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Original Article

Impact of liver enzymes on SARS-CoV-2 infection and the severity of clinical course of COVID-19☆

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ABSTRACT

Background and aim: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the current pandemic, can have multi-organ impact. Recent studies show that liver injury could be a manifestation of the disease, and that liver disease could also be related to a worse prognosis. Our aim was to compare the characteristics of patients with severe coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 who required intubation versus stable hospitalized patients to identify the early biochemical predictive factors of a severe course of COVID-19 and subsequent requirement for intubation, specifically in Mexican.

Methods: This was an observational case-control study nested in a cohort study. Complete medical records of patients admitted for confirmed COVID-19 at a tertiary level center in Mexico City were reviewed. Clinical and biochemical data were collected, and the characteristics of patients who required invasive mechanical ventilation (IMV) (cases) were compared with stable hospitalized patients without ventilation (controls).

Results: We evaluated 166 patients with COVID-19 due to SARS-CoV-2 infection; 114 (68.7%) were men, the mean age was 50.6 ± 13.3 years, and 27 (16.3%) required IMV. The comparative analysis between cases and controls showed (respectively) significantly lower blood oxygen saturation (SpO_2) (73.5 ± 12.0% *vs.* 83.0 ± 6.8%, $P < 0.0001$) and elevated alanine aminotransferase (ALT) (128 (14–1123) IU/L *vs.* 33 (8–453) IU/L, $P = 0.003$), aspartate aminotransferase (AST) (214 (17–1247) *vs.* 44 (12–498) IU/L, $P = 0.001$), lactic dehydrogenase (LDH) (764.6 ± 401.9 IU/L *vs.* 461.0 ± 185.6 IU/L, $P = 0.001$), and D-dimer (3463 (524–34,227) ng/mL *vs.* 829 (152–41,923) ng/mL, $P = 0.003$) concentrations. Patients in the cases group were older (58.6 ± 12.7 years *vs.* 49.1 ± 12.8 years, P=0.001). Multivariate analysis showed that important factors at admission predicting the requirement for IMV during hospitalization for COVID-19 were AST ≥250 IU/L (odds ratio (OR) = 64.8, 95% confidence interval (CI) 7.5–560.3, $P < 0.0001$) and D-dimer ≥ 3500 ng/mL (OR = 4.1, 95% CI 1.2–13.7, P=0.02).

Conclusions: Our study confirms the importance of monitoring liver enzymes in hospitalized patients with COVID-19; seriously ill patients have significantly elevated AST and D-dimer concentrations, which have prognostic implications in the SARS-CoV-2 disease course.

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1. Introduction

Approximately 3.2% of patients with coronavirus disease 2019 (COVID-19) require intubation and invasive mechanical ventilation (IMV) at some point in the disease course. However, the early predictive factors that could help identify which patients will require IMV are not yet completely understood.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the current pandemic, can have multi-organ impact.[2] The body's hyperinflammatory response and the plausible direct effects of SARS-CoV-2 on multiple organs via angiotensin-converting enzyme 2 (ACE2), has been associated with complications of the disease. SARS, heart failure, renal failure, liver injury, shock, and multi-organ failure have led to death.[3]

The World Health Organization has emphasized that one of the most important questions to address regarding the COVID-19 pandemic is understanding the risk factors for disease severity. The approximately 60 predictors of disease severity, factors with high consistency of association, are older age; C-reactive protein, D-dimer, and albumin concentrations; body temperature; sequential organ failure assessment score (SOFA); and diabetes.[4]

Recent studies show that liver involvement could be a common manifestation of COVID-19, with up to 76.3% of patients having abnormal liver test results. The presence of abnormal liver test results is more pronounced during the first 2 weeks of hospitalization, with patients having alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), and gamma-glutamyl transferase (GGT) concentrations elevated to more than three times the upper limits of normal. Patients with abnormal liver test results characterized by hepatocellular injury or mixed injury have higher odds of progressing to a severe disease course.[5] In the current COVID-19 pandemic, hepatic dysfunction has been reported in 14–53% of patients, particularly in those with severe disease.[6] Preexisting chronic liver disease could also be related to a worse prognosis and higher mortality.[7,8] Racial differences also have been reported, and the Hispanic and black populations in New York City appear to be disproportionately affected by the COVID-19 pandemic, considering the higher mortality rates, and factors such as obesity may play a role in the high mortality in these ethnic groups.[9]

