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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic performance of an index based on lactic dehydrogenase and transaminases for patients with liver steatosis and COVID-19

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Abstract

BACKGROUND

Metabolic associated fatty liver disease (MAFLD) is associated with complications and mortality in patients with coronavirus disease 2019 (COVID-19). However, there are no prognostic scores aimed to evaluate the risk of severe disease specifically in patients with MAFLD, despite its high prevalence. Lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase have been used as markers of liver damage. Therefore, we propose an index based on lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase for the prediction of complications and mortality in patients with MAFLD and COVID-19.

AIM

To evaluate the prognostic performance of an index based on lactate dehydro-

genase and transaminases (aspartate aminotransferase/alanine aminotransferase) in patients with COVID-19 and MAFLD [liver fibrosis and nutrition (LNF)-COVID-19 index].

METHODS

In this retrospective cohort study, two cohorts from two different tertiary centers were included. The first was the derivation cohort to obtain the score cutoffs, and the second was the validation cohort. We included hospitalized patients with severe COVID-19 and MAFLD. Liver steatosis was evaluated by computed tomography scan. Area under the receiver operating characteristic (ROC) curve analysis and survival analysis were used.

RESULTS

In the derivation cohort, 44.6% had MAFLD; ROC curve analysis yielded a LFN-COVID-19 index > 1.67 as the best cutoff, with a sensitivity of 78%, specificity of 63%, negative predictive value of 91% and an area under the ROC curve of 0.77. In the multivariate analysis, the LFN-COVID-19 index > 1.67 was independently associated with the development of acute kidney injury (odds ratio: 1.8, 95% confidence interval: 1.3-2.5, $P < 0.001$), orotracheal intubation (odds ratio: 1.9, 95% confidence interval: 1.4-2.4, $P < 0.001$), and death (odds ratio: 2.86, 95% confidence interval: 1.6-4.5, $P < 0.001$) in both cohorts.

CONCLUSION

LFN-COVID-19 index has a good performance to predict prognosis in patients with MAFLD and COVID-19, which could be useful for the MAFLD population.

Key Words: COVID-19; Metabolic associated fatty liver disease; Lactate dehydrogenase; Transaminases; Prognosis; Nonalcoholic fatty liver disease

Core Tip: The liver fibrosis and nutrition-coronavirus disease 2019 (LFN-COVID-19) index that includes lactate dehydrogenase and transaminases is a new prognostic index for patients with metabolic associated fatty liver disease and COVID-19; it was developed to specifically predict adverse clinical outcomes, including mortality, in this population with both conditions. The variables included in this index allow an easy, quick and reliable risk assessment in this population with simple markers, allowing for broad implementation.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (coronavirus disease 2019, COVID-19) still affects the entire world. As of June 15, 2022, 536720870 people have been infected, of whom 6312601 have died[1].

Different risk factors associated with the development of complications and mortality in patients with COVID-19 have been identified, including age > 60 years, the presence of cirrhosis, diabetes, immunodeficiencies, obesity, cardiovascular disease, chronic kidney disease and chronic obstructive pulmonary disease, among others[2-4]. Metabolic dysfunction associated fatty liver disease (MAFLD), regarded as the hepatic manifestation of metabolic syndrome, has a controversial role in the prognosis of patients with COVID-19. Some studies have reported a poor prognosis in patients with MAFLD, while others have only showed this finding when fibrosis was present. This could be explained by a more pronounced baseline systemic inflammatory profile and activation of the immune response in patients with liver fibrosis, which contributes to increased inflammation when SARS-CoV-2 infection is added[5, 6].

Acute respiratory distress syndrome is the major complication in patients with severe COVID-19; other complications such as cardiac or cardiovascular, renal and secondary infections may occur[7]. These patients, mainly those admitted to the intensive care unit, may present with laboratory abnormalities, such as leukopenia, lymphopenia (< 800 mm^3 at admission), elevated prothrombin time, elevated serum levels of D-dimer (> 1000 ng/mL), elevated inflammatory markers (ferritin > 300 μg/L), elevated lactate dehydrogenase (LDH), elevated liver enzymes, elevated creatine phosphokinase (twice the upper limit of normal) and elevated troponin I[7-9].

In patients with pneumonia associated with SARS-CoV-2 infection, high LDH levels correlate with lung damage, severe disease and mortality at day 30[10-13]. In the study by Yan *et al*[14], LDH (> 365 U/L), lymphocyte count (< 14.7%) and C-reactive protein (> 41.2 mg/L) were identified as the three laboratory abnormalities that predicted mortality risk with 90% accuracy, which represented a simple way to promptly recognize severe illness.

Likewise, in patients with acute liver injury (non-COVID-19 related), an increase in LDH levels has been reported, secondary to endothelial damage induced by macrophages during acute inflammation, conditioning microcirculation alterations and hypoxia. Thus, it has been suggested that LDH may have a discriminatory role in identifying the etiology of liver damage. As a marker of damage due to liver ischemia, it must be taken into account that LDH has a shorter half-life. Therefore, a faster fall occurs when the damage disappears, and it has been suggested as a parameter to monitor the evolution of patients with acute liver injury. The ubiquitous nature of LHD in the human body makes it a nonspecific but sensitive biomarker, which in the context of organ damage can provide information with diagnostic and prognostic potential. In the same way, increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and the AST/ALT ratio has been associated to adverse clinical outcomes including mortality in patients with COVID-19[10-13,15].

