs 48 [7–416] IU/L; P = 0.015), and median Gamma-glutamyl transferase (GGT) levels (72.5 [14–272] vs 55 [8–823] IU/L; P = 0.016) in this group (Table 3). Despite these differences, the mortality between the two groups was not different (10 [12.98%] vs 49 [13.53%] died; P = 0.898). Like in the group with fatty liver, patients with severe fatty liver also had higher mean COVID-19 CTSI score (14.08 [5.03] vs 12.58 [5.37]; P = 0.024.; Table 4).

Fatty Liver with High FIB-4 Index

To assess the impact of the presence of advanced liver fibrosis (using a noninvasive marker; FIB 4 index >3.25) in patients with fatty liver, on the primary outcome

Table 2 Outcomes of COVID-19 Pneumonia Patients with Fatty Liver.

Outcomes	Fatty liver (n = 289)	No fatty liver (n = 157)	*P* value
Final outcome (died), n (%)	38 (13.24)	21 (13.81)	0.866
COVID-19 CTSI, mean (SD)	13.40 (5.16)	11.81 (5.51)	0.003
ICU requirement, n (%)	94 (32.52)	62 (39.49)	0.752
Ventilatory support, n (%)	27 (9.34)	14 (8.91)	0.385
Duration ICU stay (days), mean (SD)	8.29 (6.87)	7.07 (5.71)	0.208
Hospital stay (days), mean (SD)	10.10 (7.14)	10.69 (8.13)	0.430

CTSI: computed tomography severity index; ICU: intensive care unit.

Table 3 Demographic and Laboratory Parameters of Patients of COVID-19 Pneumonia with Severe Fatty Liver.

Parameters	Severe fatty liver (n = 78)	No/mild fatty liver (n = 368)	*P* value
Age (years), mean (SD)	51.55 (14.18)	58.18 (15.63)	0.001
Sex (males), n (%)	49 (62.82)	239 (64.94)	0.722
BMI (kg/m^2), mean (SD)	26.73 (5.60)	26.29 (4.97)	0.678
Hb (gm%), mean (SD)	13.0 (1.93)	12.38 (1.90)	0.010
TLC ($\times 10^3$/cumm), mean (SD)	10.24 (6.05)	10.65 (6.15)	0.592
Platelets (10^9/L), mean (SD)	247.47 (105.55)	240.67 (95.38)	0.575
Bilirubin (mg%), mean (SD)	0.62 (0.33)	0.59 (0.33)	0.489
AST (IU/L), median (range)	53.50 (11–190)	49 (10–102)	0.017
ALT (IU/L), median (range)	54.50 (13–195)	48 (7–416)	0.015
SAP (IU/L), median (range)	74 (35–218)	72 (25–408)	0.597
GGT (IU/L), median (range)	72.5 (14–272)	55 (8–823)	0.016
Albumin (gm%), mean (SD)	3.5 (0.42)	3.45 (0.45)	0.339
Diabetes, n (%)	31 (39.74)	166 (45.10)	0.386
HT, n (%)	23 (29.48)	167 (45.38)	0.010
LDH (IU/L), median (range)	336 (218–539)	354 (132–802)	0.817
D-Dimer (μg/mL), median (range)	0.85 (0.23–12.82)	0.75 (0.14–22.34)	0.722
CRP (mg/L), median (range)	63.02 (2.54–283.92)	49.67 (0.52–305.53)	0.456
Ferritin (ng/mL), median (range)	265.70 (0.00–2455.50)	182.80 (0.00–6260)	0.217

TLC, Total leucocyte count; AST, Aspartate aminotransferase; SAP, Serum alkaline phosphatase; CRP, C-reactive protein; GGT, Gamma-glutamyl transferase; HT, Hypertension; LDH, Lactate dehydrogenase; FIB, Fibrosis-4.

measure, another subgroup analysis was done comparing patients with fatty liver and advanced fibrosis with fatty liver without advanced liver fibrosis. There were 28 patients with COVID-19 who had FIB-4 value >3.25. No difference in mortality was found (5/28 [17.85%] in the fatty liver with high FIB-4 group vs 25/225 [11.11%] in the fatty liver with low FIB-4 group died; $P = 0.347$).

Factors Associated with In-hospital Mortality

Fifty-nine patients with COVID-19 pneumonia died in the hospital, with a mortality rate of 13.22% (Table 5). On univariate analysis, the factors associated with mortality were the presence of diabetes, presence of hypertension, low body mass index, low hemoglobin, high TLC, LDH, ALT, high FIB-4 index, and higher COVID-19 CTSI score. On multivariable logistic regression analysis, using the enter method and entering the variables found to be significant in univariate analysis, only high total leukocyte count (TLC) (OR: 1.082; 95% CI: 1.005–1.165) and high FIB-4 (OR: 1.606; 95% CI: 1.002–2.576) values were independently found to be associated with in-hospital mortality (Table 6).

