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Minimal liver enzymes abnormalities at admission are related to severe COVID-19 clinical course in a large Brazilian cohort

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HIGLIGHTS

- Abnormal AST and/or ALT on admission in COVID-19 patients are frequent.
- Male gender, previous liver disease and elevated bilirubin at admission are predictors of abnormal liver enzymes.
- Even mild abnormalities in AST and/or ALT are associated with COVID-19 severity in hospitalized patients.

ABSTRACT – Background – COVID-19 is a multisystemic disease, primarily affecting the respiratory system. Liver involvement is frequent, but the impact on the clinical course and outcomes are controversial. **Objective –** The aim was to assess liver function at the admission and evaluate its effects on severity and mortality in hospitalized patients with COVID-19. **Methods –** This is a retrospective study of hospitalized patients in a tertiary hospital in Brazil, with a PCR-confirmed SARS-CoV-2 infection between April and October 2020. 1080 out of 1229 patients had liver enzymes on admission and were divided in two cohorts, based on the presence or absence of abnormal liver enzymes (ALE). Demographic, clinical, laboratory, imaging, clinical severity, and mortality were evaluated. Patients were followed until discharge, death or transfer to another institution. **Results –** Median age was 60 years and 51.5% were male. The more frequent comorbidities were hypertension (51.2%), and diabetes (31.6%). Chronic liver disease and cirrhosis were present in 8.6% and 2.3%, respectively. ALE (aminotransferases higher than 40 IU/L) were present in 56.9% of patients [mild (1–2 times): 63.9%; moderate (2–5 times): 29.8%; severe (>5 times): 6.3%]. Male gender [RR 1.49, P=0.007], increased total bilirubin [RR 1.18, P<0.001] and chronic liver disease [RR 1.47, P=0.015] were predictors of abnormal aminotransferases on admission. Patients with ALE had a higher risk of disease severity [RR 1.19; P=0.004]. There was no association among ALE and mortality. **Conclusion –** ALE is common in COVID-19 hospitalized patients and were independently correlated with severe COVID-19. Even mild ALE at admission may be a severity prognostic marker.

Keywords – Liver; COVID-19; COVID-19 severity; abnormal aminotransferases; SARS-COV-2.

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INTRODUCTION

Coronavirus infectious disease 2019 (COVID-19), caused by SARS-CoV-2, surprised the world in the early 2020 and has become a challenge, remaining unpredictable until now. More than 296.496.809 cases of COVID-19 among them 5.462.631 deaths in the world were reported by WHO by January 2022. In Brazil, more than 600,000 deaths were reported[1].

COVID-19 is a multisystemic disease, mainly affecting the respiratory system with a broad spectrum of disease, from mild to critical, with complications as pulmonary thromboembolism until multi-organ failure[2,3]. Liver is involved, and several studies reported a wide range of prevalence of abnormal liver enzymes[4-9]. The exact pathophysiology of liver damage is unknown, and it is attributed to multiple factors as: a) SARS-CoV-2 liver replication, b) systemic inflammatory response or hypoxia; c) hepatotoxic drugs, and d) pre-existing comorbidities[10]. Even liver biopsy available data showed variables histological changes, suggesting a multiple insult[11,12].

Varying levels of abnormal liver enzymes, most increased transaminases have been associated with disease severity, complications, and mortality in some studies[13,14], although its impact on clinical course is still controversial[15]. Furthermore, very few studies in Latin America have addressed this issue. The aim of present study was to evaluate the prevalence of abnormal liver enzymes on admission in patients with COVID-19 admitted a tertiary general hospital in South of Brazil, as well as assess its impact on in-hospital severity and mortality.

METHODS

Study design

This is a retrospective single-center cohort study analyzing patients admitted between April 1st and October 31, 2020, at a university hospital in Porto Alegre, Brazil. The study was approved by the Ethics Committee of the *Hospital de Clíncas de Porto Alegre* (project Nº 20200340).

Patients' characteristics

Patients aged ≥18 years with nasopharyngeal or oropharyngeal swab samples RT-PCR SARS-CoV2 positive were enrolled and followed until discharge of hospital, or death.