The aim of our study was to compare the characteristics at admission of patients with severe COVID-19 due to SARS-CoV-2 requiring IMV versus those who remained stable during their hospitalization, to identify early biochemical predictive factors of a severe course of COVID-19 and subsequent requirement for IMV, specifically in Mexican.

2. Patients and methods

2.1. Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital General de México Dr. Eduardo Liceaga. All patients provided written informed consent prior to enrollment in the study.

2.2. Study design and participants

This was an observational, case-controlled study nested in a cohort study performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The inclusion criteria were as follows: the main cohort constituted patients admitted to the COVID-19 hospitalization area at Mexico City's General Hospital Dr. Eduardo Liceaga. This hospital represents the largest and most important hospital of the Ministry of Health in Mexico's central geographic area. The hospital was converted to a COVID-19 center during the SARS-CoV-2 pandemic. We included patients admitted between March and May 2020 for COVID-19 symptoms and who were confirmed positive for SARS-CoV-2 infection by nasopharyngeal and oropharyngeal swabs using real-time reverse transcription polymerase chain reaction (RT-PCR), at admission. The exclusion criteria were as follows: all identified patients who requested voluntary discharge from our hospital were excluded from the study because this impeded knowledge of their entire clinical course and outcome. Cases were defined as those who required IMV at any point in their clinical disease course during hospitalization. Because there is no consensus on the timing of intubation in patients with COVID-19, the decision to intubate a patient was made by the intensive care specialist physicians mainly in accordance with previous Chinese reports as follows: patients admitted to hospital first received oxygen inhalational therapy with a standard nasal catheter if one of the following conditions were present: (i) respiratory rate $\geq$ 30 breaths per minute; (ii) blood oxygen saturation (SpO_2) $\leq$ 90%; (iii) ratio of partial arterial oxygen pressure (PaO_2)/fractional inspired oxygen (FIO_2) $\leq$ 300 mmHg; and (iv) radiological images showed lesion progression within 24–48 h. If conventional oxygen inhalational therapy failed to improve a patient's hypoxemia, non-invasive ventilation (oxygen by mask with a reservoir) was provided, and finally, if this method also failed, patients were considered for admission to the intensive care unit (ICU) and IMV. Controls were defined as patients who remained stable during their entire hospitalization, improved with oxygen inhalational therapy with a standard nasal catheter or with non-invasive ventilation, and did not require IMV during their clinical disease course. A flow chart of the study design is presented in Fig. 1.

2.3. Procedure and data collection

Following approval of this observational retrospective study by our local Institutional Review Board, we reviewed the medical records of patients admitted because of COVID-19. Clinical and biochemical data at admission were retrospectively collected from the medical records, and baseline characteristics were compared between patients who required IMV during hospitalization because of the development of SARS, versus stable hospitalized patients who did not require IMV during hospitalization.

2.3.1. Patients' clinical characteristics and medical history data

Specifically, we recorded the patients' age, gender, tobacco consumption, alcohol intake, previous history of type 2 diabetes, overweight or obese, hypertension, dyslipidemia, chronic liver disease (CLD), chronic kidney disease (CKD), cardiovascular disease (CVD), any chronic rheumatic disease, cancer, chronic obstructive pulmonary disease (COPD), previous chronic steroid therapy, previous chronic other immunosuppressive medications, pregnancy, and human immunodeficiency virus infection (HIV).

2.3.2. COVID-19 symptoms, baseline characteristics, and treatment initiated at admission to our hospital

We recorded the patients' symptoms as well as oxygen saturation and biochemical, hematological, coagulation, inflammatory, myocardial, and muscular data from baseline laboratory analyses at admission. Treatment measures initiated for COVID-19 at admission were collected from the patients' medical records.