DISCUSSION

In a case–control format, we demonstrated in patients with COVID-19 pneumonia that the presence of fatty liver or severe fatty liver or fatty liver with high FIB-4 was not associated with either mortality or other adverse outcomes such as need for ICU care or need for ventilatory support.

We have in a significant number of patients (289 cases and 157 controls), convincingly demonstrated that the presence of fatty liver is not associated with an increased risk of in-hospital mortality if they develop COVID-19 pneumonia. The study was done in a homogenous group of patients who already had a severe variety of SARS-CoV-2 infection in the form of COVID-19 pneumonia rather than a simple upper respiratory infection. We selected only those patients who had a CTSI score of at least 1 on HRCT chest and were admitted to the hospital because of their illness. Previous studies also have not been able to demonstrate an increased mortality risk in COVID-19 patients in the presence of fatty liver. But all the previous studies were done in a heterogenous population of COVID-19 patients with small number of cases.[17] The earlier studies have used very different criteria (past history of presence of fatty liver, hepatic steatosis index,[18] presence of obesity with raised transaminases in the past,[19] MAFLD[13,20–22] for defining the presence of fatty liver). Some of these criteria may not be so robust when it comes to defining fatty liver among patients suffering from COVID-19. For example, the hepatic steatosis index uses the values of AST and ALT to calculate the presence of fatty liver, and we know that liver enzymes are

Table 4 Outcomes in COVID-19 Pneumonia Patients with Severe Fatty Liver.

Outcomes	Severe fatty liver (n = 78)	No/mild fatty liver (n = 368)	*P* value
Final outcome (died), n (%)]	10 (12.98)	49 (13.53)	0.898
COVID-19 CTSI, mean (SD)	14.08 (5.03)	12.58 (5.37)	0.024
ICU requirement, n (%)	25 (32.05)	131 (35.59)	0.551
Ventilatory support, n (%)	7 (8.97)	34 (9.23)	0.941
Duration ICU stay (days), mean (SD)	8.62 (7.81)	7.65 (6.33)	0.495
Hospital stay (days), mean (SD)	9.22 (5.70)	10.54 (7.81)	0.085

CTSI: computed tomography severity index; ICU: intensive care unit; SD: standard deviation.

frequently elevated among patients with COVID-19. This may lead to an overestimation of the presence of fatty liver in this group of patients. Furthermore, the new MAFLD criterion is a consensus-derived criterion,[11] and it needs to be validated by more evidence for its use as a definition of fatty liver disease. We feel that using MAFLD for defining fatty liver in other extrahepatic conditions appears too premature. Furthermore, this criterion is biased toward making a diagnosis of metabolic dysfunction rather than fatty liver per se. One of the parameters for making a diagnosis of MAFLD is diabetes mellitus, and there is now significant evidence suggesting the development of new-onset diabetes among patients with COVID-19, which might again lead to overestimation of fatty liver.[23–25] Similarly, the parameter of elevated CRP, which is used as one of the parameters to define the presence of metabolic dysfunction (within the definition of MAFLD), is also very frequently present during the course of COVID-19.[26] We, on the other hand, defined fatty liver on the basis of validated radiological criterion (LAI <5) irrespective of metabolic predisposition to fatty liver.[27] The radiological criteria used for making a diagnosis of fatty liver in the present study were not affected by the current disease state (COVID-19). So, we believe that our study more appropriately assesses the relationship between fatty liver (irrespective of its affiliation with metabolic dysfunction or etiology) and COVID-19. To test the robustness of the association, we also did a subgroup analysis of patients with severe fatty liver (LAI score <−10), and even in this group, no association was found with mortality or other adverse events. A recent meta-analysis also failed to demonstrate any impact of fatty liver on mortality in patients with COVID-19.[8] Other studies have also demonstrated that factors other than NAFLD per se are associated with mortality in patients with COVID-19. A study in 61 NAFLD patients with COVID-19 demonstrated that in the NAFLD group, male gender and high ferritin were associated with increased mortality, although NAFLD per se was not associated with adverse outcomes.[28] Few more studies have also demonstrated that only those patients with underlying cirrhosis, alcoholic liver disease, and hepatocellular carcinoma but not NAFLD were associated with increased mortality due to COVID-19.[29,30]

