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Liver, Pancreas and Biliary Tract

Liver fibrosis in patients with metabolic associated fatty liver disease is a risk factor for adverse outcomes in COVID-19



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ABSTRACT

Background: Metabolic diseases are risk factors for severe Coronavirus disease (COVID-19), which have a close relationship with metabolic dysfunction-associated fatty liver disease (MAFLD).

Aims: To evaluate the presence of MAFLD and fibrosis in patients with COVID-19 and its association with prognosis.

Methods: Retrospective cohort study. In hospitalized patients with COVID-19, the presence of liver steatosis was determined by computed tomography scan (CT). Liver fibrosis was assessed using the NAFLD fibrosis score (NFS score), and when altered, the AST to platelet ratio index (APRI) score. Mann-Whitney U, Student's t-test, logistic regression analysis, Kaplan-Meier curves and Cox regression analysis were used.

Results: 432 patients were analyzed, finding steatosis in 40.6%. No differences in pulmonary involvement on CT scan, treatment, or number of days between the onset of symptoms and hospital admission were found between patients with and without MAFLD. The presence of liver fibrosis was associated with higher severity scores, higher levels of inflammatory markers, requirement of mechanical ventilation, incidence of acute kidney injury (AKI), and higher mortality than patients without fibrosis.

Conclusion: The presence of fibrosis rather than the presence of MAFLD is associated with increased risk for mechanical ventilation, development of AKI, and higher mortality in COVID-19 patients.

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1. Introduction

Coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus, was first reported in December 2019 and the initial cases were reported in Wuhan, China; currently, this pandemic is seen all over the world, affecting more than 92.1 million people globally, from which more than 1 973 000 patients have died to date [1]. The mortality rate among patients with severe COVID-19 ranges from 21% to 30%, varying according the population studied [2]. The

known risk factors associated with the development of complications and mortality in patients with COVID-19 include the presence of obesity, hypertension, type 2 diabetes mellitus (T2DM), cardiovascular diseases, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), as well as other diseases causing immunosuppression (human immunodeficiency virus (HIV), transplantation, malignancy, chemotherapy), although the role of immunosuppression is still controversial [3–5]. No curative treatment is available to date, the only drug that has proven a decrement in mortality is dexamethasone [6]. Predicting which patients will develop a severe disease based on the known risk factors (as well as the upcoming predictors), is highly important to timely allocate the available resources to the patients at the higher risk, and possibly, modify their outcome.

On the other hand, non-alcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated fatty liver disease (MAFLD), is the main cause of liver disease globally, and due to its close relationship with features of the metabolic syndrome, including obesity and insulin resistance, it is becoming one of the main etiologies of chronic liver disease in the world [7–10]. A common factor in the pathophysiology with other metabolic diseases, including MAFLD, is the presence of systemic chronic inflammation [11], that in turn promotes the development and progression of liver fibrosis. In terms of liver fibrosis, according to the National Health and Nutrition Examination Survey, up to 10% of the patients with MAFLD have advanced fibrosis [12], and importantly, its presence is associated with the presence of concomitant diseases (e.g. infections), and increases the risk of both liver related and non-liver related adverse clinical outcomes [13]. (Alejandro WJG) Regarding this, pneumonia is one of the most common infections in patients with advanced liver fibrosis, and in fact, respiratory virus are detected in up to 20% of cirrhotic patients admitted in critical care units, exhibiting a higher mortality rate [14].

The poor outcome in patients with COVID-19 and metabolic disorders could be a consequence of an “acute on chronic inflammation” process, where perhaps the chronic basal inflammation milieu of patients with metabolic disorders such as MAFLD and even more in those with MAFLD and liver fibrosis could increase the risk of a hyperinflammatory response in patients with COVID-19. Recognizing an additional risk factor for adverse outcomes among patients with metabolic diseases could help to accurately allocate those with known MAFLD and those with high risk of MAFLD and liver fibrosis into a closer monitoring and early treatment. Therefore, the aim of the study was to evaluate the prevalence of MAFLD and liver fibrosis in patients with COVID-19 and its association with the development of complications, inflammatory markers, higher values in severity scores, increased risk of requirement mechanical ventilation, and overall mortality.

2. Materials and methods

This was a retrospective cohort study performed in a tertiary care center in Mexico City (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán), from March to May 2020. The study was conducted according to the Declaration of Helsinki and was approved by the Institutional Ethics and Research Committees (Ref. Number 3405).

2.1. Patients

All patients admitted to our center from March 1st to May 19th, 2020, older than 18 years old, any gender, with a confirmed diagnosis of SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) [15] were included in the study. Only patients with severe disease requiring treatment with oxygen were included. Patients transferred from or to another hospital, those who solicited

voluntary discharge or those lacking follow-up data were not included. Patients with known liver disease at admission, or positive for viral hepatitis or relevant alcohol intake were excluded from the analysis.

2.2. Biochemical tests

Upon admission, every patient underwent a blood draw and the following measurements were done: complete blood count, glucose, creatinine, serum electrolytes, acute phase reactants (ferritin, C-reactive protein, lactate dehydrogenase (LDH)), liver function tests, creatine phosphokinase (CPK), arterial blood gases, D-dimer, high-sensitivity troponin I (hsTnI), and fibrinogen. HIV test and viral hepatitis panel (HBV, HCV) were also performed. All tests were performed according to the standards of the Institutional central laboratory which is accredited by the College of American Pathologists (CAP).