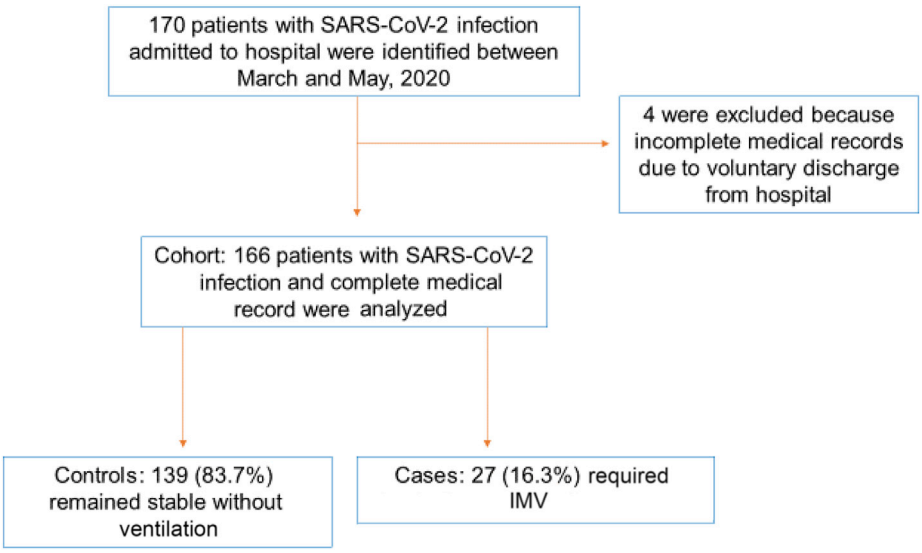

Fig. 1. Flow chart of the study design. Abbreviations: IMV, invasive mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

2.4. Statistical analysis

Comparisons between groups were performed with Student's *t*-test for normally-distributed variables, the Mann–Whitney test for non-normally distributed variables, and chi-squared tests for categorical variables. Quantitative and qualitative variables were expressed as mean ± standard deviation or median (range) and percentage, respectively. Univariate and multivariate logistic regression analyses using the successive backward stepwise (conditional) method were performed to identify the main predictive risk factors at admission for subsequently developing SARS and requiring IMV during hospitalization. Data were analyzed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA). A *P*-value < 0.05 was considered significant.

3. Results

3.1. Clinical characteristics of the patients

We identified 170 patients admitted to our hospital between March 2020 and May 2020; 4 were excluded because of incomplete medical records owing to voluntary discharge from the hospital. We analyzed data for 166 patients with COVID-19 due to SARS-CoV-2 infection; 114 (68.7%) were men, the mean age was 50.6 ± 13.3 years, 139 (83.7%) remained stable without requiring IMV, and 27 (16.3%) were assessed as seriously ill patients requiring IMV and monitoring in the ICU after developing SARS.

According to body mass index, 56 (33.7%) patients had normal body weight, 63 (37.9%) were overweight, and 51 (30.7%) were obese (grade 1: 34 (20.5%), grade 2: 11 (6.6%), grade 3: 6 (3.6%)). Diabetes mellitus was found in 56 (33.7%) patients, hypertension in 50 (30.1%), previous COPD in 14 (8.4%), dyslipidemia in 26 (15.7%), CKD in 9 (5.4%), cancer in 15 (9.0%), chronic CVD in 13 (7.8%), and CLD in 17 (10.2%). Among the patients with CLD, 10 had alcoholic liver cirrhosis, 4 had non-alcoholic fatty liver disease-related cirrhosis, 2 had autoimmune hepatitis, and 1 had hepatitis C-related cirrhosis. Rheumatologic disease was found in 7 (4.2%), HIV infection in 2 (1.2%), chronic immunosuppressive medications in 8 (4.8%), history of tobacco consumption in 34 (20.5%), and chronic alcohol abuse in 16 (9.6%); none of our patients was pregnant. The main symptoms in this cohort are shown in Table 1.

Table 1
Main symptoms at admission in patients for COVID-19 ($N = 166$).

