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NAFLD determined by Dallas Steatosis Index is associated with poor outcomes in COVID-19 pneumonia: a cohort study

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Abstract

Coronavirus disease 2019 is a worldwide health challenge. Liver steatosis diagnosis based on imaging studies has been implicated in poor outcomes of COVID-19 pneumonia, but results are inconsistent. The Dallas Steatosis Index (DSI) is an available calculator developed to identify patients with non-alcoholic fatty liver disease (NAFLD). We hypothesized that it would be associated with in-hospital mortality, intensive care unit admission (ICU), and invasive mechanical ventilation (IMV). We conducted a retrospective cohort study on inpatients with confirmed COVID-19 pneumonia between February 26 and April 11, 2020. We computed the DSI on admission, and patients with high DSI were considered with NAFLD. We employed logistic regression to study the association between NAFLD, mortality, ICU admission, and IMV. We studied the association between liver steatosis on computed tomography (CT) and these outcomes, and also between Metabolic Associated Fatty Liver Disease (MAFLD) based on CT findings and risk factors and the outcomes. 470 patients were included; 359 had NAFLD according to the DSI. They had a higher frequency of type 2 diabetes (31% vs 14%, $p<0.001$), obesity (58% vs 14%, $p<0.001$), and arterial hypertension (34% vs 22%, $p=0.02$). In univariable analysis, NAFLD was associated with mortality, ICU admission, and IMV. Liver steatosis by CT and MAFLD were not associated with any of these outcomes. In multivariable logistic regression, high DSI remained significantly associated with IMV and death. High DSI, which can be easily computed on admission, was associated with IMV and death, and its use to better stratify the prognosis of these patients should be explored. On the other hand, liver steatosis by CT and MAFLD were not associated with poor outcomes.

Keywords COVID-19 · NAFLD · Liver steatosis · Fatty liver disease · Coronavirus

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Introduction

By the end of 2019, an outbreak of pneumonia of an unknown cause was identified in Wuhan, the capital of Hubei province, China. A novel coronavirus, later designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as its aetiological agent, and this condition was named coronavirus disease 2019 (COVID-19) [1]. As of June 21, 2021, COVID-19 has been confirmed in 178,118,597 patients and has caused 3,864,180 deaths around the world [2]. Using data from China, the overall case–fatality ratio (CFR) of COVID-19 has been estimated at around 1.38% (95% confidence interval [CI] 1.23–1.53) [3]. Nonetheless, the probability of survival is largely influenced by several factors, such as age, sex, and the presence of some comorbidities [4].

Several comorbidities have been related to a worse prognosis of COVID-19, including a history of cardiovascular disease, diabetes, chronic respiratory disease, hypertension, cancer, and obesity [5–7]. The role of liver steatosis detected on imaging studies has been controversial: Zheng et al. [8] found steatosis to be a marker of a more severe disease course, as well as others [9–12], while Campos-Murguia et al. [13] found that it was liver fibrosis, assessed by the non-alcoholic fatty liver disease (NAFLD) Fibrosis Score, rather than steatosis, the one associated with the need for invasive mechanical ventilation (IMV) and mortality [13, 14]. In opposition to this, Castro et al. [15] failed to stablish an association between fibrosis and COVID-19 outcomes; in this work, steatosis was determined by the Hepatic Steatosis Index, and liver fibrosis was assessed by the AST to platelet ratio index, the NAFLD Fibrosis Score, and the Fiborisis-4 index. Therefore, more studies exploring the role of steatosis on the prognosis of COVID-19 beyond its association with disease severity are needed. The Dallas Steatosis Index (DSI) is a clinical tool that uses clinical variables and laboratory test results to identify patients at high risk of NAFLD; it has the advantage of not requiring imaging and therefore is readily available. The aim of this study was to determine the association between the DSI and poor COVID-19 outcomes: in-hospital mortality, ICU, and IMV. Secondary aims were to evaluate the association between liver steatosis determined by computed tomography (CT), and these outcomes, and also between Metabolic Associated Fatty Liver Disease (MAFLD) diagnosis based on CT and risk factors, and the outcomes of interest.