Identifying factors associated with poor prognosis that may be related to a pathophysiological mechanism is ideal in patients with COVID-19 since those patients at risk of progressing to a severe illness could be identified promptly. Therefore, measures could be taken to influence the outcomes of those patients. In this sense, having a prognostic index specific for patients with MAFLD who develop COVID-19 may be useful to identify individuals at risk of developing adverse clinical outcomes.

Therefore, the aim of this study was to evaluate the performance of a prognostic index based on LDH, AST and ALT in patients with MAFLD and COVID-19 and its association with the development of adverse clinical outcomes and mortality.

MATERIALS AND METHODS

This was a retrospective cohort study performed at two third-level hospitals in Mexico, (INCMNSZ and ISSEMYM) from March 2020 to July 2020, during the first phase of the COVID-19 pandemic and before steroids became a standard of care for severe COVID-19. The study was carried out according to the Declaration of Helsinki and was approved by the institutional Ethics Committee, ref. No. 3777).

Validation process

This study consisted of two phases. Phase 1, a derivation/training cohort, (its methods are described below) used to create and evaluate the newly proposed prognostic index. This cohort was derived from a tertiary care center hospital in Mexico City (INCMNSZ). Phase 2, the validation cohort aimed to evaluate the diagnostic performance of the proposed index in patients with COVID-19 and liver steatosis at a different center. This cohort was derived from a tertiary care center hospital in Toluca, in the center of Mexico (ISSEMYM).

Patients

All patients admitted during the period of study, > 18 years of age, either sex and with a confirmed diagnosis of SARS-CoV-2 infection by RT-PCR and with severe disease (pneumonia + respiratory rate > 30/respiratory distress/SaO_2 < 90%), were included in the study[19]. Patients without an adequate follow-up were excluded from the analysis (*e.g.*, those requiring referral to another hospital, those with insufficient information in the clinical records, *etc*). Follow-up and evaluation of the clinical outcomes were conducted through revision of electronic clinical records.

Biochemical tests

Upon admission, a blood sample was drawn for determination of the following tests: complete blood count, glucose, creatinine, electrolytes, ferritin, C-reactive protein, LDH, liver chemistry, creatine phosphokinase, arterial blood gases, D-dimer, troponin I and fibrinogen. HIV (human Immunodeficiency virus) and viral hepatitis panel (HCV and HBV) were performed in all participants. All the tests met the quality standards from our central laboratory, accredited by the College of American Pathologists.

Computed tomography scan

In order to evaluate the severity of pulmonary involvement, all patients underwent a pulmonary computed tomography scan, where a portion of the liver was also evaluated for the presence of steatosis. The methodology was previously described from our group[16]. Briefly, an expert radiologist blinded to the patient´s clinical status evaluated computed tomography scans to detect liver steatosis, according to the following criteria: (1) Attenuation coefficient ≤ 40 Hounsfield units in the liver (segments VII and VIII); and (2) Attenuation coefficient ≥ 10 Hounsfield units between the splenic and liver parenchyma.

Estimation of the LFN-COVID-19 index

The liver fibrosis and nutrition (LNF)-COVID-19 index was calculated according to the following formula:

LFN-COVID-19 index = (AST/ALT) × (LDH/LDH_{ULN}).

Where AST/ALT ratio included transaminase levels expressed in U/L and was multiplied by the times above the upper limit of normal value for LDH (U/L). The final value was included in the statistical analysis for characterization of clinical outcomes.

Statistical analysis

Sample size estimation considered a hypothetical area under the receiver operating characteristic curve (AUROC) of 0.8 for LFN-COVID-19 index and 0.7 as null hypothesis. Considering an alpha error of 0.05 and beta 0.20 and a negative/positive ratio of 1/1, estimation yielded 81 negative/positive cases (162 patients in total).

Normality of the data was evaluated with Kolmogorov-Smirnov test. Data was presented as mean ± standard deviation, median (P25-P75) or absolute frequencies. Comparisons between the groups were made through Mann-Whitney *U* or Student's *t* test. ROC curve analysis was performed to obtain the best cutoff from the LFN-COVID-19 index for mortality, through the Youden index as well as sensitivity, specificity, positive and negative predictive values and likelihood ratios.

Clinical outcomes were evaluated by logistic regression and a time-dependent survival analysis, including Kaplan-Meier and Cox regression (Cox proportional-hazards model) for 28-d mortality and general mortality. Statistical analysis was carried out with the statistics software SPSS version 20.0 (IBM, Armonk, NY, United States) and ROC analysis with MedCalc Statistical Software version 19.4.1 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

In the validation cohort a total of 457 patients were included in the final analysis (Figure 1), after excluding those without an adequate follow-up, those with computed tomography scan issues (artifacts, unable to evaluate liver or spleen tissue, post-surgical changes) or those with known autoimmune liver diseases, HIV, hepatitis C or B chronic infection or cancer.

Participant's characteristics

General characteristics of the study population, with and without MAFLD are presented in Table 1. Mean age in the total population was 50.4 ± 13.3 years, most of the patients were male (65.2%), and the mean body mass index (BMI) was 30.1 ± 5.6 kg/m^2. In general, in the group of patients with MAFLD there was a higher prevalence of overweight and obese patients, they were younger than those without MAFLD, and they had a higher prevalence of diabetes and metabolic syndrome.