Cohort characteristics

We collected from electronic medical records the following data: demographics, medical history, clinical characteristics, admission laboratory [complete blood count, C-reactive protein, creatine kinase, lactate dehydrogenase, D-dimer, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), creatinine, international normalized radio (INR) and prothrombin time (PT)], radiological reports and medication history. COVID-19 therapy, including antibiotic, antivirals, steroids, and others, were evaluated before admission. Lymphopenia was considered less than 1000 x 10^3/uL[16]. Liver injury was defined as increase of transaminases: AST and/or ALT level of ≥2 ULN, with total bilirubin ≥2 times ULN and/or disorder of coagulation (INR ≥1.7), according to previous studies[17]. Liver enzymes enabled to separate the cohort into two subgroups based on AST and/or ALT ≥41 IU/L: abnormal liver enzymes (ALE) and normal liver enzymes (NLE)[18]. Liver enzymes elevations on admission (AST and/or ALT), were categorized as mild (<2 times ULN), moderate (2–5 times ULN), and severe (>5 times ULN) as previously described elsewhere[6,19].

COVID-19 severity

Severe COVID-19 was defined as a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg or organ failure (ventilatory support requirement, vasoactive drug, or renal substitute therapy with hemodialysis[20]. Patients were categorized in severe and no severe and compared.

Definitions of comorbidities

Chronic kidney disease and end-stage renal disease were defined as usual[21] and included as "kidney disease". Coronary artery disease and congestive heart failure were grouped as "cardiovascular disease".

Outcomes

The main outcomes assessed were COVID-19 severity and mortality during hospitalization.

Statistical analysis

Categorical variables were reported as percentages and comparisons were made using chi-square test or Fisher's exact test. Continuous variables were reported as median (minimum - maximum) or mean with standard deviation, comparisons were made with Student's *t* test or Mann-Whitney U test, according to distribution (Shapiro - Wilk test). $P<0.05$ was considered as statical significance. To explore independent factor associated with severe disease and mortality was performed a univariate analysis including demographic, clinical and laboratory data which were statistically significant after comparison. Next step significant variables ($P<0.05$) were considered to perform a model of multivariate analysis with dichotomus outcomes using Cox regression in mortality and robust Poisson regression in disease severity. In the same way were explored factors associated with abnormal liver enzymes. Multivariate analysis in each case was adjusted for age >60, sex, hypertension, T2DM and previous history of liver disease. Data analysis was performed with IBM SPSS Statistics, version 25.0. (IBM Corp., Armonk, N.Y., USA).

RESULTS

Of 1,508 medical records referring to 1,454 patients, 1,229 were included as showed in a FIGURE 1

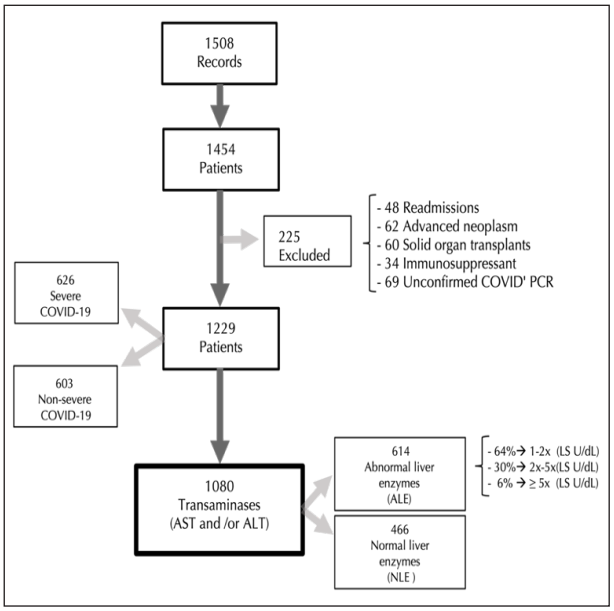

FIGURE 1. Patient's inclusion scheme. (Prism 9 graphic program).