2.3. Computed tomography

Upon admission, a non-contrast thorax CT scan was performed in all patients to evaluate the extent of lung damage. For the purposes of the study, only CT scans with images from the liver at the level of the right portal vein branch and from the upper pole of the spleen to the splenic hilum were included. All CT scans were performed with the same device (CT, Revolution EVO, General Electric Healthcare, Waukesha, WI, USA); the employed protocol was low dose CT for thorax assessment and includes the following parameters: helicoidal acquisition, acquisition field from the thoracic outlet to the L1 vertebral body, 120 kV voltage, 2–6 mAs, 1.5 pitch, 0.4 s rotation time, and 5 mm helicoidal thickness.

A single highly trained radiologist blinded to the patients' status evaluated the CT scans, aiming to quantitatively detect the presence of liver steatosis, according to the following criteria: a) attenuation coefficient ≤ 40 Hounsfield units (HU), in an area of 20 cm² between the segments VII and VIII in the liver; and b) attenuation coefficient ≥ 10 HU in an area of 5 cm² in the splenic parenchyma than in the area previously described in the liver; to better illustrate the described evaluation, representative images are shown in Supplementary Figure 1. Furthermore, a qualitative assessment was also performed, evaluating the presence of liver steatosis by comparing the density of the liver versus the spleen; when the liver attenuation was lower than the splenic attenuation was considered as liver steatosis.

To assess the degree of fatty liver infiltration, the liver/spleen ratio (L/S ratio) < 0.70 was used as a cutoff value to discriminate between patients with or without severe liver steatosis, as described previously [16].

2.4. Estimation of liver fibrosis

In order to estimate the presence of liver fibrosis, a bi-step approach was done in patients with diagnosis of liver steatosis by CT scan, using as a first evaluation the NAFLD fibrosis score (NFS) [17]. The participants with values $> -1.455 - 0.675$ (indeterminate) or > 0.675 (severe fibrosis F3,F4) were further analyzed by the AST to Platelet Ratio Index (APRI) [18], and when the result in this index was > 1.0 , the individuals were finally classified as high-risk of severe liver fibrosis.

2.5. Statistical analysis

The sample size was estimated according to a previous study in patients with COVID-19, where mortality in the non-diabetic population admitted to hospital was 17.5%, vs 29.6% in people with diabetes [19]. At our center, the general mortality is around 20%

in COVID patients. We assumed an increase in mortality of 15% in those patients with MAFLD. Finally, with α y β error of 0.05 and 0.2, the final number was 151 patients per group (302 patients in total).

The normality of the data was evaluated using Shapiro-Wilk test. Data is presented as mean \pm SD, median (P25-P75), or absolute frequencies. Results at baseline and final evaluations in each group (paired data) were analyzed with the Wilcoxon signed-rank test. For comparisons between groups, Mann-Whitney U or Student's t-test were used. Logistic regression analysis was used to assess clinical outcomes, and time dependent survival analysis including Kaplan-Meier curves and Cox regression analysis was performed to assess overall mortality. To ensure that the patients in the analysis had proportional risks, those patients with in-hospital stay longer than 28-days (n=5) were excluded, survival analysis both by Kaplan-Meier and by multivariate analysis (Cox-proportional hazards regression) was conducted for 28-day prognosis.

Statistical analysis was carried out with the package software SPSS version 20.0 (IBM, Armonk, NY, USA).

3. Results

Hospital records from March to May 2020, showed 547 patients with the diagnosis of COVID-19, from which 53 were excluded for lack of complete follow-up or negative RT-PCR. From the eligible patients 19 did not have an appropriate CT scan (showing artifacts, post-surgical findings, or not reaching the proposed level at the liver and spleen), therefore we included and collected data from 475 patients. To ensure the validity of the data we eliminated records from patients with known or recent diagnosis of liver disease different from MAFLD (e.g. autoimmune liver diseases, alcohol, hepatitis C or B infections, history of liver transplantation) and those with cancer, HIV or use of drugs that could cause fatty liver, thus analyzing 432 patients.

The baseline characteristics of the total population and according to the presence or absence of MAFLD are shown in Table 1. In total, 432 patients were analyzed, from which 40.6% had fatty liver by CT scan assessment (Supplementary Figure 2). Most of the patients were men, with an average age of 51 ± 13 years. When classified by body mass index (BMI), 44.6% of the population had obesity of some degree. The prevalence of other features of the metabolic syndrome was high, with 24% of T2DM and 27.8% of hypertension. The presence of other comorbidities (CKD, COPD, immunosuppression, etc.) was <5% in the total population with the same distribution among the groups. Severity scores, as well as markers of inflammation, were increased in total population, where 80.8% of the patients had a moderate or severe pulmonary involvement on CT scan.

When the population was analyzed according to the presence of fatty liver on CT scan, patients with MAFLD were found to be younger, with higher BMI, and a higher proportion of grade 2 or 3 obesity, metabolic syndrome and T2DM. Regarding severity scores, only the SOFA score was statistically different in patients with MAFLD, although this result probably has no clinical relevance. In general, inflammatory markers showed a trend towards higher levels in patients with MAFLD, however, only CPK showed statistical significance. The PaO₂/FiO₂ ratio was lower in patients with MAFLD. Finally, there were no differences in the distribution of pulmonary involvement on CT scan, treatment, or the number of days between the onset of symptoms and hospital admission.

In order to fully assess the severity of the disease in patients with MAFLD by CT scan, a newly proposed cutoff of <0.7 in the liver/spleen ratio was set to classify patients as severe fatty liver infiltration [16]. This resulted in 108 (61.4%) patients being clas-

sified as severe fatty liver infiltration and 68 (38.6%) as mild-moderate fatty liver.