Symptom	*n* (%)
Cough	151 (91.0)
Dyspnea	148 (89.2)
Fever	130 (78.3)
Headache	121 (72.9)
Malaise	108 (65.1)
Anosmia	110 (66.3)
Myalgias	101 (60.8)
Ageusia	100 (60.2)
Diarrhea	53 (31.9)
Articular pain	52 (31.3)

3.2. Comparative analysis between cases and controls

Because there are no specific therapies for COVID-19, in our center, the most commonly prescribed medications were: enoxaparin in 150 (90.4%), acetaminophen in 136 (81.9%), hydroxychloroquine in 86 (51.8%), azithromycin in 130 (78.3%), cephalosporines in 94 (56.6%), steroids (mainly dexamethasone or methylprednisolone) in 21 (12.7%), and oseltamivir in 35 (21.1%). Other medications, such as ivermectin, remdesivir, other antivirals, and tocilizumab, were not prescribed in our patients.

The comparative analysis between those who required IMV versus those who did not, respectively, revealed significantly lower SpO_2 (73.5 ± 12.0% *vs.* 83.0 ± 6.8%, $P < 0.0001$); significantly elevated ALT (128 (14–1123) IU/L *vs.* 33 (8–453) IU/L, $P=0.003$), AST (214 (17–1247) IU/L *vs.* 44 (12–498) IU/L, $P=0.001$), lactate dehydrogenase (LDH) (764.6 ± 401.9 IU/L *vs.* 461.0 ± 185.6 IU/L, $P = 0.001$), and D-dimer (3463 (524–34,227) ng/mL *vs.* 829 (152–41,923) ng/mL, $P = 0.003$) concentrations; and older age (58.6 ± 12.7 years *vs.* 49.1 ± 12.8 years, $P=0.001$) in the cases. A history of COPD was more common in patients requiring IMV *vs.* not requiring IMV (22.2% *vs.* 5.7%, $P=0.01$) (Table 2).

3.3. Univariate and multivariate logistic regression analysis to identify early predictors (at admission) of the risk of requiring IMV during hospitalization for COVID-19

We performed a univariate analysis using the statistically significantly different variables in the comparisons of cases and

Table 2
Baseline characteristics of patients due to SARS-CoV-2 requiring IMV and stable hospitalized patients without ventilation.