Biochemical tests

Biochemical tests related to proinflammatory status, such as LDH, creatine phosphokinase, lymphocytes and neutrophil/lymphocyte ratio, were higher in the MAFLD group, as well as liver chemistry abnormalities, glucose, triglycerides and prognostic scores (SOFA: sequential organ failure assessment;).

Index diagnostic performance

In the group of patients with MAFLD, diagnostic yield of the LFN-COVID-19 index [(AST/ALT) × (LDH/LDH_{ULN})] was investigated through the AUROC analysis to determine the prognostic value of the index as a prognostic marker in patients with COVID-19. Characteristics related to diagnostic yield of the LFN-COVID-19 index are shown in Table 2. According to Youden's index, the best cutoff value of the LFN-COVID-19 index for mortality in patients with MAFLD was > 1.67. This cutoff value showed an AUROC of 0.77 [95% confidence interval (CI): 0.709-0.823, $P < 0.0001$], with a sensitivity of 78.7% and specificity of 63.8% (Figure 2A). In general, the AUROC in this group of patients was better than in patients without MAFLD (AUROC: 0.703, 95%CI: 0.647-0.755, $P < 0.0001$) (Figure 2B).

Table 3 shows the characteristics of patients with MAFLD according to the LFN-COVID-19 index. Similitudes in both groups regarding metabolic syndrome and BMI were observed, while other

Table 1 Baseline characteristics of the total population and according to metabolic associated fatty liver disease presence

Characteristics	All, *n* = 457	No MAFLD, *n* = 253	MAFLD, *n* = 204	*P* value
Demographic features				
Sex as male/female, %	65.2/34.8	63.6/36.4	67.2/32.8	0.432
Age in yr	50.4 ± 13.3	52.4 ± 14.0	47.8 ± 11.8	< 0.0001
BMI in kg/m^2	30.1 ± 5.6	28.7 ± 4.9	31.8 ± 5.8	< 0.0001
Comorbidities, n (%)				
Malnutrition	10 (2.8)	7 (3.4)	3 (1.9)	< 0.0001
Normal weight	49 (13.6)	43 (21.0)	6 (3.9)	
Overweight	136 (37.9)	82 (40.0)	54 (35.1)	
Obesity G1	110 (30.6)	51 (24.9)	59 (38.3)	
Obesity G2	36 (10.0)	16 (7.8)	20 (13.0)	
Obesity G3	18 (5.0)	6 (2.9)	12 (7.8)	
T2DM	107 (23.5)	47 (18.7)	60 (29.6)	0.006
Hypertension	122 (26.8)	60 (23.8)	62 (30.5)	0.107
Chronic kidney disease	8 (1.8)	6 (2.4)	2 (1.0)	0.225
Pulmonary obstructive disease	4 (0.9)	1 (0.4)	3 (1.5)	0.235
Autoimmune disease	6 (1.3)	3 (1.2)	3 (1.5)	0.551
Immunosuppression	3 (0.7)	3 (1.2)	0 (0)	0.169
Metabolic syndrome	155 (36.0)	61 (25.5)	94 (49.0)	< 0.0001
Prognostic scores				
qSOFA	1 (0-1)	1 (0-1)	1 (0-1)	0.800
SOFA	2 (1-2)	2 (1-2)	2 (1-2)	0.034
NEWS	6.7 ± 2.3	6.6 ± 2.3	6.8 ± 2.2	0.190
PSI/PORT	62 (50-80)	62 (50-82)	61 (49-77)	0.316
SMART COP	3 (2-4)	3 (2-4)	3 (2-4)	0.091
Biochemical values				
CRP, ref: 0-1 mg/dL	13.2 (6.6-20.7)	13.1 (6.6-20.0)	13.7 (6.2-21.5)	0.286
Ferritin, ref: 11.0-306.8 ng/mL	747.8 ± 665.0	717.2 ± 662.0	784.0 ± 668.0	0.290
D-dimer, ref: 0-500 ng/mL	707 (426-1146)	699 (413-1138)	721 (451-1182)	0.418
LDH, ref: 120-246 U/L	388 ± 160	374 ± 149	406 ± 173	0.032
Troponin, ref: < 15 pg/mL	4.7 (3.2-8.2)	4.7 (3.1-10.4)	4.6 (3.2-7.1)	0.525
CPK, ref: 30-233 U/L	110 (59-242)	98 (55-210)	133 (66-311)	0.006
Bilirubin, ref: 0/3-1 mg/dL	0.68 ± 0.49	0.66 ± 0.54	0.69 ± 0.43	0.593
ALT, ref: 7-52 U/L	37.5 (25.0-56.0)	33.0 (23.8-54.7)	41.0 (28.0-59.0)	0.004
AST, ref: 13-39 U/L	42.0 (30.0-62.0)	40.0 (29.0-58.0)	43.9 (32.9-64.3)	0.051
Globulins, ref: 1.9-3.7 g/dL	3.2 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	0.560
Albumin, ref: 3.5-5.7 g/dL	3.7 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	0.051
ALP, ref: 34-104 U/L	86 (70-111)	86 (70-113)	85 (69-109)	0.505
Creatinine, ref: 0.6-1.2 mg/dL	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.877
Glucose, ref: 70-99 mg/dL	116 (102-144)	110 (99-131)	124 (105-184)	< 0.0001
Leukocytes, ref: 4-12 × 10^3/μL	7.6 (5.6-10.0)	7.2 (5.4-9.8)	7.9 (5.7-10.3)	0.191
Lymphocytes, ref: 1-3.9 × 10^3/μL	881.6 ± 509.0	835.0 ± 352.0	938.0 ± 649.0	0.043