TABLE 1. Demographics characteristics of patients with COVID-19

Variables	n	n (%)
Age, median (minimum - maximum)	1229	60 (18–102)
Age >60	1229	615 (50)
Age <60	1229	614 (50)
Gender		
Male	1229	633 (51.5)
Female	1229	596 (48.5)
Comorbidities		
Hypertension	1227	629 (51.2)
Diabetes	1227	388 (31.6)
Obesity	981	428 (34.8)
Cardiovascular disease	1227	209 (17)
Kidney chronic disease	1227	97 (7.9)
Cirrhosis	1227	28 (2.3)
Clinical symptoms		
Dyspnea	1208	781(63.5)
Fever	1208	653 (53.1)
Cough	1208	191 (15.5)
Myalgia	1208	270 (22.0)
Diarrhea	1208	218 (17.7)
Abdominal pain	1208	51 (4.1)
Nausea and vomiting	1208	140 (11.4)
Anorexia	1208	107 (8.7)
Anosmia	1208	166 (13.5)
Ageusia	1208	100 (8.1)
Chest imaging		
Ground glass pattern	1164	883 (71.8)
Uniilateral consolidation pattern	1164	47 (3.8)
Bilateral consolidation pattern	1164	54 (4.4)
No lesions	1164	180 (14.6)
Complications		
Liver injury	1080	16 (1.3%)
Pulmonary thromboembolism	263	77 (6.3)
Extrapulmonary thrombosis	263	39 (3.2)
Severe COVID-19	1229	639 (52.0)
Oxygen support	1229	952 (77.5)
ICU admission	1229	615 (50.0)
Mechanical ventilation	1229	441 (35.9)
Hemodialysis support	1229	203 (16.5)
Vasoactive drugs support	1229	437 (35.6)
ECMO support	1229	11 (0.9)
Scores ICU		
APACHE	561	11 (0–33)
SAPS3	555	58 (27–145)
SOFA	477	5 (1–16)
Treatment before admission		
Antibiotic therapy	810	492 (40)
Antiviral therapy	810	64 (5.2)
Steroids therapy	810	124 (10.1)
Others therapies	810	26 (2.1)
Treatment in hospital		
Antibiotics	1229	1016 (82.7)
Antiviral therapy	1229	167 (13.6)
Steroids	1229	785 (63.9)
Other	1229	264 (21.5)
Hospital stay		
Emergency	1229	0 (0-5)
Hospitalization	1229	5 (0–169)
ICU	1229	10 (0–94)
Total hospital stay	1229	8 (0–176)
Clinical evolution		
Discharge	1229	802 (65.3)
Transfer	1229	137 (11.1)
Death	1229	290 (23.6)

ICU: intensive care unit; MAFLD: metabolic dysfunction associated fatty liver disease.

and TABLE 1 summarizes demographic and clinical data. Median age was of 60 years, most patients were male, and comorbidities were common, especially hypertension, obesity, and diabetes. Chronic liver disease was present in 106 (8.6%) patients. Among COVID-19 symptoms, dyspnea and fever were present in more than 50%. Chest imaging abnormalities were present in 882 (71.80%). Half of the included patients were admitted to the intensive care unit (ICU). Liver injury, defined as AST and/or ALT ≥2 x ULN, and total bilirubin ≥2 x ULN and/or 1.7 ≥ INR), was present in only 1.3%. A significant number of patients received COVID-19 intended treatment before admission, as demonstrated.

Baseline laboratory on admission. Median AST and ALT were 40 and 36 UI, respectively, and median bilirubin was 0.5 mg/dL. Canalicular enzymes were seldom requested. Inflammatory markers such as CRP and LDH were usually high, as well as d-dimer. During hospitalization, antibiotics and steroids were highly prescribed (TABLE 1). Investigational products were given to 126 (10.3%), including convalescent plasma therapy and baricitinib.

Characteristics of patients with abnormal liver enzyme

Of total 1,229 patients, 1,080 (87.9%) patients had record of AST and/or ALT available on admission, among whom 614 (56.9%) had abnormal liver enzymes (ALE group). TABLE 2 details the obtained results, comparing patients with normal and abnormal liver enzymes.

Patients with ALE were younger, male, and had a more frequent history of previous liver disease. It is noteworthy that inpatients with elevated AST and/or ALT, mild elevation was present in 63.8%, while 29.8% had moderate and 6.36% severe abnormalities. TABLE 3 displays a Poisson regression of factors associated with abnormal liver enzymes. Inflammatory markers were higher in ALE patients, as well as were a list of variables, including COVID-19 severity. However, in multivariable analysis only male gender, previous liver disease and bilirubin were significantly associated as independent risk factors of liver enzymes abnormalities. ALE patients presented a higher length of stay [9 days (0–94) vs 7.5 days (0–64), *P*=0.009].

Characteristics of patients with severe COVID-19

Of the total 1,229, 639 (51.9%) patients presented severe COVID-19. Compared with non- severe disease, they were older, male, and presented more comorbidities (TABLE 4).

A multivariate analysis confirmed that ALE, age above 60 years old, the presence of diabetes and some laboratory abnormalities, such as high CRP and d-dimer levels were independently related to the disease severity.