A number of previous studies have shown that the presence of fatty liver is associated with more severe COVID-19 illness.[6,7,10,16–22] The postulated mechanism is that patients with NAFLD also have an inflammatory milieu with elevated levels of inflammatory cytokines,[31,32] which somehow aggravate the systemic inflammatory response in the presence of COVID-19. It has also been shown that the ACE2 levels (the receptors used by SARS-CoV-2 to enter the cells) are upregulated in the presence of chronic liver injury.[33] However, the earlier studies have used a variety of means to define the presence of fatty liver and have used a variety of outcomes to define the severity of COVID-19. Using the definition of MAFLD, it was demonstrated in two case–control studies (number of patients being 55–65) that the risk of severe COVID-19 disease was fourfold higher among patients who had MAFLD and that the risk increased for each metabolic risk factor that was added.[20,21] Chen et al diagnosed fatty liver by hepatic steatosis index and demonstrated that among 178 patients with fatty liver and COVID-19, there was an increased need for intubation and vasopressor use.[16] In another study, 367 patients with COVID-19 were diagnosed as having underlying NAFLD/nonalcoholic steatohepatitis (NASH) based on past documentation or history of obesity along with elevated liver enzymes on three prior occasions. They found that the presence of NAFLD/NASH was associated with higher odds for hospitalization.[19] The increased severity has also been documented in patients with fatty liver who are aged <60 years.[22] So, it is evident that different studies have demonstrated the association of fatty liver with a variety of severity defining parameters without any predetermined criteria for defining severity. In our study, we had predefined secondary outcome measures defining severity, such as COVID-19 CTSI score, need for ICU admission, need for ventilatory support, length of hospital stay, and length of ICU stay. Of these, only the CTSI score was found to be significantly higher among patients who had fatty liver. It was also found to be higher among those who had severe fatty liver compared with those with mild or no fatty liver, suggesting a strong association with presence and with degree of fatty liver. Radiological severity has also been highlighted by previous reports of COVID-19 in the presence of underlying fatty liver.[6,7] But although the CTSI was found to be higher in patients with fatty liver, we could not demonstrate any association of fatty liver with clinical parameters of severity. Furthermore, CTSI score was also not independently associated with mortality. Similar to our study, a few other studies have also

Table 5 Factors Associated With In-Hospital Mortality Among Patient With COVID-19 Pneumonia.

Factors	Died (n = 59)	Survived (n = 379)	*P* value
Age (years), mean (SD)	64.54 (13.67)	55.85 (15.44)	<0.001
Sex (males), n (%)	43 (72.88)	241 (63.42)	0.157
BMI (kg/m^2), mean (SD)	24 (4.44)	26.59 (4.71)	0.012
Hb (gm%), mean (SD)	11.87 (2.11)	12.59 (1.84)	0.006
TLC ($\times 10^3$/cumm), mean (SD)	13.45 (10.10)	10.18 (5.16)	0.018
Platelets (10^9/L), mean (SD)	219.47 (92.22)	245.72 (97.66)	0.054
Total bilirubin (mg%), mean (SD)	0.70 (0.46)	0.58 (0.31)	0.068
AST (IU/L), median (range)	49 (15–1021)	44 (10–473)	0.040
ALT (IU/L), median (range)	49 (13–416)	48 (7–322)	0.196
SAP (IU/L), median (range)	76 (38–408)	73 (25–408)	0.445
GGT (IU/L), median (range)	67 (18–263)	58 (8–823)	0.431
Albumin (gm%), mean (SD)	3.35 (0.39)	3.47 (0.45)	0.048
Diabetes, n (%)	36 (61.01)	160 (42.10)	0.007
HT, n (%)	32 (54.23)	156 (41.05)	0.057
LDH (IU/L), median (range)	446 (169–634)	339 (132–802)	0.018
D-Dimer (μg/mL), median (range)	0.87 (0.21–20.56)	0.75 (0.14–22.34)	0.179
CRP (mg/L), median (range)	58.59 (2.5–305.52)	50.27 (0.52–283.92)	0.324
Ferritin (ng/mL), median (range)	262.05 (0.00–6260)	204 (0.00–2772.60)	0.720
Fatty liver, n (%)	38 (64.40)	253 (66.75)	0.836
Severe fatty liver, n (%)	10 (16.94)	67 (17.67)	0.928
FIB 4, median (range)	2.14 (0.45–25.7)	1.56 (0.31–9.17)	0.018
COVID-19 CTSI, mean (SD)	15.14 (5.34)	12.51 (5.28)	<0.001
ICU requirement, n (%)	47 (79.66)	107 (28.15)	0.0001
Ventilatory support, n (%)]	37 (62.71)	4 (1.05)	0.0001
Duration ICU stay (days), mean (SD)	7.89 (5.56)	7.86 (6.80)	0.991
Hospital stay (days), mean (SD)	11.34 (7.23)	10.12 (7.55)	0.249