Platelets, ref: 150-450 K/μL	239 ± 88	248 ± 95	227 ± 78	0.012
25 (HO) vitamin D, ref: 30-100 ng/mL	21.5 ± 8.0	21.6 ± 8.1	21.5 ± 8.0	0.917
Triglycerides, ref: < 150 mg/dL	159 ± 85	155 ± 60	165 ± 110	0.264
CT scan results, pulmonary involvement				
Mild, < 20%	91 (20.0)	51 (20.3)	40 (19.6)	0.281
Moderate, 20%-50%	172 (37.8)	102 (40.6)	70 (34.3)	
Severe, > 50%	192 (42.2)	98 (39.0)	94 (46.1)	
Treatment, n (%)				
Antibiotics	402 (88.4)	228 (90.8)	174 (85.3)	0.096
Antimalarials	132 (28.9)	72 (28.5)	60 (29.4)	0.823
Tocilizumab	51 (11.2)	26 (10.3)	25 (12.3)	0.504
Remdesivir	9 (2.0)	7 (2.8)	2 (1.0)	0.152
PaO2/FiO2 ratio	233.9 ± 109.9	239.0 ± 91.0	227.0 ± 130.0	0.011
Neutrophil/lymphocyte ratio	7.0 (4.4-11.6)	7.2 (4.5-12.0)	6.7 (4.0-10.8)	0.860
Days between the beginning of symptoms and hospitalization	8.2 ± 4.4	8.6 ± 4.6	7.8 ± 4.0	0.110

BMI: Body mass index; T2DM: Type 2 diabetes mellitus; q-SOFA: Quick sequential organ failure assessment; SOFA: Sequential organ failure assessment; NEWS: National early warning score; PSI/PORT: Pneumonia severity index; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CT: Computed tomography; MAFLD: Metabolic associated fatty liver disease; PaO2/FiO2 ratio: Ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table 2 Diagnostic yield of the LFN-COVID-19 index in patients with metabolic associated fatty liver disease

Diagnostic yield	
Sensitivity	0.787 (0.643-0.893)
Specificity	0.638 (0.563-0.709)
Positive predictive value, %	0.360 (0.273-0.468)
Negative predictive value, %	0.910 (0.855-0.960)
+ Likelihood ratio	2.18 (1.70-2.80)
- Likelihood ratio	0.33 (0.20-0.60)
AUROC	0.770 (0.709-0.823), $P < 0.0001$
Youden index	0.4257

AUROC: Area under the receiver operating characteristic.

variables including age, prognostic scores, and biomarkers related to proinflammatory and prothrombotic status, severe COVID-19 (PaO_2/FiO_2 < 100 mmHg), orotracheal intubation and other clinical outcomes, including mortality, were higher in the > 1.67 group.

Prognostic performance

In order to determine if the LFN-COVID-19 index was independently associated with the presence of acute kidney injury or orotracheal intubation during hospitalization, a logistic regression was performed, observing that a value of > 1.67 was associated to adverse clinical outcomes, independently of metabolic factors, severity scores and demographic variables (Table 4).

A marker of mortality was studied by a 28-d Kaplan-Meier survival analysis (Figure 3), observing that patients with a value > 1.67 have a lower survival than those with a value < 1.67 ($P < 0.001$). The influence of other variables on mortality was evaluated through univariate and multivariate Cox proportional hazard analysis. Table 5 summarized the variables that were significant in the univariate analysis, with the results subjected to the multivariate analysis where the variables that were independently associated with mortality were the LFN-COVID-19 index, the neutrophil/lymphocyte

Table 3 Characteristics and outcomes in patients with metabolic associated fatty liver disease according to the LFN-COVID-19 index