Materials and methods

Study design, patients, and SARS-CoV-2 testing

We conducted a retrospective cohort study in a tertiary care center in Mexico City dedicated to the care of adults with severe and critical COVID-19 based on the US Coronavirus Disease 2019 (COVID-19) Treatment Guidelines illness categories [16]. We included 470 consecutive subjects with SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) that were admitted between February 26 and April 11, 2020. COVID-19 diagnosis was based on the definitions described by the World Health Organization. Inpatients were followed until discharge or death (last status update was on May 15th, 2020). SARS-CoV-2 testing was carried out on nasopharyngeal or oropharyngeal swabs. Nucleic acid extraction was performed using the NucliSens EasyMAG system® (bioMérieux, Boxtel, The Netherlands). RT-PCR was carried out on an Applied Biosystems 7500 thermocycler (Applied Biosystems, Foster City, CA, USA) using primers and conditions described elsewhere [17]. The study was reviewed and approved by the Institutional Review Board (ref. no. 3333). Written informed consent was waived because of the observational nature of the study.

Data collection

We extracted clinical and epidemiological data at presentation using a standardized case report form [18]. The rest of the information was obtained from electronic clinical records. Imaging and laboratory studies were performed according to our institutional recommendations. Suggested basal assessment includes complete blood cell count, a comprehensive metabolic panel, inflammatory markers (i.e., C-reactive protein, ferritin, and procalcitonin), creatine kinase, fibrinogen, D-dimer, and lactate dehydrogenase.

Assessment of non-alcoholic fatty liver disease with the Dallas Steatosis Index

The DSI is a calculator to identify patients at high risk of NAFLD, and it was developed using logistic regression, considering NAFLD as liver steatosis detected by magnetic resonance spectroscopy in the absence of secondary causes of liver steatosis, including significant alcohol intake. The DSI has a C-statistic of 0.824 [19], and it takes into account age, ALT, triglycerides, body mass index, glucose, ethnicity, sex, type 2 diabetes, and arterial hypertension. The DSI was computed with an online calculator according to the original formula (https://dsi.wustl.edu). According to the original publication, patients with a DSI ≥ 0 are considered at high risk of NAFLD, and therefore, for this study, all patients with DIS ≥ 0 were considered to have NAFLD. The logistic regression equation is the following:

DSILOGIT = −9.4 + 0.316 (if age ≥ 50 and female) + 2.4 (if known diabetes) + 0.02 × (equals 0 if diabetic; if not diabetic equals the glucose concentration in mg/dl) + 0.3 (if known hypertension) + 0.5 (if Hispanic/Asian/Other race/

ethnicity + Ln triglycerides in mg/dl + 0.4 if ALT 13.5 − 19.49 IU/L + 1.1 (if ALT 19.5 − 40 IU/L + 1.5 if ALT > 40 IU/L + 0.7 if not black and BMI 25 – 27.49 kg/m^2 and + 1.4 if not black and BMI 27.5 – 34.9 kg/m^2 + 1.9 if not black and 35 – 37.49 kg/m^2 + 2.6 if not black and > 37.5 kg/m^2 − 0.2 if black and BMI 25 – 27.49 kg/m^2 and + 0.8 if black and BMI 27.5 – 34.9 kg/m^2 + 0.8 if black and 35 – 37.49 kg/m^2 + 1.8 if black and > 37.5 kg/m^2.

Assessment of liver steatosis with computed tomography and diagnosis of metabolic-associated fatty liver disease

A computed tomography (CT) of the chest is suggested in our institution for all hospitalized patients before admission. The diagnosis of liver steatosis was made by an experienced radiologist (JAGM) blinded to patient outcomes. For this purpose, we analyzed six liver (four in the right lobe and two in the left lobe) and two spleen regions of interest (ROI) in non-contrast CT scans (1.0 ± 0.2 cm) per patient. Attenuation measures were collected from each ROI, and the mean value in Hounsfield Units (HU) was obtained for each tissue and used to compute the liver/spleen ratio. The cut-off value to consider liver steatosis was liver/spleen ratio < 1 [20]. MAFLD was diagnosed when a patient with steatosis on CT had any of the following three conditions: (1) BMI ≥ 25 kg/m^2; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dl; arterial hypertension; prediabetes.