Mortality

Factors associated with mortality are presented in TABLE 5. After an adjusted multivariate analysis, age above 60, coagulation abnormalities and higher d-dimer levels were significantly associated with it.

DISCUSSION

This study evaluated a large cohort of patients with COVID-19 admitted to a tertiary hospital and demonstrated that even mild AST and ALT abnormalities are predictors of disease severity. Over half of our cohort (58.6%) presented abnormal liver enzymes on admission; this figure is within of wide range (14–81.7%) reported by other studies that observed abnormal liver enzymes on admission or during hospitalization[22-30]. The results' variability is related to different liver enzymes cutoffs used and to the significant difference among studied populations. We considered AST and/or ALT ≥41, as a marker of liver enzymes abnormality, in line with other studies[7,23,25]. Having this cutoff as reference we found that ALE on admission was significantly associated to the COVID-19 severity in a multivariate model. ALE on admission, may be a manifestation of liver and multisystemic COVID-19 involvement could lead clumsy evolution with adverse outcomes, as reported by other[7,31-33]. There are few previous studies in South America suggesting association between ALE and severity of the disease. A Brazilian multicenter study included 406 patients with COVID-19 and reported a prevalence of twice elevated AST and ALT levels (ALEx2) at admission of 14%. Adjusted for age and sex, in-hospital all-cause mortality was higher in this group than inpatients with lower enzymes[34]. In the present study we found 29.8% of patients with

TABLE 2. Clinical characteristics and laboratory on admission among patients with abnormal liver enzymes and normal liver enzymes with severe or no severe COVID-19.