	< 1.67, *n* = 115	> 1.67, *n* = 89	*P* value
Demographic features			
Sex as male/female, %	63.5/36.5	71.9/28.1	0.203
Age in yr	46 ± 10	50 ± 12	0.011
BMI in kg/m^2	31.1 ± 4.8	32.5 ± 6.9	0.111
Prognostic scores			
qSOFA	1 (0-1)	1 (1-1)	0.007
SOFA	2 (1-2)	2 (2-3)	0.004
NEWS	7 (5-8)	7 (6-9)	0.035
PSI/PORT	56 (47-69)	66 (53-85)	< 0.0001
SMART COP	3 (2-4)	4 (3-4)	0.012
Biochemical values			
CRP, ref: 0-1 mg/dL	8.5 (4.2-18.1)	17.2 (11.6-23.8)	< 0.0001
Ferritin, ref: 11.0-306.8 ng/mL	503 (266-970)	795 (412-1114)	0.003
D-dimer, ref: 0-500 ng/mL	587 (399-962)	967 (606-1549)	< 0.0001
LDH, ref: 120-246 µ/L	312 ± 86	529 ± 180	< 0.0001
Troponin, ref: < 15 pg/mL	3.7 (2.9-5.7)	6.1 (3.8-10.9)	< 0.0001
CPK, ref: 30-223 µ/L	107 (58-222)	190 (78-414)	0.001
Bilirubin, ref: 0/3-1 mg/dL	0.62 ± 0.30	0.78 ± 0.54	0.017
ALT, ref: 7-52 U/L	43.2 (31.0-61.2)	37.0 (26.3-52.8)	0.026
AST, ref: 13-39 U/L	38.3 (27.8-52.2)	52.4 (42.0-73.7)	< 0.0001
Globulins, ref: 1.9-3.7 g/dL	3.22 ± 0.39	3.29 ± 0.43	0.259
Albumin, ref: 3.5-5.7 g/dL	3.90 ± 0.42	3.50 ± 0.40	< 0.0001
ALP, ref: 34-104 µ/L	85 (70-109)	85 (67-110.5)	0.786
Creatinine, ref: 0.6-1.2 mg/dL	0.85 (0.69-1.00)	0.95 (0.79-1.16)	0.005
Glucose, ref: 70-99 mg/dL	118 (102-180)	135 (114-187)	0.03
Leukocytes, ref: 4-12 × 10^3/µL	7.6 (5.6-9.9)	8.3 (6.3-10.8)	0.089
Lymphocytes, ref: 1-3.9 × 10^3/µL	937 (693-1210)	715 (510-967)	< 0.0001
Platelets, ref: 150-450 K/µL	228 ± 78	226 ± 79	0.827
25 (HO) vitamin D, ref: 30-100 ng/mL	21.9 ± 7.8	20.9 ± 8.3	0.488
Triglycerides, ref: < 150 mg/dL	151 (118-187)	137 (111-184)	0.13
PaO2/FiO2 ratio	240 (161-287)	159 (96-245)	< 0.0001
Neutrophil/lymphocyte ratio	5.9 (3.5-9.9)	9.6 (6.4-13.7)	< 0.0001
Other, *n* (%)			
Metabolic syndrome	49.0 (46.2)	45.0 (52.3)	0.401
Severe COVID-19, PaO_2/FiO_2 < 100 mmHg	9 (8.2)	23 (26.7)	< 0.0001
Orotracheal intubation	13 (11.3)	36 (40.9)	< 0.0001
Acute kidney injury	11 (11)	26 (34.7)	< 0.0001
Thrombotic event	1 (1.0)	2 (2.7)	0.576
Death	6 (5.3)	25 (29.8)	< 0.0001
Days between the beginning of symptoms and hospitalization	7.2 ± 3.4	8.6 ± 4.9	0.027

Length of hospital stay in days	7 (4-10)	8 (6-10)	0.131
Days in ICU	7 (5-12)	12 (6-13)	0.395
Days between ICU requirement and death	7 (6-7)	5 (3-7)	0.203

BMI: Body mass index; q-SOFA: Quick-sequential organ failure assessment; SOFA: Sequential organ failure assessment; NEWS: National early warning score; PSI/PORT: Pneumonia severity 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; PaO2/FiO2 ratio: Ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table 4 Logistic regression analysis to evaluate the association between LFN-COVID-19 index and clinical outcomes

	Orotracheal intubation				Acute kidney injury			
	OR	95%CI	B coefficient	*P* value	OR	95%CI	B coefficient	*P* value
LFN-COVID-19 index	1.900	1.481-2.437	0.642	0.000	1.849	1.366-2.504	0.615	0.000
Sex	0.605	0.288-1.271	-0.502	0.185	0.280	0.103-0.765	-1.272	0.013
Age	0.966	0.939-0.993	-0.035	0.015	1.021	0.988-1.054	0.021	0.209
BMI	1.054	0.997-1.114	0.053	0.061	1.085	1.011-1.164	0.081	0.023

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; COVID-19: Coronavirus disease 2019.

Table 5 Cox proportional hazard multivariate analysis for mortality in patients with metabolic associated fatty liver disease according to the LFN-COVID-19 index

	OR	B coefficient	*P* value	95%CI
LFN-COVID-19 index	0.241	-1.422	0.013	0.079-0.741
PaO_2/FiO_2 ratio	1.000	0.000	0.877	0.996-1.004
Neutrophil/lymphocyte ratio	1.043	0.042	0.030	1.004-1.083
Creatine phosphokinase	1.001	0.001	0.340	0.999-1.002
Body mass index in kg/m^2	1.093	0.089	0.002	1.033-1.157

OR: Odds ratio; CI: Confidence interval; COVID-19: Coronavirus disease 2019; PaO2/FiO2 ratio: Ratio of arterial oxygen partial pressure to fractional inspired oxygen.

ratio and BMI.