Statistical analysis

Categorical variables were reported as frequencies and proportions. Continuous variables were described using median and interquartile range (IQR). Variables between patients with and without NAFLD as per the DSI were compared with the chi-squared test and the Mann–Whitney *U* test, as appropriate. Patients were followed until death and were censored at the time of discharge. We used univariable logistic regression to evaluate the association between the different variables and the outcomes of interest (i.e., in-hospital death, ICU, IMV). Afterward, variables with a *p* value of ≤ 0.1 were included in multivariable analysis. A two-sided *p* value of less than 0.05 was considered statistically significant. We used the Liu method of empirical point estimation to determine a suitable cut-off point of the DSI to identify MAFLD. All the analyses were performed using Stata 14 (StataCorp, Texas, USA). The study was reviewed and approved by the Institutional Review Board (ref. no. 3333). Written informed consent was waived because of the observational nature of the study.

Results

General characteristics of patients

We identified 470 patients with SARS-CoV-2 infection that were admitted during the study period. Two hundred ninety-eight (63%) patients were male; the median age was 51 years (IQR 42–62). The prevalence of obesity, diabetes mellitus, and hypertension were 47%, 27%, and 31%, respectively. Three hundred and fifty-nine patients (76.38%) were considered to have NAFLD according to the DSI. According to the CT analysis, 320 patients (70%) had liver steatosis, and of them, 292 (92%) had MAFLD. One hundred twenty-seven (27%) patients died, 206 (44%) required ICU admission, and 128 (27%) IMV. The rest of the characteristics are shown in Table 1.

Variables associated with NAFLD

When compared to patients without NAFLD as per the DSI, patients with NAFLD had a higher body mass index [30.8 (IQR 28.3–34.7) vs 25.4 (IQR 23.7–27.4) kg/m^2, $p < 0.001$], and a higher rate of obesity (58 vs 14%, $p < 0.001$), type 2 diabetes (31 vs 14%, $p < 0.001$), arterial hypertension (34 vs 22%, $p < 0.001$), and liver steatosis detected on CT (74 vs 55%, $p < 0.001$). Patients with NAFLD as per the DSI had lower oxygen saturation levels at admission [84 (IQR 70–88) vs 86% (IQR 80–89), $p = 0.002$],and higher D-dimer [727.5 (IQR 453–1136) vs 616 (IQR 391–1094) ng/mL $p = 0.04$] and lactate dehydrogenase levels [399.5 (IQR 316–540) vs 347.5 (IQR 264–472) U/L, $p < 0.001$], but also higher lymphocyte count [808.5 (IQR 589–1088) vs 737.3 (IQR 504–976) µL, $p = 0.03$].

Association between NAFLD and mortality

There were 127 deaths: 21 (19%) and 106 (30%) in patients without and with NAFLD as per the DSI ($p = 0.03$). On univariable logistic regression analysis, features related with in-hospital mortality were age (OR 1.05, 95% CI 1.04–1.07, $p < 0.001$), sex (OR 1.94, 95% CI 1.23–3.04, $p = 0.004$), diabetes mellitus, (OR 1.78, 95% CI 1.14–2.76, $p = 0.01$), arterial hypertension (OR 1.64, 95% CI 1.07–2.52, $p = 0.02$), oxygen saturation on room air (OR 0.92, 95% CI 0.90–0.94, $p < 0.001$), total lymphocytes (OR 0.99, 95% CI 0.997–0.999, $p < 0.001$), triglyceride levels (OR 1.00, 95% CI 1.00–1.004, $p = 0.004$), and NAFLD as per the DSI (OR 1.79, 95% CI 1.06–3.04 $p = 0.03$). On multivariable analysis, NAFLD as per the DSI remained significantly associated with mortality (OR 2.13, 95% CI 1.05–4.34, $p = 0.04$) (Table 2).