CTSI: computed tomography severity index; ICU: intensive care unit; TLC, Total leucocyte count; AST, Aspartate aminotransferase; CRP, C-reactive protein; SAP, Serum alkaline phosphatase; GGT, Gamma-glutamyl transferase; HT, Hypertension; LDH, Lactate dehydrogenase; FIB, Fibrosis-4.

not found any association of fatty liver with clinical outcomes in patients with COVID-19.[18,29] Moreover, we feel that if the association of fatty liver with clinically severe disease was indeed a true association, then it should have also translated into higher risk of mortality in the fatty liver group.

We also carried out the analysis of factors associated with mortality. On multivariable analysis, high total leukocyte counts and high FIB-4 values were independently associated with mortality in the cohort of 446 patients. Targher et al have demonstrated that MAFLD with intermediate or high FIB-4 values is associated with severe COVID-19, but no association with mortality was reported.[13] Lopez-Mendez et al also demonstrated that FIB-4 was associated with ICU admission and mortality, but only on univariate analysis, and no independent associations could be demonstrated.[18] The presence of advanced fibrosis (detected using noninvasive parameter in the entire group but not in association with fatty liver) may suggest the increased disease severity due to cirrhosis, rather than by NAFLD per se. However, using FIB-4 in this particular condition to diagnose advanced fibrosis is fraught with bias. Age, AST, ALT, and platelet counts are used to calculate FIB-4. AST and ALT values, which are used for calculating FIB-4, may be elevated and platelet counts may be as such altered in critically ill patients with COVID-19 because of a number of reasons. These reasons may include drug-induced liver injury, secondary sepsis, inflammatory response, and direct viral-induced liver injury. High FIB-4 in this situation may be a reflection of COVID-19 rather than liver fibrosis. So, one needs to be careful before accepting at face value, the association of FIB-4 (representing liver fibrosis) with either severe disease or mortality in patients with COVID-19.

Table 6 Multivariable Analysis for Factors Associated With Mortality.

Factors	B	*P* value	OR	95% CI
Total leucocyte counts	0.079	0.036	1.082	1.005–1.165
FIB-4	0.474	0.049	1.606	1.002–2.576

FIB-4, Fibrosis-4.

One of the limitations of our study was its retrospective nature. We believe that the best study to answer the questions at hand would be a prospective study where known patients with proven NAFLD and those in whom NAFLD is excluded, develop COVID-19, and are then followed up. Such a study would be difficult to carry out because the patients need to be strictly isolated and cannot be subjected to the optimal tests. However, unlike previous studies, we had standard definitions for fatty liver and COVID-19 pneumonia and specific criteria for outcomes (mortality and morbidity). Because of the retrospective nature of the study, we were also not able to have information on alcohol intake and markers for hepatitis B and C. So, the impact of etiology of fatty liver could not be studied. Although we have called these patients as fatty liver only because they were picked up radiologically, but most of them can be presumed to have NAFLD. As mentioned earlier also, the noninvasive assessment of fibrosis in the setting of COVID-19 may not be a robust marker of liver fibrosis, and its association with mortality may not be reliable. Finally, the sample size needed to detect a difference of 10% in mortality (our primary outcome measure) with a power of 80% and significance level 5% was 240 in each group. The study was planned to include these many cases in each group. However, the pandemic wave abated, and we could not complete 240 cases in the nonfatty liver group. This was partially compensated by the increased number of cases with steatosis. With 289 cases and 157 controls, the power still was 76%.

In conclusion, we have demonstrated in a case–control study that fatty liver may not be associated with increased mortality or morbidity in patients who have COVID-19 pneumonia.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Kaushal Madan: conceptualization and writing – original draft, review and editing; Ruchi Rastogi: conceptualization, writing – original draft, and radiologic data analysis. Richa Bhargava: conceptualization, supervision, and writing initial drafts. Vineeta Dagar: radiologic inputs, input, review and editing, and supervision. Vikas Singla: conceptualization, supervision, and intellectual inputs. Amit Sahu: conceptualization, editing, and radiologic data collection. Pankaj Singh: writing initial draft and editing. Pallavi Garg: review, editing, and supervision. Bharat Aggarwal: radiologic intellectual inputs, supervision, and editing. Ramkrishna Kumar Singh: radiologic data collection.

CONFLICTS OF INTEREST

The authors have none to declare.

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