On the other hand, the presence of liver fibrosis was addressed by a successive evaluation using the NFS score first, and when altered, APRI score was calculated. The probability of liver fibrosis according to NFS score in patients with liver steatosis was low in 8.5% (n=15), intermediate in 32.4% (n=57), and high in 54% (n=95), 9 patients had no BMI data, therefore the score was not calculated. When the APRI score was calculated at the same time, 22.7% of patients (n=40) were classified as high probability of liver fibrosis. And when the successive approach above mention was used, where only patients with intermediate and high probability of fibrosis by NFS had APRI calculated, 21% of patients (n=37) met the criteria for high risk of liver fibrosis.

In MAFLD patients, the presence of liver fibrosis was associated with higher values in severity scores such as NEWS score, and the recently developed population-specific Bello-Chavolla et al. score [20] as well as higher levels of inflammatory markers including LDH, CPK, fibrinogen, and ferritin, and higher levels of transaminases and leukocytes; interestingly, vitamin D levels were lower in the group of patients with fibrosis. Also, patients with fibrosis required mechanical ventilation more frequently, had a higher incidence of acute kidney injury (AKI) and had higher mortality. (Table 2)

With the aim of delimiting the specific role of liver fibrosis in the different outcomes of patients with COVID-19 and MAFLD, we constructed different logistic regression models, including demographic and biochemical variables as well as prognostic scores and markers and a combined model. Fibrosis by NFS/APRI was associated with the need for orotracheal intubation independently of demographic characteristics [OR: 2.59 (1.18-5.66)], biochemical markers [OR: 2.86 (1.18-6.97)], severity scores [OR: 2.60 (1.11-6.08)] and in the combined model [OR: 3.24 (1.35-7.76)]. With regards to the development of AKI, several variables were associated with the development of AKI, including age, gender, LDH, systolic blood pressure and PaO₂/FiO₂ ratio, while fibrosis showed statistical significance in all the constructed models. (Table 3)

Finally, to further assess the implications of liver disease in the prognosis of COVID-19 patients accounting for time-dependence, we conducted survival analysis in which first Kaplan-Meier curves were created to evaluate the effect of both MAFLD and liver fibrosis on the survival of patients with MAFLD and COVID-19, where fibrosis rather than MAFLD was significantly associated with 28-day mortality (p=0.036) (Fig. 1). Then a Cox regression analysis was performed, specifically to evaluate if the role of fibrosis in mortality was truly independent of other variables; Table 4, shows both univariate and multivariate analysis where four different models were created to avoid collinearity and saturation of the models. These results show fibrosis by NFS/APRI remained independently associated with mortality independently of demographic characteristics [HR: 2.33 (1.07-5.25)] and severity scores and markers [HR: 2.90 (1.14-7.37)], as well as in the combined model [HR: 2.54 (1.14-5.63)], however it lost statistical significance in the model with AKI and endotracheal intubation, where only the last two remained statistically significant associated with mortality.

4. Discussion

In the present study from a tertiary care center, reconverted for the care of COVID-19 patients, we present the outcomes of patients with COVID-19 and MAFLD diagnosed by CT scan. The overall prevalence of MAFLD was 40.6%, which is similar to the prevalence in the Hispanic population, thus perhaps the presence of MAFLD *per se* does not imply an increased risk of hospitalization in patients with COVID-19 [21]. Likewise, we did not find significant differences in the outcomes of hospitalized patients with MAFLD and

Table 1
Baseline characteristics of the total population and according to MAFLD presence.