Variable	Patients required IMV (cases; $n = 27$)	Stable hospitalized patients without ventilation (controls; $n = 139$)	*P*-value
Demographic and clinical characteristics			
Male, *n* (%)	20 (74.1)	94 (67.6)	0.5100
Age, years	58.6 ± 12.7	49.1 ± 12.8	0.0010*
Tobacco consumption, *n* (%)	7 (25.9)	26 (18.7)	0.4300
Alcohol intake, *n* (%)	3 (11.1)	13 (9.3)	0.7300
Diabetes, *n* (%)	8 (29.6)	48 (34.5)	0.8200
Hypertension, *n* (%)	5 (18.5)	45 (32.4)	0.2500
Weight			
Normal, *n* (%)	11 (40.7)	45 (32.4)	0.5300
Obesity, *n* (%)	16 (59.3)	94 (67.6)	
COPD, *n* (%)	6 (22.2)	8 (5.7)	0.0100*
Cardiovascular disease, *n* (%)	3 (11.1)	10 (7.2)	0.4500
Chronic liver disease, *n* (%)	4 (14.8)	13 (9.3)	0.3000
Chronic rheumatic disease, *n* (%)	2 (7.4)	5 (3.6)	0.3200
Dyslipidemia, *n* (%)	9 (33.3)	17 (12.2)	0.0200
Chronic kidney disease, *n* (%)	3 (11.1)	6 (22.2)	0.1200
Cancer, *n* (%)	1 (3.7)	14 (10.1)	0.4600
AIDS, *n* (%)	1 (3.7)	1 (0.7)	0.3000
Use of immunosuppressive medication different than steroids, *n* (%)	2 (7.4)	6 (4.3)	0.6200
Chronic use of steroids			
No, *n* (%)	27 (100)	133 (95.7)	0.5500
Low dose, *n* (%)	0 (0)	4 (2.9)	
High dose, *n* (%)	0 (0)	2 (1.4)	
Therapy for COVID-19 received			
Enoxaparin, *n* (%)	24 (88.9)	126 (90.6)	0.7300
Acetaminophen, *n* (%)	19 (70.4)	117 (84.2)	0.1500
Hydroxychloroquine, *n* (%)	14 (51.9)	72 (51.8)	1.0000
Azithromycin, *n* (%)	22 (81.5)	108 (77.7)	0.8000
Cephalosporines, *n* (%)	11 (40.7)	83 (59.7)	0.0700
Steroids, *n* (%)	2 (7.4)	19 (13.7)	0.5300
Oseltamivir, *n* (%)	4 (14.8)	31 (22.3)	0.4500
Biochemical characteristics			
Basal SpO_2, %	73.5 ± 12.0	83.0 ± 6.8	<0.0001*
Albumin, g/dL	3.27 ± 0.52	3.48 ± 0.50	0.0900
ALT, IU/L	128 (14–1123)	33 (8–453)	0.0030*
AST, IU/L	214 (17–1247)	44 (12–498)	0.0010*
Alkaline phosphatase, IU/L	109.1 ± 74.8	96.8 ± 54.4	0.3900
GGT, IU/L	103 (18–1577)	75 (11–1215)	0.3500
Direct bilirubin, mg/dL	0.8 ± 1.7	0.3 ± 0.3	0.2300
Indirect bilirubin, mg/dL	0.8 ± 1.1	0.5 ± 0.3	0.3100
Glucose, mg/dL	168.2 ± 95.0	149.8 ± 97.8	0.5400
Urea, mg/dL	54.7 ± 37.0	42.1 ± 37.7	0.1400
Creatinine, mg/dL	1.1 ± 0.7	0.9 ± 0.7	0.2900
Cholesterol, mg/dL	102.9 ± 33.8	123.0 ± 27.0	0.0300
Triglycerides, mg/dL	142.4 ± 45.8	145.7 ± 49.4	0.8300
Total proteins, g/dL	6.5 ± 0.7	6.3 ± 1.0	0.6000
LDH, IU/L	764.6 ± 401.9	461.0 ± 185.6	0.0010*
Sodium, mmol/L	128.8 ± 26.8	135.8 ± 3.5	0.3800
Potassium, mmol/L	4.2 ± 0.4	4.0 ± 0.5	0.1900
Chlorine, mmol/L	102.20 ± 5.04	100.60 ± 4.35	0.2500
Calcium, mg/dL	7.80 ± 0.47	8.00 ± 0.44	0.7700
Phosphorus, mg/dL	3.2 ± 1.0	3.1 ± 0.8	0.7500
Magnesium, mg/dL	2.3 ± 0.3	2.2 ± 0.4	0.2700
Hematological assessment			
Leukocytes, cells/mm^3	10.3 ± 5.1	8.7 ± 4.5	0.2300
Neutrophils, cells/mm^3	8.9 ± 4.6	7.1 ± 4.2	0.0900
Lymphocytes, cells/mm^3	1.0 ± 0.4	1.0 ± 0.6	0.9900
Hemoglobin, g/dL	14.7 ± 1.7	14.5 ± 2.3	0.8200
Red cells distribution width, fl	14.8 ± 1.4	14.2 ± 1.4	0.1500
Platelets, cells/μL	219.7 ± 73.1	226.4 ± 86.2	0.7700
Mean platelet volume, fL	8.9 ± 0.9	8.4 ± 0.9	0.1100
Coagulation tests and inflammatory profile			
International normalized ratio	1.1 ± 0.2	1.0 ± 0.3	0.6300
Fibrinogen, mg/dL	640.7 ± 207.5	608.6 ± 168.9	0.5400
D-dimer, ng/mL	3463 (524–34,227)	829 (152–41,923)	0.0030*
Reactive C protein, mg/L	210.3 ± 157.4	142.7 ± 121.2	0.1700
Ferritin, ng/mL	605 (256–2341)	662 (32–7500)	0.9800
Muscle enzymes			
Creatine phosphokinase, IU/L	125 (15–695)	106 (15–2646)	0.3600
Myoglobin, ng/mL	107 (23–625)	55 (11–1200)	0.4700
Cardiac enzymes and peptides			
Troponin I, ng/L	6.8 (1.7–482.5)	4.6 (1.8–735.8)	0.4500