Clinical characteristics	n	All patients			*P*-value[a]	All patients with liver enzymes			*P*-value[a]
		COVID-19, No (%)	No severe COVID-19 (NSC19)	Severe COVID-19 (SC19)		Liver enzymes	Normal liver enzymes (NLE)	Abnormal liver enzymes (ALE)	
		(n=1229)	(n=590)	(n=639)		(n=1080)	(n=466)	(n=614)	
Age, median (minimum - maximum)	1229	60 (18–102)	54 (18–95)	63 (19–102)	<0.001	59 (19–102)	62.5 (19–102)	57 (19–94)	0.001
Age above 60	1229	615 (50)	238 (40.3)	377 (59.0)*	<0.001	538 (49.8)	265 (56.9)*	273 (44.5)	<0.001
Age below 60	1229	614 (50)	352 (59.7)*	262 (41.0)		542 (50.2)	201 (43.1)	341 (55.5)*	
Gender									
Male	1229	633 (51.5)	279 (47.3)	354 (55.4)*	0.005	559 (51.8)	210 (45.1)	349 (56.8)*	<0.001
Female	1229	596 (48.5)	311 (52.7)*	285 (44.6)		521 (48.2)	256 (54.9)*	265 (43.2)	
Comorbidities									
Hypertension	1227	629 (51.2)	257 (43.6)	372 (58.4)*	<0.001	561 (52.0)	259 (55.6)*	302 (49.2)	0.046
Diabetes	1227	388 (31.6)	142 (24.1)	246 (38.6)*	<0.001	339 (31.4)	177 (38.0)*	162 (26.4)	<0.001
Kidney chronic disease	1227	97 (7.9)	40 (6.8)	57 (8.9)	0.193	77 (7.1)	48 (10.3)*	29 (4.7)	0.001
Chronic liver disease	194	106(8.6)	48 (52.7)	58 (56.3)	0.724	91 (8.42)	33 (45.8)	58 (65.9)*	0.017
MAFLD	171	47 (3.8)	26 (31.0)	21 (24.1)	0.408	42 (3.9)	14 (22.6)	28 (36.4)	0.116
Cirrhosis	1227	28 (2.3)	10 (1.7)	18 (2.8)	0.257	21 (1.94)	6 (1.3)	15 (2.4)	0.253
Complications									
Pulmonary embolism	263	77 (6.3)	15 (18.8)	62 (33.9)*	0.02	69 (6.39)	25 (27.8)	44 (29.1)	0.937
Extrapulmonar thromboembolism	263	39 (3.2)	1 (7.7)	38 (46.3)*	0.02	36 (3.33)	9 (42.9)	27 (42.9)	1.00
Severe COVID-19						569 (100)	207 (44.4)	362 (59.0)	<0.001
Clinical evolution									
Discharge	1229	802 (65.3)	532 (90.2)*	270 (42.3)		705 (65.3)	326 (70.0)*	379 (61.7)	
Dead	1229	290 (23.6)	0 (0.00)	290 (45.4)*	0.001*	250 (23.1)	87 (18.7)	163 (26.5)*	0.007
Transfer	1229	137 (11.1)	58 (9.8)	79 (12.4)		125 (11.6)	53 (11.4)	72 (11.7)	
Laboratory, value, median (minimum - maximum)									
Hematology									
WBC (x 109/L)	1196	7.78 (1.47–40.01)	6.75 (1.81–34.51)	9.03 (1.47–40.01)	<0.001	7.81 (1.81–40.01)	7.43 (2.06–34.97)	8.22 (1.81–40.1)	<0.001
Neutrophils (x 10^9/L)	1192	6.05 (0.24–35.21)	4.91 (0.24–29.64)	7.37 (0.53–35.21)	<0.001	6.11 (0.24–35.21)	5.57 (0.45–26.93)	6.52 (0.24–35.1)	<0.001
Lymphocytes (x 10^9/L)	1192	0.90 (0.04–9.44)	1.11 (0.07–9.50)	0.75 (0.04–6.69)	<0.001	0.55 (0.04–9.5)	0.95 (0.13–4.02)	0.87 ()0.04–9.5)	0.096
Lymphopenia (<1000)	687	0.65 (0.04–0.99)	0.71 (0.06–0.99)	0.5 (0.04–0.9)	<0.001	0.63 (0.04–0.99)	0.64 (0.13–0.99)	0.62 (0.04–0.99)	0.548
Platelets (x 10^9/L)	1188	211 (9–722)	204 (20–722)	218 (9–685)	0.179	213 (9–713)	209.5 (22–643)	217 (9–713)	0.254
Biochemical									
AST admission (U/L)	1074	40 (8–1992)	35.5 (8–314)	44 (9–1992)	<0.001	52.5 (22–581)	27 (8–40)	57 (19–1992)	<0.001
ALT admission (U/L)	1082	36 (5–1665)	35 (5–518)	37 (6–1665)	0.095	51.5 (6–518)	22 (5–40)	56 (6–1665)	<0.001
Total bilirubin (mg/dL)	1027	0.5 (0.3–6.1)	0.5 (0.3–6.10)	0.5 (0.3–5.80)	0.017	0.6 (0.3–2.4)	0.4 (0.3–2.8)	0.5 (0.3–6.1)	<0.001
TB > 1.2 (mg/dL) No (%)						59 (5.9)	12 (2.8)	47 (8.1)	0.001
ALP (U/L)	88	95.5 (38–564)	90 (45–564)	96.5 (38–492)	0.729	93 (45–492)	84 (38–492)	117 (45–564)	0.003
GGT (U/L)	46	95 (10–1163)	109 (10–744)	80 (26–1163)	0.991	134 (18–1163)	53 (10–1163)	159 (17–144)	0.015
Albumin (g/dL)	150	3.18 (±0.69)	3.55 (±0.59)	2.88 (±0.64)	<0.001[b]	3.20 (±0.70)	3.4 (±0.63)	3.07 (±0.74)	0.023[b]
AST|ALT ≥41 No (%)	614	614 (100)	252 (49.3)	362 (63.6)	<0.001				
AST≥41 (U/L)	604	57 (19–1992)	53 (23–314)	59 (19–1992)	<0.001				
ALT≥41 (U/L)	613	56 (6–1665)	59 (6–518)	52 (11–1665)	0.001				
Inflammation									
CRP (mg/L)	1086	103.8 (1–487)	65.7 (1–374.1)	140 (1–487)	<0.001	105.8 (1–487)	89.1 (1–487)	120.35 (1–444)	<0.001
LDH (U/L)	956	374.5 (1.80–9 920)	307 (1.98–1018)	464 (1.80–9920)	<0.001	374 (1.80–9920)	296 (1.88–999)	448 (3.17–9 920)	<0.001
CK (U/L)	953	98 (4.7–18 178)	83 (8–10 203)	117 (4.70–18 178)	<0.001	101 (4.70–981)	80 (4.7–1487)	121 (8.45–16 972)	<0.001
Coagulation									
INR	1052	1.09 (1–6.22)	1.06 (1–3)	1.13 (1–6.22)	<0.001	1.09 (1–6.22)	1.08 (1–3.14)	1.10 (1–6.00)	0.032
D-dimer (ug/mL)	1040	1.05 (0.19–20)	0.76 (0.19–20)	1.45 (0.19–20)	<0.001	1.03 (0.19–20)	0.9 (0.19–20.0)	1.15 (0.19–20.0)	<0.001
Hospital stay									
Total stay	1229	8 (0–176)	5 (0–64)	14 (0–176)	<0.001	8 (0–94)	7.5 (0–64)	9 (0–94)	0.009