	All(n=432)	No MAFLD (n=256)	MAFLD (n=176)	p value
Demographic features				
Sex (% Male / Female)	64.6 / 35.4	61.2 / 38.8	69.5 / 30.5	0.083
Age	51 ± 13	52 ± 14	48 ± 12	0.000
BMI	29.4 (26.7 – 33)	28.3 (25.3 – 31.4)	30.5 (28.2 – 34.3)	0.000
Comorbidities (n / %)				
Malnutrition	12 (2.9)	8 (3.3)	6 (3.5)	0.000
Normal Weight	55 (13.3)	49 (20.2)	4 (2.4)	
Overweight	162 (39.2)	98 (40.3)	64 (37.6)	
Obesity G1	120 (29.1)	58 (23.9)	62 (36.5)	
Obesity G2	43 (10.4)	22 (9.1)	21 (12.4)	
Obesity G3	21 (5.1)	8 (3.3)	13 (7.6)	
T2DM	104 (24)	50 (19.5)	54 (30.5)	0.008
Hypertension	121 (27.8)	66 (25.7)	55 (31.1)	0.232
Chronic Kidney disease	8 (1.8)	5 (1.9)	3 (1.7)	1.000
Pulmonary obstructive disease	3 (0.7)	0 (0)	3 (1.7)	0.67
Autoimmune disease	7 (1.6)	3 (1.2)	4 (2.3)	
Immunosuppression	2 (0.5)	2 (0.8)	0 (0)	
Use of steroids	7	3 (1.7)	4 (2.3)	0.307
Metabolic syndrome	152 (35.1)	69 (26.9)	83 (47.2)	0.000
Prognostic scores				
qSOFA	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)	0.672
SOFA	2 (1 – 2)	2 (1 – 2)	2 (1 – 3)	0.016
NEWS	7 (5 – 8)	7 (5 – 8)	7 (5 – 8)	0.252
PSI/PORT	62 (50 – 81)	65 (51 – 81)	59 (48 – 74)	0.34
SMART COP	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)	0.317
Bello-Chavolla et al. score	7 (6 – 7)	7 (6 – 7)	7 (6 – 8)	0.419
Biochemical values				
CRP (Ref. value: 0 – 1mg/dL)	13.2 (6.4 – 20.1)	12.8 (6.3 – 19.6)	13.7 (6.5 – 21.5)	0.166
Ferritin (Ref. value: 11 – 306.8ng/mL)	578 (286 – 997)	515 (261 – 938)	672 (334 – 1048)	0.054
D-dimer (Ref. value: 0– 500ng/mL)	647 (420 – 1102)	665 (417 – 1138)	605 (420 – 997)	0.645
LDH (Ref. value: 120 – 246U/L)	348 (267 – 458)	342 (257 – 455)	363 (291 – 472)	0.068
Troponins (Ref. value: <15pg/mL)	4.9 (3.2 – 9.4)	4.8 (3.2 – 10.6)	4.9 (3.2 – 7.1)	0.469
CPK (Ref. value: 30 –233U/L)	108 (59 – 237)	97 (54 – 197)	141 (73 – 320)	0.000
Bilirubin (Ref. value: 0/3– 1mg/dL)	0.5 (0.4 – 0.7)	0.5 (0.4 – 0.8)	0.6 (0.5 – 0.8)	0.191
ALT (Ref. value: 7–52U/L)	37 (25 – 54)	33 (22 – 52)	42 (29 – 60)	0.000
AST (Ref. value: 13 – 39U/L)	42 (30 – 60)	40 (27 – 57)	45 (32 – 66)	0.009
Globulins (Ref. value: 1.9 – 3.7g/dL)	3.3 ± 0.4	3.3 ± 0.4	3.2 ± 0.4	0.945
Albumin (Ref. value: 3.5–5.7g/dL)	3.4 ± 0.5	3.7 ± 0.5	3.8 ± 0.4	0.004
ALP (Ref. value: 34–104U/L)	85 (70 – 109)	86 (70 – 113)	85 (67 – 105)	0.216
Creatinine (Ref. value: 0.6 0 1.2mg/dL)	0.9 (0.7 – 1.1)	0.9 (0.8 – 1.0)	0.9 (0.7 – 1.1)	0.773
Glucose (Ref. value: 70–99 mg/dL)	116 (101–143)	112 (99 – 132)	123 (105–175)	0.001
Leukocytes (Ref. value: 4–12 × 10 ³ /uL)	7.3 (5.5 – 9.6)	7.1 (5.4 – 9.6)	7.6 (5.7 – 10)	0.375
Lymphocytes (Ref. value: 1 – 3.9 × 10 ³ /uL)	811 (615 – 1058)	781 (577 – 1020)	875 (653 – 1139)	0.020
Platelets (Ref. value: 150 – 450K/uL)	215 (174 – 277)	221 (176 – 284)	207 (172 – 268)	0.081
25 (HO) vitamin D (Ref. value: 30 – 100ng/mL)	21 (16 – 27)	21 (16 – 26)	21 (15 – 28)	0.788
Triglycerides (Ref. value: <150mg7dL)	147 (114 – 189)	142 (114 – 190)	150 (115 – 189)	0.930
CT results				
Mild (Ref <20%)	83 (19.2)	51 (19.9)	32 (18.1)	
Moderate (20 – 50%)	161 (37.2)	97 (37.9)	64 (36.2)	
Severe (>50%)	189 (43.6)	108 (42.2)	81 (45.8)	
Treatment n(%)				
Antibiotics	422 (97.7)	252 (98.8)	170 (96)	
Antimalarials	146 (33.6)	81 (31.4)	65 (36.7)	
Tocilizumab	56 (12.9)	31 (12)	25 (14.1)	
Remdesivir	2 (0.5)	2 (0.8)	0 (0)	
Other				
PaO2/FiO2 ratio	233 (155–286)	240 (171–289)	220 (133–276)	0.032
Neutrophil/Lymphocyte ratio	7.1 (4.4–11.8)	7.3 (4.6–12.3)	6.6 (4.0–10.6)	0.156
Days between the beginning of symptoms and hospitalization	7 (5 – 10)	8 (5 – 10)	7 (5 – 10)	0.179

BMI, body mass index; T2DM, type 2 diabetes mellitus; CRP, c-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table 2
Characteristics and outcomes in patients with and without liver fibrosis in the MAFLD group.