Table 2 (*continued*)

Variable	Patients required IMV (cases; $n = 27$)	Stable hospitalized patients without ventilation (controls; $n = 139$)	*P*-value
CPK-MB, ng/dL	20 (12–151)	20 (9–92)	0.2900
Brain natriuretic peptide, pg/mL	27 (10–260)	12 (10–158)	0.4900

Data were expressed as mean ± standard deviation or median (range).
Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CPK-MB, creatine phosphokinase-myocardial band; GGT, gamma-glutamyl transferase; ICU, intensive care unit; IMV, invasive mechanical ventilation; LDH, lactic dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
$^{*}P < 0.05$.

controls. The univariate analysis results showed that ALT, AST, LDH, and D-dimer concentrations were the most important factors at admission predicting the requirement for IMV during hospitalization for COVID-19 ($P < 0.0001$) (Table 3). The subsequent multivariate analysis indicated that the two most important factors at admission predicting the requirement for IMV during hospitalization for COVID-19 were AST ≥250 IU/L (odds ratio (OR) = 64.8, 95% confidence interval (CI) 7.5–560.3, $P < 0.0001$) and D-dimer ≥ 3500 ng/mL (OR = 4.1, 95% CI 1.2–13.7, P=0.02) (Table 4).

4. Discussion

Mexico is one of the countries with the highest number of deaths due to the COVID-19 pandemic, with more than 70,000 deaths; a tally surpassed only by the United States of America, Brazil, and India.[10] In this catastrophic scenario, it is important to understand the main factors related to a worse prognosis in the Mexican population. Interestingly, in our study, significant elevations in liver enzymes appeared to play a crucial role in a more severe course of COVID-19. Similarly, some studies have reported higher mortality in patients with COVID-19 with elevated liver enzymes.[11–16] According to a systematic review by Kulkarni *et al.*,[17] the incidence of elevated liver enzyme concentrations was significantly higher in non-survivors (43.3%, 95% CI 30–57.6%) *vs.* survivors (19.2%, 95% CI 16.4–22.3%). Additionally, non-survivors had a higher risk of presenting with elevated liver enzyme concentrations at initial presentation *vs.* survivors (OR = 3.46; 95% CI 2.42–4.95, $P < 0.001$).[17] SARS-CoV-2 mainly affects the lungs with progression to pneumonia and SARS via the ACE2 receptor. Depending on the viral load, infection spreads through the ACE2 receptors to various organs, such as the heart, liver, kidney, brain, endothelium, gastrointestinal tract, immune cells, and red blood cells. This progression may be aggravated by cytokine storm with extensive release of proinflammatory cytokines from the deregulated immune system.[18]

Liver injury related to COVID-19 has been described as elevated serum liver enzyme serum concentrations, mainly the aminotransferases and bilirubin, during the infection course in patients with or without previous liver disease. Wide variability in the deviation of these enzyme concentrations from normal values is observed in infected patients, with an elevation frequency ranging from 16% to 62% for aminotransferases and from 5% to 21% for bilirubin.[19] As we found in our cohort, these abnormalities are seen mainly with the severe forms of COVID-19. In a study by Chen *et al.*,[20] 52% (59/113) of the patients who died had elevated AST, with a median serum concentration of 45 U/L (interquartile range (IQR) 31.0–67.0). In contrast, only 25 of 161 (16%) patients who recovered presented with AST concentrations higher than the upper normal limit, with a median serum concentration of 25.0 (IQR 20.0–33.3).[20] Similar to our findings, a recent study analyzing 554 patients with COVID-19 in Istanbul, Turkey, found that mortality rates and the need for ICU care were statistically significant in patients with elevated ALT and AST concentrations during hospitalization ($P = 0.001$). An AST/ALT ratio >1 was associated with a more severe course and increased mortality owing to COVID-19, and according to the receiver operating curve (ROC) analysis, this ratio was a good marker of mortality risk (area under the curve (AUC) = 0.713, $P = 0.001$) and the expected probability of ICU admission (AUC = 0.636, $P = 0.001$).[21]