Table 1 General characteristics

Variables	$N=470$	No NAFLD*, $N=111$	NAFLD*, $N=359$	p
Male, *n* (%)	298 (63)	67 (60)	231 (64)	0.4
Age years (IQR)	51 (42–62)	52 (42–66)	51 (42–61)	0.1
BMI kg/m^2 (IQR)	29.7 (26.7–33.4)	25.4 (23.7–27.4)	30.8 (28.3–34.7)	< 0.001
BMI ≥ 25, *n* (%)	406 (86)	62 (56)	344 (96)	< 0.001
BMI ≥ 30, *n* (%)	223 (47)	15 (14)	208 (58)	< 0.001
Type 2 diabetes mellitus, *n* (%)	126 (27)	15 (14)	111 (31)	< 0.001
Arterial hypertension, *n* (%)	147 (31)	25 (22)	122 (34)	0.02
Chronic kidney disease, *n* (%)	12 (2)	5 (4)	7 (2)	0.1
Liver steatosis on CT, *n* (%)	320 (70)	60(55)	260 (74)	< 0.001
MAFLD**, *n* (%)	294 (92%)	39 (65%)	255 (98%)	< 0.001
Heart rate (IQR)	102.5 (90–115)	102 (87–114)	103 (90–116)	0.1
Respiratory rate (IQR)	28 (22–34)	26 (21–30)	28 (22–35)	0.005
Oxygen saturation on room air % (IQR)	85 (74–88)	86 (80–89)	84 (70–88)	0.002
Mean arterial pressure mmHg (IQR)	90.2 (83.2–97.2)	88.5 (83.2–94.8)	90.9 (83.4–98.4)	0.06
Glucose, mg/dl, (IQR)	101.5 (90–126)	93 (85–105)	105 (94–130)	< 0.001
Creatinine mg/dl, (IQR)	0.95 (0.77–1.16)	0.93 (0.74–1.15)	0.95 (0.79–1.16)	0.5
Total bilirubin mg/dl (IQR)	0.59 (0.46–0.79)	0.55 (0.44–0.78)	0.6 (0.46–0.80)	0.1
ALT U/L (IQR)	37.7 (24.3–55.3)	24.1 (16.2–37.7)	41.5 (27–59.6)	< 0.001
AST U/L (IQR)	43.7 (31.6–66)	35 (25.6–50)	49.3 (34–67.8)	< 0.001
ALP U/L (IQR)	87 (70–115)	84 (68–110)	89 (70–117)	0.4
Albumin mg/dl (IQR)	3.7 (3.3–4.0)	3.7 (3.4–4.03)	3.7 (3.3–4.0)	0.4
Triglycerides, mg/dl (IQR)	151 (115–200)	121 (94–160)	164 (125–212)	< 0.001
CRP mg/dl (IQR)	15.4 (8.2–22.6)	14.6 (7.2–21.0)	16.3 (8.9–23.5)	0.06
Lymphocytes µl (IQR)	792 (558.9–1057.8)	737.3 (504–976.5)	808.5 (588.9–1087.5)	0.03
D-Dimer, ng/ml (IQR)	700 (442–1106)	616 (391–1094)	727.5 (453–1136)	0.04
CPK mg/dl (IQR)	119 (65–243.5)	107 (57–244)	125 (70–243)	0.1
LDH U/L (IQR)	393 (304.5–513)	347.5 (263.5–472)	399.5 (316.5–539.5)	< 0.001
Ferritin µg/l (IQR)	666.5 (332–1089.7)	622.7 (227.5–1104)	689.4 (353.7–1078.5)	0.1

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *CPK* creatine phosphokinase, *CRP* C-reactive protein, *CT* computed tomography, *IQR* interquartile range, *LDH* lactate dehydrogenase, *MAFLD* metabolic-associated fatty liver disease, *NAFLD* non-alcoholic fatty liver disease

*NAFLD according to the DSI (i.e. ≥ 0)

**MAFLD based on steatosis on CT plus any of the following three conditions: (1) BMI ≥ 25 kg/m^2; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dl; arterial hypertension; prediabetes

Association between NAFLD and ICU

Two hundred and six patients required ICU: 31 (28%) and 175 (49%) patients without and with NAFLD as per the DSI, respectively ($p < 0.001$). On univariable logistic regression analysis, NAFLD as per the DSI (OR 2.45, 95% CI 1.54–3.90, $p < 0.001$), age (OR 1.02, 95% CI 1.00–1.03, $p = 0.008$), sex (OR 2.18, 95% CI 1.47–2.23, $p < 0.001$), oxygen saturation on room air (OR 0.90, 95% CI 0.88–0.92, $p < 0.001$), total lymphocytes (OR 0.998, 95% CI 0.998–0.999, $p < 0.001$), and triglyceride levels (OR 1.005, 95% CI 1.002–1.007, < 0.001) were associated with ICU admission (Table 3). On multivariable analysis, NAFLD as per the DSI showed a tendency to be associated with ICU admission (OR 1.71, 95% CI 0.95–3.06, $p = 0.07$).