	No fibrosis (n=139)	Severe fibrosis (n=37)	p value
Demographic features			
Age (years)	47.4 ± 12	50.7 ± 12	0.153
BMI (kg/m ²)	31.3 ± 4.6	33.3 ± 8.7	0.196
Fibrosis scores			
NFS	0.49 ± 1.56	2.34 ± 1.58	0.000
APRI	0.57 ± 0.59	1.47 ± 0.84	0.000
Prognostic scores			
qSOFA	1.0 (0-1)	1 (1-1)	0.346
SOFA	2 (1-2)	2 (1-3)	0.202
NEWS	7 (5-8)	8 (6-9)	0.033
PSI/PORT	59 (48-74)	65 (50-76)	0.572
SMART COP	3 (3-4)	3 (2-4)	0.590
Bello-Chavolla et al. score	6 (5-7)	7 (6-8)	0.026
Biochemical values			
CRP (ref: 0-1mg/dl)	15.0 ± 10.3	14.5 ± 8.1	0.743
Ferritin (ref: 11- 306.8ng/ml)	755 ± 641	936 ± 721	0.157
D-dimer (ref: 0-500ng/ml)	1606 ± 7055	1173 ± 2183	0.732
LDH (ref: 120 - 246u/l)	380 ± 148	470 ± 200	0.004
Troponins (ref: <15pg/ml)	8.5 ± 18.4	14.0 ± 26.9	0.199
CPK (ref: 30-223u/l)	224 ± 271	526 ± 738	0.032
Bilirubin (ref: mg/dl)	0.66 ± 0.22	0.71 ± 0.36	0.169
ALT (ref: 7-52u/l)	45.8 ± 40.3	67.7 ± 38.2	0.005
AST (ref: 13-39u/l)	48.2 ± 38.3	83.0 ± 30.3	0.000
Globulins (ref: 1.9-3.7g/dl)	3.2 ± 0.4	3.3 ± 0.4	0.669
Albumin (ref: 3.5 -5.7g/dl)	3.7 ± 0.4	3.8 ± 0.4	0.888
ALP (ref: 34-104u/l)	90 ± 35	94 ± 39	0.522
Creatinine (ref: 0.6-1.2mg/dl)	0.98 ± 0.47	0.99 ± 0.33	0.917
Glucose (ref: 70-99 mg/dl)	123 (105-165)	125 (104-188.5)	0.802
Leukocytes (ref: 4- 12 × 10 ³ /ul)	8.4 ± 3.5	7.1 ± 2.5	0.021
Lymphocytes (ref: 3.9 × 10 ³ /ul)	930 ± 435	926 ± 377	0.956
Platelets (ref: 150-450k/ul)	238 ± 76	160 ± 53	0.000
25 oh vitamin D (ref: 30-100ng/ml)	22.3 ± 8.5	19.2 ± 6.8	0.078
Triglycerides (ref: <150mg7dl)	162 ± 124	172 ± 70	0.698
PaO ₂ /FiO ₂ ratio	224 (137-276)	191 (112-277)	0.435
Neutrophil/Lymphocyte ratio	7.0 (4.1-12.1)	6.1 (3.9-9.0)	0.191
Other (n / %)			
Metabolic syndrome	63 (45.3)	20 (54.1)	0.529
Severe COVID-19	100 (72.5)	26 (78.8)	0.459
Admission to ICU	32 (22.9)	13 (39.4)	0.051
Discharge from ICU	15 (46.9)	5 (38.5)	0.607
Acute kidney injury	28 (20.1)	11 (33.3)	0.104
Thrombotic event	1 (0.7)	1 (3.0)	0.346
Death	21 (15.0)	10 (32.3)	0.024
Days between the beginning of symptoms and hospitalization	7 (5-9)	8 (6-10)	0.287
Length of hospital stay (days)	8 (4-12)	9 (6-16)	0.297
Days in ICU	12 (7-23)	10 (4-12)	0.061
Days between the beginning of hospitalization and death	8 (5-20)	8 (6-14)	0.919
Days between ICU requirement and death	5 (3-8)	7 (6-12)	0.264

BMI, body mass index; NFS, NAFLD fibrosis score; APRI, AST to platelet ratio index; CRP, c-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; COVID-19, coronavirus disease 2019; ICU, Intensive care unit.

those without MAFLD. However, we did find a significant increase in the risk of mechanical ventilation requirement, acute kidney injury, and mortality in patients with MAFLD and advanced liver fibrosis diagnosed using the combined approach of high NFS and APRI. The role of MAFLD in the outcomes of patients with COVID-19 is still controversial, with some studies reporting unfavorable outcomes in all patients with MAFLD, while others, like the present study, report worse outcomes only when liver fibrosis is present [22–24].

In a recently published retrospective study where the outcome of patients with chronic liver disease and COVID-19 was evaluated, MAFLD was found in 15% of the population, and was independently associated with an increase in ICU admission (OR 2.3) and mechanical ventilation (OR 2.1), and the presence of cirrhosis was an independent predictor of mortality (OR 12.5) [22]. Another study conducted at four sites in Zhejiang Province, China, between January and February 2020, evaluated 310 patients hospitalized with COVID-19 finding 30.3% patients with MAFLD. The presence of MAFLD was diagnosed by CT scan and the presence of

fibrosis was evaluated using the originally validated cut-points for fibrosis-4 (FIB-4) index and the NFS score. This study found that patients with MAFLD and fibrosis had an increased risk of having severe COVID-19 illness, irrespective of other metabolic comorbidities [23]. In another study reported by Dong Ji et al. patients with MAFLD had a higher risk of disease progression, higher likelihood of abnormal liver tests, and longer viral shedding time compared to patients without MAFLD [24].

Our results are coherent with the fact that, in general, the prognosis of MAFLD is determined by the severity of liver fibrosis rather than by the presence of steatosis or steatohepatitis, which it is seen as well in the context of COVID-19 [12,25]. This could be explained by a more pronounced baseline systemic inflammation profile in patients with liver fibrosis influencing different organs and systems and the interaction between them, leading to further inflammation and activation of the immune response, contributing to higher inflammation when SARS-CoV-2 is added [26].

In our cohort, patients with MAFLD were younger and had a higher BMI with a higher proportion of grade 2 or 3 obesity, and

Table 3
Logistic regression analysis to evaluate the association of fibrosis with clinical outcomes.