Interestingly, in a study performed by Lei *et al.*,[5] longitudinal liver function test results were retrospectively analyzed, and results showed a correlation with liver injury as risk factor and death. The authors observed that AST elevated first, followed by ALT, in severely-affected COVID-19 patients. Abnormal AST concentration was associated with the highest mortality risk compared with the other indicators of liver injury during hospitalization. Frequent additional factors associated with elevated liver injury indicators were decreased lymphocyte count, increased neutrophil count, and male gender.[5,22]

It is important to consider that elevated AST observed in COVID-19 patients and the relationship that we found with a higher proportion of these patients requiring IMV, could represent an early change related to the development of multi-organ failure. Multi-organ failure would explain the more severe course of the disease because it is well known that AST is an organ-nonspecific enzyme located in many tissues of the human body where it catalyzes reversible reactions of transamination. AST is the only enzyme that supplies L-aspartate as a substrate for many metabolic processes, such as the urea cycle or purine and pyrimidine nucleotides in the liver, synthesis of L-arginine in the kidney, and the purine

Table 3
Univariate logistic regression analysis of main predictors (at admission) requiring IMV during hospitalization for COVID-19.

Variable	Patients required IMV (cases; $n = 27$)	Stable hospitalized patients without ventilation (controls; $n = 139$)	OR	95% CI	*P*-value
Age > 60 years	11 (40.7)	20 (14.4)	4.1	1.7–10.1	0.0020
COPD	6 (22.2)	8 (5.8)	4.7	1.5–14.8	0.0100
SpO_2 at admission < 90%	27 (100)	120 (86.3)	8.9	0.52–151.9	0.0500
ALT ≥ 225 IU/L	11 (40.7)	1 (0.7)	94.9	11.8–783.8	<0.0001
AST ≥ 250 IU/L	12 (44.4)	1 (0.7)	110.4	13.4–909.2	<0.0001
LDH ≥ 700 IU/L	12 (44.4)	15 (10.8)	6.2	2.5–16.0	<0.0001
D-dimer ≥ 3500 ng/mL	13 (48.1)	13 (9.4)	7.9	3.0–20.2	<0.0001

Data were expressed as number (%).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, novel coronavirus disease 2019; IMV, invasive mechanical ventilation; LDH, lactic dehydrogenase; OR, odds ratio; SpO_2, blood oxygen saturation.

Table 4
Multivariate logistic regression analysis[a] to identify main predictors (at admission) of the risk of requiring IMV during hospitalization for COVID-19.

Steps of the model	Variable	OR	95% CI	*P*
Step 1	ALT ≥225 IU/L	0.000	0.000	1.0000
	AST ≥250 IU/L	8494945662.2	0.000	1.0000
	D-dimer ≥ 3500 ng/mL	4.3	1.3–14.6	0.0180
	LDH ≥700 IU/L	2.7	0.7–9.7	0.1370
	Constant	0.035	–	0.0040
Step 2	AST ≥250 IU/L	40.2	4.3–372.2	0.0010
	D-dimer ≥ 3500 ng/mL	4.3	1.3–14.4	0.0200
	LDH ≥700 IU/L	2.7	0.8–9.9	0.1260
	Constant	0.030	–	0.0030
Step 3	AST ≥250 IU/L	64.8	7.5–560.3	<0.0001
	D-dimer ≥ 3500 ng/mL	4.1	1.2–13.7	0.0200
	Constant	0.044	–	0.0050
Summary of the model				
Step	Logarithm of verosimility-2	Cox and Snell's squared R	Nagelkerke's squared R	
1	98.193[b]	0.257	0.436	
2	98.452[c]	0.255	0.434	
3	100.548[c]	0.246	0.418	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; IMV, invasive mechanical ventilation; LDH, lactic dehydrogenase; OR, odds ratio.
[a] Method of successive steps backward (conditional).
[b] The estimate ended in iteration number 20 because the maximum iterations have been reached. The final solution cannot be found.
[c] The estimate ended in iteration number 5 because parameter estimates have changed by less than 0.001.