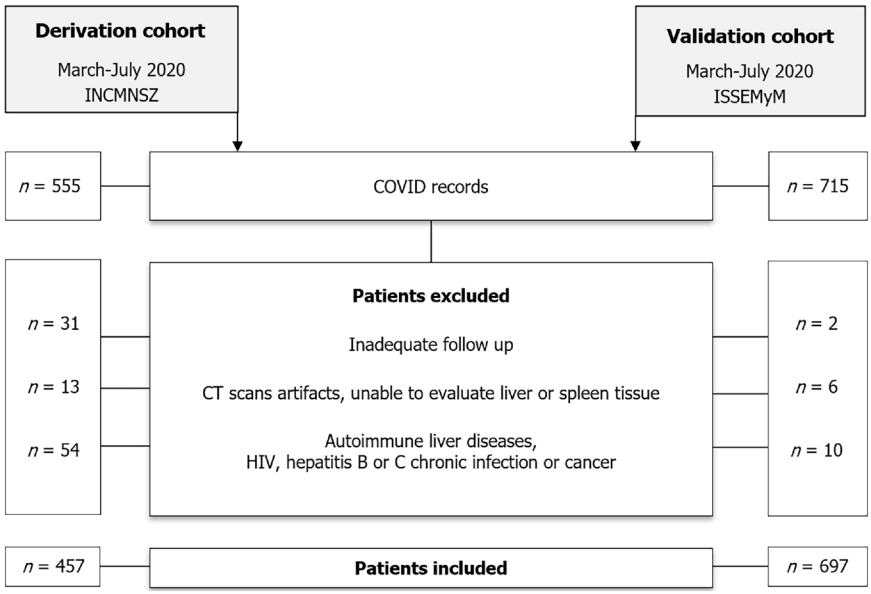
In this analysis, a LFN-COVID-19 index > 1.67 was associated independently to other variables of mortality, including severity markers, prognostic scores and general characteristics (Figure 4).

Validation cohort

From the 697 patients included in the validation cohort, 104 had MAFLD (15.0%). In general, patients with MAFLD were younger and had higher degrees of obesity and mild abnormalities in liver chemistry (Supplementary Table 1). The MAFLD group was further analyzed according to the LFN-COVID-19 index, finding higher levels of C-reactive protein and D-dimer in the group > 1.67, with little changes in the rest of the variables (Supplementary Table 2). Interestingly, mechanical intubation and clinical outcomes including mortality, were more frequent in the > 1.67 group, as was found in the initial cohort (Supplementary Table 3). These same findings in another cohort and in a different hospital highlight the validity of the LFN-COVID-19 index.

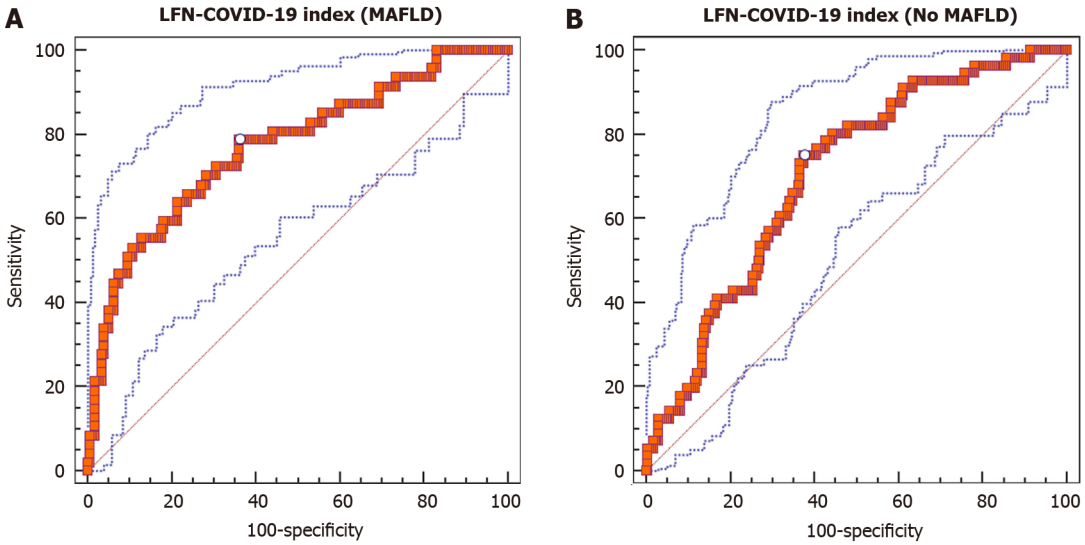
DISCUSSION

MAFLD is currently the main etiology of chronic liver disease in the world. The main associated risk factors are obesity, type 2 diabetes, dyslipidemia and metabolic syndrome, all factors with a growing incidence. Both risk factors for MAFLD and MAFLD itself have also been shown to have prognostic value in COVID-19, associating their presence with higher severity and mortality. However, it remains



DOI: 10.3748/wjg.v28.i37.5444

Figure 1 Flowchart of participants in both cohorts. COVID: Coronavirus disease 2019; CT: Computed tomography; HIV: Human Immunodeficiency virus.



DOI: 10.3748/wjg.v28.i37.5444

Figure 2 Area under the receiver operating characteristic curve for the LFN-coronavirus disease 2019 index to predict mortality. A: Patients with metabolic associated fatty liver disease and coronavirus disease 2019; B: Patients without metabolic associated fatty liver disease and coronavirus disease 2019. MAFLD: Metabolic associated fatty liver disease; COVID-19: Coronavirus disease 2019; LFN: Liver fibrosis and nutrition.

controversial whether all patients within the spectrum of MAFLD have a worse prognosis or only those who, in addition to steatosis, have fibrosis[16].