Association between NAFLD and IMV

One hundred and twenty-eight patients required IMV: 11 (10%) and 117 (32%) patients without and with NAFLD as per the DSI, respectively ($p < 0.001$). On univariate logistic regression analysis, NAFLD as per the DSI (OR 4.40, 95% CI 2.26–8.51, $p < 0.001$), sex (OR 1.60, 95% CI

Table 2 Factors associated with in-hospital mortality

	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.05	1.04–1.07	< 0.001	1.06	1.04–1.08	< 0.001
Sex	1.94	1.23–3.04	0.004	1.69	0.96–2.97	0.07
Obesity	0.95	0.63–1.42	0.8	–	–	–
DM	1.78	1.14–2.76	0.01	1.09	0.61–1.94	0.8
Arterial hypertension	1.64	1.07–2.52	0.02	0.67	0.37–1.21	0.2
Oxygen saturation on room air	0.92	0.90–0.94	< 0.001	0.93	0.91–0.94	< 0.001
Total lymphocytes	0.99	0.997–0.999	< 0.001	0.998	0.998–0.999	0.004
NAFLD*	1.79	1.06–3.04	0.03	2.13	1.05–4.34	0.04
Liver steatosis on CT	0.98	0.63–1.55	0.9	–	–	–
Triglycerides	1.00	1.00–1.004	0.004	1.00	0.99–1.00	0.5
MAFLD**	0.66	0.28–1.53	0.3	–	–	–

CI confidence interval, *CT* computed tomography, *DM* type 2 diabetes mellitus, *MAFLD* metabolic-associated fatty liver disease, *NAFLD* non-alcoholic fatty liver disease, *OR* odds ratio

*NAFLD according to the DSI (i.e. ≥ 0)

**MAFLD based on steatosis on CT plus any of the following three conditions: (1) BMI ≥ 25 kg/m^2; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dl; arterial hypertension; prediabetes

Table 3 Factors associated with intensive care unit admission

	Univariable			Multivariable		
	OR	95% CI	–	OR	95% CI	*p*
Age	1.02	1.00–1.03	0.008	1.01	0.99–1.03	0.2
Sex	2.18	1.47–2.23	< 0.001	2.14	1.31–3.49	0.002
Obesity	1.16	0.80–1.66	0.4	–	–	–
DM	1.40	0.93–2.11	0.1	0.82	0.48–1.38	0.4
Arterial hypertension	0.98	0.66–1.45	0.9	–	–	–
Oxygen saturation on room air	0.90	0.88–0.92	< 0.001	0.91	0.89–0.93	< 0.001
Total lymphocytes	0.998	0.998–0.999	< 0.001	0.999	0.998–0.999	0.02
NAFLD*	2.45	1.54–3.90	< 0.001	1.71	0.95–3.06	0.07
Liver steatosis on CT	1.11	0.74–1.67	0.6	–	–	–
Triglycerides	1.005	1.002–1.007	< 0.001	1.003	1.00–1.006	0.01
MAFLD**	1.86	0.78–4.41	0.2	–	–	–

CI confidence interval, *CT* computed tomography, *DM* type 2 diabetes mellitus, *MAFLD* metabolic-associated fatty liver disease, *NAFLD* non-alcoholic fatty liver disease, *OR* odds ratio

*NAFLD according to the DSI (i.e. ≥ 0)

**MAFLD based on steatosis on CT plus any of the following three conditions: (1) BMI ≥ 25 kg/m^2; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dl; arterial hypertension; prediabetes

1.03–2.49, $p = 0.03$), obesity (OR 1.56, 95% CI 1.03–2.34, $p = 0.03$), oxygen saturation on room air (OR 0.96, 95% CI 0.94–0.97, $p < 0.001$), and triglyceride levels (OR 1.006, 95% CI 1.003–1.008, $p < 0.001$) were associated with IMV. On multivariable analysis, NAFLD as per the DSI remained statistically significantly associated with IMV (OR 2.50, 95% CI 1.20–5.21, $p = 0.01$) (Table 4).

Association between liver steatosis by CT and outcomes of interest

There was no association between liver steatosis evaluated by CT and mortality (OR 0.98, 95% CI 0.63–1.55, $p = 0.9$), ICU admission (OR 1.11, 95% CI 0.74–1.67, $p = 0.6$), or IMV (OR 1.30, 95% CI 0.81–2.06, $p = 0.3$).