Endotracheal intubation – demographic variables				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.595	1.187 – 5.662	0.954	0.017
Gender (Female)	0.478	0.202 – 1.131	-0.738	0.093
Age	0.980	0.969 – 0.991	-0.020	0.001
BMI > 30 kg/m ²	0.788	0.409 – 1.519	-0.238	0.477
-2 log likelihood → block 0: 245.37, block 1:192.90; Cox & Snell R ² : 0.257; Nagelkerke R ² : 0.342; Hosmer and Lemeshow: 0.420				
Endotracheal intubation – Biochemical variables				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.869	1.181 – 6.970	1.054	0.020
LDH	1.000	0.997 – 1.002	0.001	0.889
CRP	1.038	0.993 – 1.086	0.038	0.099
CPK	1.000	0.999 – 1.001	0.000	0.514
Total lymphocytes	0.998	0.997 – 0.999	-0.002	0.000
-2 log likelihood → block 0: 227.35, block 1:195.675; Cox & Snell R ² : 0.302; Nagelkerke R ² : 0.402; Hosmer and Lemeshow: 0.202				
Endotracheal intubation –Severity scores and markers				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.601	1.112 – 6.084	0.956	0.027
PSI/PORT score	0.992	0.980 – 1.004	-0.008	0.185
qSOFA score	3.288	1.380 – 7.836	1.190	0.007
PaO ₂ /FiO ₂ ratio	0.992	0.989 – 0.995	-0.008	0.000
NLR	1.003	0.973 – 1.035	0.003	0.827
-2 log likelihood → block 0: 238.44, block 1:169.73; Cox & Snell R ² : 0.329; Nagelkerke R ² : 0.439; Hosmer and Lemeshow: 0.359				
Endotracheal intubation – Combined model				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	3.243	1.355 – 7.760	1.176	0.008
Age	0.974	0.953 – 0.995	-0.026	0.017
Total lymphocytes	1.000	0.999 – 1.001	0.000	0.690
qSOFA	5.067	2.002 – 12.825	1.623	0.001
PaO ₂ /FiO ₂ ratio	0.994	0.990 – 0.997	-0.006	0.001
-2 log likelihood → block 0: 239.82, block 1:163.66; Cox & Snell R ² : 0.356; Nagelkerke R ² : 0.475; Hosmer and Lemeshow: 0.154				
Acute kidney injury – Demographic variables				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.522	1.123 – 5.665	0.925	0.025
Gender (Female)	0.281	0.102 – 0.773	-1.268	0.014
Age	0.982	0.971 – 0.994	-0.018	0.002
BMI > 30 kg/m ²	0.622	0.314 – 1.231	-0.476	0.173
-2 log likelihood → block 0: 243.98, block 1:179.58; Cox & Snell R ² : 0.307; Nagelkerke R ² : 0.409; Hosmer and Lemeshow: 0.868				
Acute kidney injury –Biochemical variables				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.634	1.031 – 6.732	0.968	0.043
LDH	1.004	1.001 – 1.007	0.004	0.019
CRP	1.039	0.990 – 1.091	0.093	0.118
CPK	1.000	0.999 – 1.001	0.000	0.994
Glucose	1.002	0.997 – 1.007	0.002	0.413
SBP	0.967	0.955 – 0.980	-0.033	0.000
-2 log likelihood → block 0: 221.80, block 1: 138.47; Cox & Snell R ² : 0.406; Nagelkerke R ² : 0.541; Hosmer and Lemeshow: 0.176				
Acute kidney injury – Severity scores and markers				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.640	1.077 – 6.470	0.971	0.034
SOFA	1.169	0.949 – 1.440	0.156	0.143
Bello-Chavolla score	0.973	0.865 – 1.095	-0.027	0.655
PaO ₂ /FiO ₂ ratio	0.991	0.987 – 0.994	-0.009	0.000
NLR	1.021	0.991 – 1.051	0.021	0.168
-2 log likelihood → block 0: 232.89, block 1: 152.32; Cox & Snell R ² : 0.381; Nagelkerke R ² : 0.508; Hosmer and Lemeshow: 0.285				
Acute kidney injury – Combined model				
	OR	CI 95%	β	p value
Fibrosis APRI/NFS	2.511	1.000 – 6.304	0.921	0.050
Gender	0.397	0.130 – 1.206	-0.925	0.103
Age	1.014	0.981 – 1.049	0.014	0.405
PaO ₂ /FiO ₂ ratio	0.995	0.991 – 0.999	0.005	0.028
LDH	1.004	1.001 – 1.007	0.004	0.007
SBP	0.979	0.961 – 0.997	0.021	0.024
-2 log likelihood → block 0: 230.12, block 1: 140.95; Cox & Snell R ² : 0.416; Nagelkerke R ² : 0.554; Hosmer and Lemeshow: 0.247				

APRI, AST to platelet ratio index; NAFLD fibrosis score; BMI, body mass index; LDH, lactate dehydrogenase; CRP, c-reactive protein; CPK, creatine phosphokinase; NLR, Neutrophil/Lymphocyte ratio, SBP, systolic blood pressure.