Evidence pointing to MAFLD as a prognostic factor emerged from different studies around the world. A retrospective study in patients with COVID-19 found an association of MAFLD with higher intensive care unit admittance (OR: 2.3, 95%CI: 1.27-4.17), mechanical ventilation (2.08, 95%CI: 1.2-3.6) and in patients with cirrhosis with higher mortality (12.5, 95%CI: 2.16-72.5)[6]. In a cohort study in patients with COVID-19 and chronic liver disease (42% MAFLD), the authors observed a relative risk of 2.8 (95%CI: 1.9-4.0) for death in this group of patients, regardless of age, race, BMI, presence of hypertension or diabetes[12]. Another study conducted in Zhejiang, China found that hospitalized COVID-19 patients who had MAFLD with fibrosis (evaluated through FIB-4 and NFS - nonalcoholic fatty liver disease fibrosis score) were at increased risk of severe disease, regardless of other comorbidities[5]. Lastly, a study conducted by Lucifora *et al*[17] showed that patients with COVID-19 and MAFLD had a higher prevalence of alterations in the liver biochemistry test as well as a longer viral clearance time compared with patients without MAFLD.

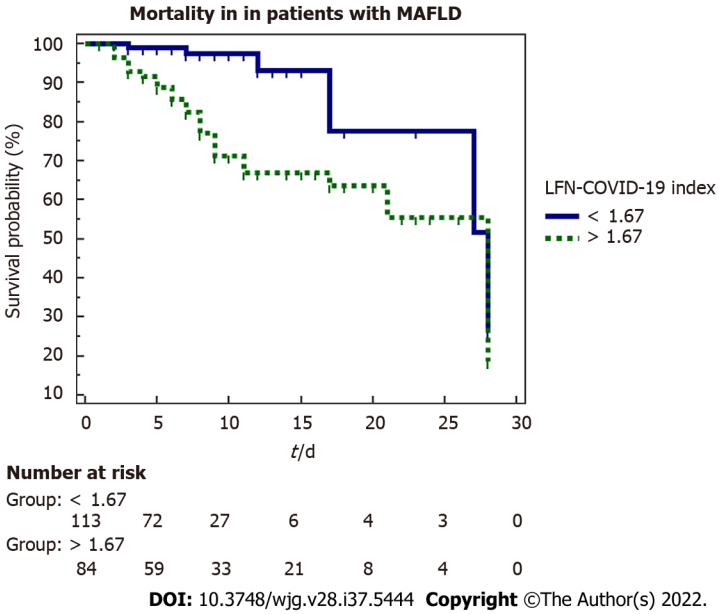


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Figure 3 Kaplan-Meier curve for 28-d mortality according to the LFN-coronavirus disease 2019 index. MAFLD: Metabolic associated fatty liver disease; COVID-19: Coronavirus disease 2019; LFN: Liver fibrosis and nutrition.

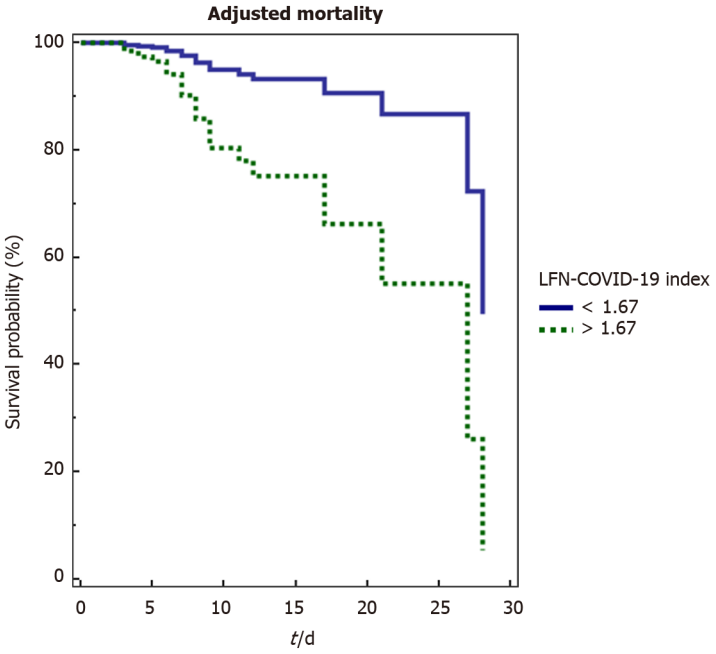

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Figure 4 Adjusted mortality analysis (Cox regression) for 28-d mortality according to LFN-coronavirus disease 2019 index. COVID-19: Coronavirus disease 2019; LFN: Liver fibrosis and nutrition.

Considering the evidence mentioned above, it is possible that the synergism between the baseline proinflammatory state of patients with MAFLD together with the body's inflammatory response to COVID-19 could be the pathophysiological support that explains greater severity and worse prognosis in these patients. Another important component in multiorgan damage in COVID-19, is the state of hypoxemia, cell death and hypoperfusion reflected by biomarkers such as LDH, which correlates positively with worse clinical outcomes (including mortality). Although it is not specific for liver damage, it can be a sensitive and dynamic marker of hypoxic tissue damage due to its short half-life, together with other well-known markers of liver damage, such as AST, ALT and the AST/ALT ratio[10].

Due to the link between MAFLD and COVID-19 and the higher risk of mortality and adverse clinical outcomes, we conceived a prognostic index intended to be used in patients with MAFLD, including variables reflecting the pathophysiology of liver damage, mainly hepatocyte cell death induced by the factors previously mentioned, and associating it with hard clinical outcomes, including mortality[18].