Table 4 Factors associated with invasive mechanical ventilation need

	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	P
Age	0.98	0.97–1.00	0.1	0.98	0.96–0.99	0.01
Sex	1.60	1.03–2.49	0.03	1.33	0.81–2.21	0.3
Obesity	1.56	1.03–2.34	0.03	1.04	0.63–1.72	0.9
DM	1.28	0.82–2.01	0.3	–	–	–
Arterial hypertension	0.73	0.46–1.15	0.2	–	–	–
Oxygen saturation on room air	0.96	0.94–0.97	< 0.001	0.97	0.95–0.98	< 0.001
Total lymphocytes	0.999	0.998–1.00	0.07	0.99	0.99–1.00	0.1
NAFLD*	4.40	2.26–8.51	< 0.001	2.50	1.20–5.21	0.01
Liver steatosis on CT	1.30	0.81–2.06	0.3	–	–	–
Triglycerides	1.006	1.003–1.008	< 0.001	1.004	1.001–1.006	< 0.001
MAFLD**	3.22	0.94–11.01	0.06	–	–	–

CI confidence interval, *CT* computed tomography, *DM* type 2 diabetes mellitus, *MAFLD* metabolic-associated fatty liver disease, *NAFLD* non-alcoholic fatty liver disease, *OR* odds ratio

*NAFLD according to the DSI (i.e. ≥ 0)

**MAFLD based on steatosis on CT plus any of the following three conditions: (1) BMI ≥ 25 kg/m^2; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dl; arterial hypertension; prediabetes

Association between MAFLD and outcomes of interest

Two hundred ninety-two (92%) patients out of 320 who had steatosis on CT had MAFLD. There was no association between MAFLD and mortality (OR 0.66, 95% CI 0.28–1.53, $p = 0.3$), ICU admission (OR 1.86, 95% CI 0.78–4.41, $p = 0.2$), or IMV (OR 3.22, 95% CI 0.94–11.01, $p = 0.06$).

Performance of the DSI to diagnose MAFLD

The DSI had sensitivity, specificity, positive predictive value, negative predictive value, and an area under the curve of 86.7%, 80.8%, 98.1%, 35%, and 0.840, respectively, for the diagnosis of MAFLD. We used the Liu method for empirical cut point estimation and found DSI > 0.16 as a suitable cut-off point to identify MAFLD, with sensitivity, specificity, and area under the curve of 84%, 92%, and 0.880, respectively. Based on this new cut-off point, 342 (73%) patients would have MAFLD in our sample.

Discussion

Metabolic syndrome and its components are associated with worse outcomes in patients with COVID-19 [7]. Nevertheless, the role of NAFLD on COVID-19 prognosis, recently redefined as "metabolic associated fatty liver disease" (MAFLD) [21], has only been partially evaluated, perhaps because of the indolent course of steatosis, the poor awareness of the general population about this condition, and limitations inherent to how NAFLD/MAFLD is diagnosed. In this study, we assessed the relationship between NAFLD diagnosed by the DSI and different COVID-19 outcomes, and we found NAFLD as per the DSI to be associated with death and IMV need in hospitalized patients with COVID-19.

Our findings can be explained by the pathophysiological link between preexisting chronic liver diseases like liver steatosis, exacerbated by COVID-19. Both assaults (liver steatosis and COVID-19) lead to an amplified pro-inflammatory state with high levels of inflammatory cytokines and, consequently, poor outcomes [22–24]. Unfortunately, we did not measure cytokine levels, which could help clarify this association. Moreover, cholangiocytes and hepatocytes express angiotensin-converting enzyme 2, and SARS CoV-2 could be acting as a *second hit* in the presence of liver steatosis to trigger a pro-inflammatory state [25]. Importantly, obesity based on the BMI was not associated with the outcomes of interest after adjusting by NAFLD as per the DSI, suggesting that it is fat distribution more than a patient's weight what matters, as it is visceral obesity the pro-inflammatory one.