ALT: alanine aminotransferase; ALP: alkalina phosphatase; AST: aspartate aminotransferase; CK: creatine kinasa; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; GGT: gamma-glutamyl transferase; INR: international normalized ratio; LDH: lactate dehydrogenase; MAFLD: metabolic dysfunction associated fatty liver disease; SOFA: sequential organ failure assessment; WBC: white blood cells. a: chi-square test was used for comparisons of categorical variables, and Mann-Whitney U test was used for comparisons of continuous asymmetric variables; b: Srudent's t-test was used for comparisons of continuous symmetric variables. *adjusted residual.

TABLE 3. Factors associated with abnormal liver enzymes (Poisson Regression).

Patient characteristics and findings	Univariate			Multivariate		
	RR	(95%CI)	*P*-value	RR	(95%CI)	*P*-value
Clinical characteristics and comorbidities						
Male gender	1.23	(1.10–1.37)	<.001	1.49	(1.12–1.99)	0.007
Chronic liver disease	1.51	(1.10–2.06)	0.01	1.47	(1.08–2.01)	0.015
Severe COVID-19	1.29	(1.16–1.44)	<.001			
Laboratory						
Hematology						
White blood cells (x 10^9/L)	1.02	(1.01–1.03)	<.001			
Total bilirrubin (mg/dL)	1.27	(1.17–1.37)	<.001	1.18	(1.09–1.27)	<.001
Inflammatory markers						
CRP (mg/dL)	1.001	(1.001–1.002)	<.001			
LDH (U/L)	1.00	(1.00–1.00)	0.001			
CK (U/L)	1.00	(1.00–1.00)	<.001			
Coagulation						
INR	1.14	(1.07–1.21)	<.001			
D-dimer (ug/mL)	1.02	(1.02–1.01)	<.001			

CK: creatine kinasa; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; INR: international normalized ratio; LDH: lactate dehydrogenase; WBC: white blood cells.

TABLE 4. Factors associated with severe COVID-19 (Poisson Regression).

Patient characteristics and findings	Univariate			Multivariate		
	RR	(95%CI)	*P*-value	RR	(95%CI)	*P*-value
Clinical characteistics						
Age above 60 years	1.44	(1.29–1.61)	<.001	1.22	(1.09–1.37)	0.001
Male gender	1.17	(1.05–1.30)	0.005			
Comorbidities						
Diabetes	1.36	(1.23–1.51)	<.001	1.21	(1.08–1.35)	0.001
Hypertension	1.34	(1.20–1.49)	<.001			
Complications						
Pulmonary tromboembolism	1.24	(1.06–1.44)	0.006			
Laboratory						
Hematology						
White blood cells (x 10^9/L)	1.04	(1.03–1.05)	<.001	1.03	(1.02–1.04)	<0.001
Lymphopenia (<1000 x 10^9/L)	1.69	(1.49–1.92)	<.001	1.51	(1.32–1.72)	<0.001
Biochemical						
AST and/or ALT ≥41 (U/L)	1.33	(1.18–1.50)	<.001	1.19	(1.06–1.34)	0.004
Total bilirrubin (mg/dL)	1.16	(1.05–1.28)	0.003			
Inflammatory markers						
CRP (mg/dL)	1.003	(1.003–1.004)	<.001	1.002	(1.001–1.002)	<0.001
LDH (U/L)	1.00	(1.00–1.00)	<.001			
CK (U/L)	1.00	(1.00–1.00)	<.001			
Coagulation						
INR	1.28	(1.19–1.37)	<.001			
D-dimer (ug/mL)	1.04	(1.04–1.05)	<.001	1.01	(1.006–1.021)	<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CRP: C-reactive protein; INR: international normalized ratio; LDH: lactate dehydrogenase; WBC: white blood cells.

TABLE 5. Factors associated with mortality in patients with COVID-19 (Cox Regression).