The LFN-COVID-19 index includes the AST/ALT ratio as well as LDH levels normalized by the laboratory's upper limit of normal, facilitating the implementation of the index by non-restricting its usefulness to a specific cutoff value (AST, ALT or LDH). This overcomes the problem of regional variations in laboratory values. The use of this index has potential implications in clinical practice establishing a prognosis of patients. On the other hand, the simplicity of the index allows easy calculation and includes widely available, cheap and reliable laboratory tests.

In the present study, we found a good diagnostic performance of the LFN-COVID-19 index in hospitalized patients with MAFLD and COVID-19. In the ROC curve analysis, a cutoff value of > 1.67 was associated with adverse clinical outcomes including the need for mechanical ventilation, acute kidney injury and higher mortality. This was reproduced in the validation cohort performed at a different center finding this cutoff point as the best for predicting these outcomes[19].

An interesting finding was that there were no differences in the days of stay in the intensive care unit based on this cutoff point. The same length of stay in the intensive care unit could be explained by the severity of the disease, where those with an index below 1.67 were discharged from the critical care area earlier and those with an index above 1.67 present earlier mortality.

Among the weaknesses of this study was the fact that the diagnosis of hepatic steatosis was made with computed tomography. However, given the high risk of transmission of SARS-CoV-2 to healthcare workers, this safer approach was chosen in order to reduce the exposure involved in carrying out a study such as transient hepatic elastography or magnetic resonance imaging requiring more time to perform it. Another aspect to highlight is that patients with COVID-19 usually present with elevated transaminases and LDH from multifactorial causes. Nevertheless, both biomarkers have been widely used as markers of hepatocyte cell death and may reflect liver damage occurring during SARS-CoV-2 infection and exacerbated in patients with MAFLD.

This study has several strengths. The sample size was adequate and sufficient due to the fact that the study was carried out in a center fully converted for the care of COVID-19 patients and included the general population in a country with a highest prevalence of MAFLD and a genetic profile that predisposes the population to the development of metabolic diseases such as type 2 diabetes mellitus, obesity and metabolic syndrome. In addition, we included an external validation cohort, where the results were replicated, enhancing the validity of the LFN-COVID-19 index.

CONCLUSION

Based on the findings of this study, we propose a new prognostic index based on markers of liver damage and severity in patients with MAFLD and COVID-19, which can be used in clinical practice to stratify the risk of adverse outcomes in MAFLD patients. Timely actions to reduce the associated morbidity and mortality in this population could be achieved through the implementation of this index.

ARTICLE HIGHLIGHTS

Research background

This article was conceived considering the high prevalence of metabolic associated fatty liver disease (MAFLD) in the general population amid the coronavirus disease 2019 (COVID-19) pandemic and the risk of these patients in clinical settings with limited resources.

Research motivation

The growing evidence showing worse clinical outcomes in patients with metabolic diseases and COVID-19, including those with fatty liver disease, and the lack of a specific index to specifically stratify patients with both conditions motivated the creation of an index capable of discriminating those patients with an unfavorable outcome.

Research objectives

To evaluate the diagnostic yield of the liver fibrosis and nutrition (LNF)-COVID-19 index (includes lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase values), to predict adverse clinical outcomes, including mortality, in patients with both COVID-19 and MAFLD.

Research methods

Data from a derivation cohort, including patients admitted with a diagnosis of severe COVID-19 and meeting the MAFLD criteria identified the best LFN-COVID-19 index cutoff value for risk stratification. The results were evaluated using a validation cohort.

Research results

The LFN-COVID-19 index with a cutoff point > 1.67 was associated with higher mortality ($P < 0.001$) with an area under the curve of 0.77 (95% confidence interval: 0.709-0.823), sensitivity of 78.7% and specificity of 63.8%. It was independently associated with worse outcomes such as higher mortality, intubation rate and acute kidney injury in both cohorts.

Research conclusions

The LFN-COVID-19 index with a cutoff point > 1.67 showed good discrimination capability in patients with severe COVID-19 and MAFLD, identifying patients with an unfavorable prognosis associated with the need for mechanical ventilation, acute kidney injury and higher mortality.

Research perspectives

The use of this prognostic index will allow timely identification of patients with MAFLD and COVID-19 at higher risk of adverse clinical outcomes, leading to better therapeutic decision-making and resource allocation.

FOOTNOTES

Author contributions: Macías-Rodríguez RU contributed to conception and design of the study; Macías-Rodríguez RU, Solís-Ortega AA and Ornelas-Arroyo VJ contributed with data extraction, literature review and writing; Macías-Rodríguez RU, Ruiz-Margáin A and Román-Calleja BM contributed with writing and analysis of data; Macías-Rodríguez RU, Solís-Ortega AA, Ornelas-Arroyo VJ, Ruiz-Margáin A, Román-Calleja BM, González-Huezo MS, Urdiales-Morán NA, Mayorquín-Aguilar JM, González-Regueiro JA, Campos-Murguía A, Toledo-Coronado IV, Chapa-Ibargüengoitia M, Valencia-Peña B, Martínez-Cabrera CF and Flores-García NC contributed to drafting, critical revision, supervision and editing of the content of the manuscript.

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