nucleotide cycle in the brain and skeletal muscle. AST is also involved in D-aspartate production, which regulates metabolic activity in the autocrine, paracrine, and endocrine systems. AST is also part of the malate–aspartate shuttle in the myocardium, and is involved in gluconeogenesis in the liver and kidney, gluconeogenesis in adipose tissue, and the synthesis of neurotransmitters and the neuroglial pathway in the brain.[23] For example, in other pathological conditions, such as in severely emaciated patients, AST elevation can be a sign of multi-organ failure in patients with a critical life-threatening condition, with elevations in other biochemical markers, such as LDH and creatine phosphokinase (CK),[24] similar to the described findings in COVID-19 patients.[11–16]

Our study confirmed other important findings regarding associated factors in COVID-19, such as elevated D-dimer concentration and older age, with poor outcomes and higher mortality. Thromboinflammatory features are well defined predictors of mortality in patients with COVID-19. In a study by Wang *et al.*,[25] elevated ferritin, tumor necrosis factor-α, and D-dimer concentrations and decreased albumin concentration were associated with disease severity. In the same study, older age, elevated ferritin and elevated interleukin-6 concentrations were associated with 28-day mortality. Xu *et al.*,[26] also found that higher D-dimer concentrations in COVID-19 patients correlated with inflammatory factors and organ function, and the authors proposed that these factors can be used to predict organ injury. Another study by Yu *et al.*,[27] also found that non-survivors were significantly older than survivors (median 69 (IQR 57–77) years *vs.* 55 (41–63) years, $P < 0.001$), and had higher D-dimer concentrations (0.99 (0.44–2.96) mg/L *vs.* 0.52 (0.26–0.96) mg/L, $P < 0.001$). The authors also identified additional factors related to poor outcome in non-survivors, such as higher highly-sensitive troponin I (0.03 (0–0.06) ng/L *vs.* 0 (0–0.01) ng/L, $P < 0.001$), C-reactive protein (85.75 (57.39–164.65) mg/L *vs.* 23.49 (10.1–53.59) mg/L, $P < 0.001$), and α-hydroxybutyrate dehydrogenase (306.5 (268.75–377.25) *vs.* 194.5 (160.75–247.5), $P < 0.001$) concentrations and lower lymphocyte counts (0.74 (0.41–0.96) $\times 10^9$/L *vs.* 0.98 (0.77–1.26) $\times 10^9$/L, $P < 0.001$) compared with survivors.[27]

The limitations of our study are, first, its retrospective nature and the fact that observational studies can suggest associations, but not causation. To establish whether AST and ALT abnormalities are caused by direct liver injury owing to SARS-CoV-2 or whether these changes are a response to inflammation and represent early multiorgan dysfunction needs to be investigated further in prospective and histopathologic studies.

5. Conclusions

Our study confirms the importance of measuring liver enzyme concentrations at admission, then monitoring the concentrations in hospitalized patients with COVID-19. Seriously ill patients have significantly elevated AST and D-dimer concentrations, and these changes have prognostic implications in the SARS-CoV-2 disease course.

Authors' contributions

F. Higuera-de la Tijera and A. Servín-Caamaño planned the study. D. Reyes-Herrera, A. Flores-López, E.J.A. Robiou-Vivero, F. Martínez-Rivera, V. Galindo-Hernández, O. Chapa-Azuela, A. Chávez-Morales, V. H. Rosales-Salyano collected data. F. Higuera-de la Tijera and A. Servín-Caamaño performed the statistic analysis, interpreted and drafted the manuscript. All authors approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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