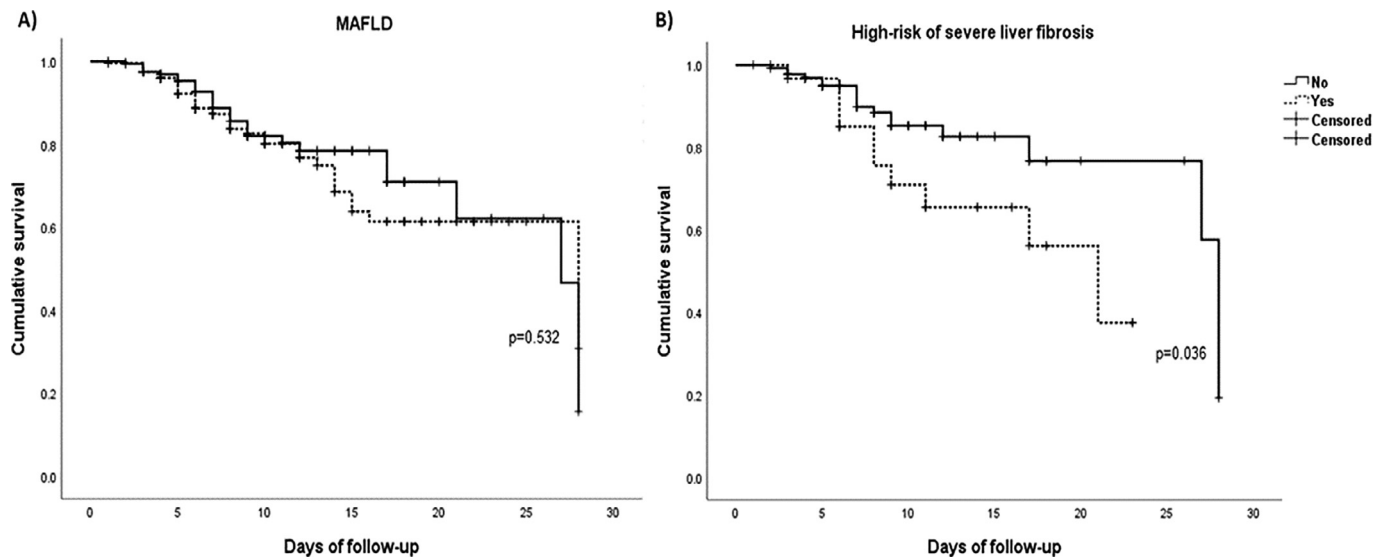


Fig. 1. Kaplan–Meier curves for survival in patients with MAFLD (A) and in patients with high-risk of severe fibrosis by NFS/APRI (B). Mean survival time: 21.07 ± 0.9 days (non-MAFLD) and 21.95 ± 1.11 days (MAFLD; and 23.5 ± 1.1 days (no fibrosis) and 16.7 ± 1.5 days (fibrosis). MAFLD, metabolic associated fatty liver disease.

Table 4

Cox regression analysis for survival in patients with and without fibrosis.

SURVIVAL – demographic variables				
	HR	CI 95%	β	p value
Fibrosis APRI/NFS	2.332	1.077 – 5.049	0.847	0.032
Gender (Female)	0.424	0.154 – 1.171	-0.858	0.098
Age	1.035	1.002 – 1.070	0.035	0.040
BMI	1.087	1.029 – 1.147	0.083	0.003
-2 log likelihood → block 0: 245.43, block 1: 228.41, Chi-square:18.999, df:4, sig.: 0.001				
Survival – severity scores and markers				
	HR	CI 95%	β	p value
Fibrosis APRI/NFS	2.901	1.141 – 7.370	1.065	0.025
NLR	1.014	0.977 – 1.053	0.014	0.457
LDH	1.002	1.000 – 1.004	0.002	0.053
PSI-PORT	1.024	1.007 – 1.041	0.023	0.005
CRP	1.062	1.015 – 1.111	0.060	0.010
qSOFA	0.693	0.254 – 1.890	-0.367	0.474
PaO2/FiO2 ratio	1.001	0.998 – 1.004	0.001	0.468
-2 log likelihood → block 218.91:, block 1:187.18, Chi-square:35.72, df:7, sig.:0.000				
Survival – combined model				
	HR	CI 95%	β	p value
Fibrosis APRI/NFS	2.543	1.147 – 5.637	0.933	0.022
PSI-PORT	1.017	1.000 – 1.034	0.017	0.050
CRP	1.070	1.025 – 1.118	0.068	0.002
Age	1.018	0.982 – 1.055	0.018	0.336
BMI	1.086	1.025–1.150	0.082	0.005
-2 log likelihood → block 0:235.13, block 1: 203.17, Chi-square:35.06, df:5, sig.: 0.000				
Survival – other outcomes				
	HR	CI 95%	β	p value
Fibrosis APRI/NFS	1.655	0.749 – 3.661	0.504	0.213
AKI	3.022	1.181 – 7.735	1.106	0.021
Endotracheal intubation	3.441	1.226 – 9.661	1.236	0.019
-2 log likelihood → block 247:, block 1: 181:, Chi-square:36.58, df:3, sig.:0.000				

APRI, AST to platelet ratio index; NAFLD fibrosis score; BMI, body mass index; T2DM, type 2 diabetes mellitus; LDH, lactate dehydrogenase; AKI, acute kidney injury; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

a higher proportion of T2DM. In a previous report by K.I. Zheng et al., the risk of severe disease in MAFLD patients with co-existing obesity was six times greater after adjustment for confounders, suggesting a synergistic effect between MAFLD and obesity when assessing the risk of severe COVID-19 [27].

The information in the present study was collected before the release of the results of the RECOVERY trial (ref), therefore no changes in survival are attributed to steroid use.