The role of NAFLD in COVID-19 has been explored previously, but this is the first study using the DSI score, which is more accurate for diagnosing NAFLD when compared to other methods and risk tools [19]. In particular, CT has poor sensitivity for the diagnosis of mild steatosis, whereas the DSI was developed using magnetic resonance spectroscopy, which has high sensitivity even for mild steatosis [26]. Two meta-analyses about liver steatosis and COVID-19 concluded that NAFLD is associated with a severe disease course and ICU admission, but not with

mortality [27]. These results are partly following our findings where patients with NAFLD as per the DSI had an OR 2.50 for IMV in multivariate analysis. In a study by Zheng et al. [8] in 66 patients with MAFLD, obesity was associated with increased COVID-19 severity; however, since all patients had MAFLD determined by CT and the criteria described in 2020 [21], its prognostic role in terms of outcomes of interest could not be assessed. A case–control study evaluating the severity of the disease rather than the outcomes [12] was able to link MAFLD defined by CT scan, with severe COVID-19; the same results were confirmed by other authors [10, 11, 28].

Part of the intrinsic difficulties of studying NAFLD in these patients includes how to define this entity. For example, some studies have relied exclusively on imaging, which has some limitations, the first of them being that ultrasound and CT have poor sensitivity for mild steatosis. Also, even if it is very probable that most liver steatosis found on CT is NAFLD, strictly speaking, secondary causes need to be excluded, and also, it should be taken into account that COVID-19 itself may induce liver steatosis [28]. In this fashion, Ibañez et al. [29] found no association between MAFLD and poor outcomes, though MAFLD was defined exclusively based on CT findings and not on the recently proposed definition of MAFLD [21]. In this same study, the authors described an association between fibrosis and IMV need, but the authors assessed fibrosis with the FIB-4 index, which takes into account AST and ALT levels, which can be elevated due to different reasons during the disease course. It also has to be taken into account that criteria for ICU admission or initiation of IMV vary across centers and may be subject to availability, which may in part explain the inconsistency in the results between the different studies.

To the best of our knowledge, this is the first study assessing NAFLD by the DSI and COVID-19 outcomes, and it is also one of the few studies reporting the association between NAFLD and mortality. The DSI, unlike other methods, does not require imaging studies and was developed to diagnose NAFLD per se, including cases with mild steatosis. At this point, we cannot know if it is NAFLD that is associated with death and IMV or the combination of variables included in the DSI, many of which are well-known risk factors for poor outcomes in this population. However, even after adjusting for triglyceride levels, DM, obesity, arterial hypertension, and age, the DSI was still associated with poor outcomes. Of note, triglyceride levels were also associated with IMV and with ICU admission, and more recently have caught attention as a potential prognostic marker in patients with COVID-19. The intense reaction induced in COVID-19 ends up decreasing the activity of the lipoprotein lipase resulting in high triglyceride levels, which may be a valuable marker of the inflammatory state [30].

We acknowledge that our study does have limitations. First, the DSI takes into account glucose and triglycerides which in some patients were probably not taken in a fasting state, and AST and ALT levels, which may be elevated in COVID-19 due to other reasons. However, being our results in consonance with those found in other studies supports that these patients did have NAFLD, and that NAFLD is associated with poor outcomes. Also, our study was restricted to inpatients, and therefore, we could not evaluate the role of NAFLD in outpatients. Then, the prevalence of NAFLD as per the DSI that we found in our study is one of the highest reported in the literature so far and raises concern about some sort of overdiagnosis; however, this could be primarily due to two reasons: first, there is a *baseline* high prevalence of NAFLD in our population (i.e., Hispanics); and second, our study was conducted in patients with severe COVID-19, who are known to have a higher prevalence of comorbid conditions, including metabolic and cardiovascular diseases, when compared to non-severe cases. For example, the prevalence of DM in our study was 27% compared to the 6% reported by Wang et al. [31] Kreling et al. [32] also found a higher prevalence of liver steatosis, diagnosed by CT scan, among patients with COVID-19 when compared with negative controls. Finally, we did not have information available about each patient's usual alcohol intake, and therefore, it may be possible for some cases of steatosis to be alcohol-related, which is the reason why we decided to stick to the term "steatosis on CT" instead of "NAFLD by CT", and also because the COVID-19 itself has been associated with histopathological findings of steatosis [28].

In conclusion, NAFLD as per the DSI is associated with the need for IMV and death in patients with severe COVID-19, and its use to better stratify the prognosis of these patients should be explored.

Declarations

Conflict of interest The authors declare no conflict of interests and we have no disclosures.

Human and animal rights statement The study was reviewed and approved by the Institutional Review Board (ref. no. 3333).

Informed consent Written informed consent was waived because of the observational nature of the study.

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