This study has several limitations, the first is the retrospective nature of the study, and the fact that liver steatosis was diagnosed by CT scan, and fibrosis by non-invasive scores which are not the standard methods for diagnosing these entities. However, given the high risk of SARS-CoV-2 transmission to healthcare workers, this approach is safer than exposing them to perform an additional study, such as transient elastography. Another noteworthy aspect is that COVID-19 patients often have elevated

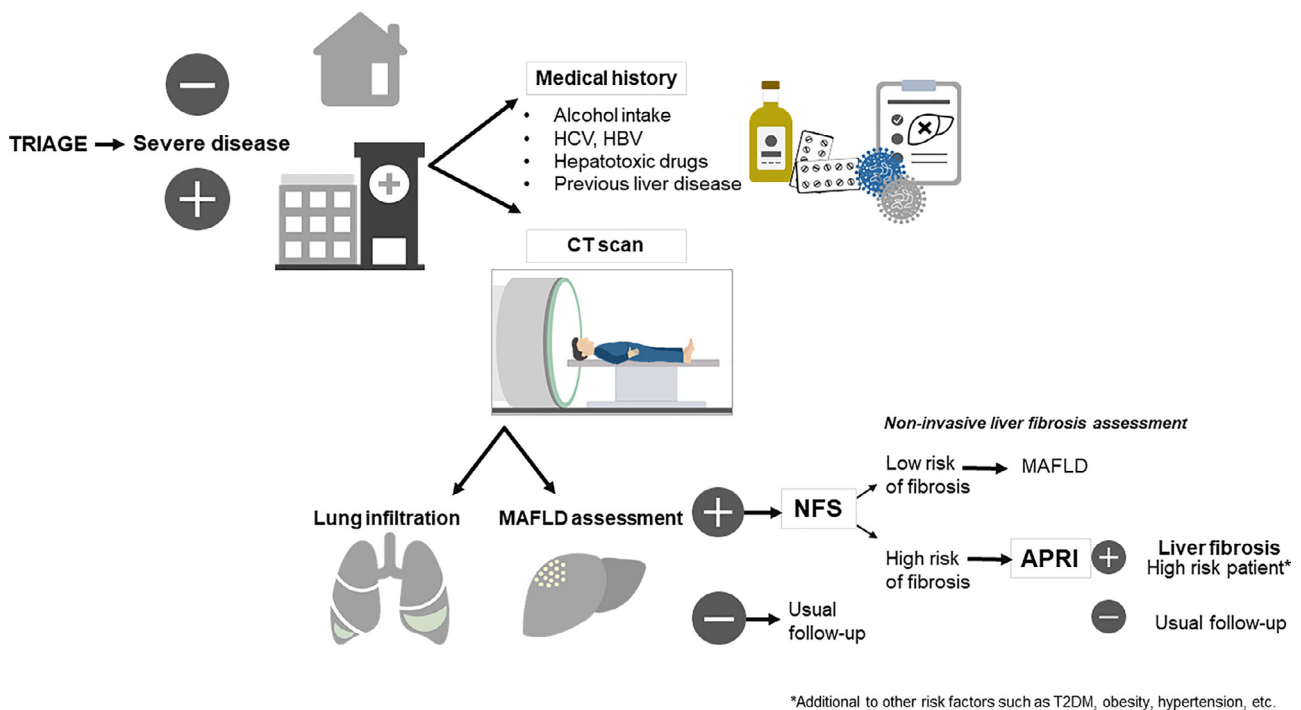


Fig. 2. Proposed assessment of MAFLD and liver fibrosis in hospitalized patients with COVID-19. This diagnostic approach highlights the importance of liver fibrosis in patients with MAFLD and COVID-19 as an additional risk factor for adverse clinical outcomes. For individuals admitted for inpatient medical care, three points are critical in the proposed assessment: 1) To investigate risk factors related to liver disease different from MAFLD; 2) The assessment of liver steatosis with the already available lung CT scan, to avoid unnecessary exposure to radiation and to expedite the assessment; and 3) To sequentially assess the risk of severe liver fibrosis with the NAFLD fibrosis score (NFS) and then with the AST to platelet ratio index (APRI). This approach for detecting patients with MAFLD and liver fibrosis among those with COVID-19 requiring inpatient care, provides a reliable algorithm using already available resources (CT scan and biochemical tests), and therefore accelerating the diagnostic time, limiting the costs and the exposure to radiation, as well as limiting the contact with healthcare staff. MAFLD, metabolic associated fatty liver disease; NFS, NAFLD fibrosis score; APRI, AST to platelet ratio index; HCV, hepatitis C virus; HBV, hepatitis B virus.

transaminases, which could affect the diagnostic precision of the fibrosis predictive scores, since most of them use these values to predict liver fibrosis, increasing the risk of over-diagnosis of advanced fibrosis in our cohort. It is not clear whether COVID-19 is solely responsible for the development of liver injury, or whether liver injury is a consequence of the systemic inflammation caused by the virus or by drug-induced liver injury [28]. The main advantage of this study is that it was conducted in a country with one of the highest prevalence of MAFLD, and with a different genetic background also accounting for higher prevalence of other metabolic diseases including T2D and obesity; therefore are able to evaluate a good proportion of these patients and the statistical approach that was carried out allows for solid results. Finally, based in the findings of the present study, we propose a sequential approach to identify patients with MAFLD and high risk of advanced fibrosis, emphasizing the fact that an adequate diagnosis can be done with the studies performed upon admittance (i.e. chest CT scan, history and biochemical tests). (Fig. 2)

In conclusion, the presence of fibrosis rather than the presence of MAFLD has an impact on the risk of mechanical ventilation requirement, development of acute kidney injury, and higher mortality in patients with COVID-19.

Declaration of Competing Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.01.019.

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