Patient characteristics and findings	Univariate			Multivariate		
	HR	(95%CI)	*P*-value	HR	(95%CI)	*P*-value
Clinical characteristics						
Age above 60 years	2.62	(2.00–3.42)	<.001	2.34	(1.73–3.16)	<.001
Male gender	0.92	(0.73–1.16)	0.5			
Comorbidities						
Diabetes	1.21	(0.96–1.53)	0.11			
Hypertension	1.16	(0.92–1.47)	0.22			
Chronic liver disease	1.15	(0.67–1.97)	0.62			
Complications						
Severe COVID-19	34.15	(9.76–119.28)	<.001			
Pulmonary tromboembolism	1.12	(0.73–1.73)	0.59			
Laboratory						
Hematology						
White blood cells (x 10^9/L)	1.04	(1.03–1.06)	<.001			
Lymphopenia (<1000 x 10^9/L)	1.38	(1.05–1.81)	0.02			
Biochemical						
AST (U/L)	1.00	(1.00–1.00)	0.033			
ALT (U/L)	1.00	(1.00–1.00)	0.08			
AST ≥41 (U/L)	1.20	(0.93–1.55)	0.17			
ALT ≥41 (U/L)	0.84	(0.65–1.08)	0.18			
AST and/or ALT ≥41 (U/L)	1.12	(0.86–1.45)	0.40			
AST highest hospitalization (U/L)	1.00	(1.00–1.00)	0.19			
ALT highest hospitalization (U/L)	1.00	(1.00–1.00)	0.56			
Total bilirrubin (mg/dL)	1.18	(0.94–1.49)	0.18			
Inflammatory markers						
CRP (mg/dL)	1.00	(1.00–1.00)	0.002			
LDH (U/L)	1.00	(1.00–1.00)	0.48			
CK (U/L)	1.00	(1.00–1.00)	0.49			
Coagulation						
INR	1.06	(1.04–1.08)	<.001	1.26	(1.05–1.52)	0.013
D-dimer (ug/mL)	1.05	(1.04–1.08)	<.001	1.05	(1.03–1.07)	<.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; INR: international normalized ratio; LDH: lactate dehydrogenase; WBC: white blood cells.

ALEx2 at admission, but they did not correlate to COVID-19 severity or mortality. One smaller Latin American study included 298 patients and demonstrated that ALEx2 on admission was independently associated with 1-week mortality. In addition, patients without ALEx2 at admission who developed 1-week *de novo*-ALEx2 (39.8%) presented a higher mortality during the second week[35]. Cai et al., reported 76.3% of liver enzymes increment during hospitalization in COVID-19 patients, and found association with Lopinavir/Ritonavir[7]. In the present study, only 15.87% of patients presented de novo AST and/or ALT abnormalities during the hospital stay without association to severity and mortality. However, a little sample size in the sub-analysis limits ours results.

Severe COVID-19 (SC-19) patients were older (>60 years old), presented more comorbidities and higher inflammatory markers, such as leukocytes, CRP, LDH and CPK with lower lymphocytes similar to some other reports[36-39]. We found higher levels of inflammatory markers in ALE patients, suggesting SARS-CoV-2 induced inflammatory response could be related to of liver injury as inflammatory reaction could lead to cytokine storm which is a key in the severe disease[39,40]. We also found increased D-dimer as risk factor of SC19, the same described by some other authors[37,41], and could be unchained by inflammatory response. We found association among D-dimer and ALE in univariate, although it lost significance in the multivariate analyze. D-dimer is a he-

mostatic biomarker, higher levels of D-dimer indicate that there is fibrin generation and fibrinolysis, in patients with COVID-19 could be extrahepatic origin[42].

In this study, male gender, CLD and increased total bilirubin were predictors of ALE at admission. Previous studies reported ACE2 receptors are mediated by androgens, being higher in men[39]. CLD was reported in 8.6%, similar to the prevalence reported by Hao et al.[43] but higher than the results of a systematic review (3.6%)[42]. Some reports suggest CLD increases the risk of complications or mortality. However, we did not find any association here, the same reported in some studies[42,44], including a meta-analysis of 8,800 patients[44]. On the other hand, a recent Brazilian study with 1,034 COVID-19 patients showed that CLD is linked to the mortality[45]. Moreover, patients with CLD could present higher expression of ACE2 receptor and could be more susceptible to the virus[10], and Child-Pugh C cirrhotic have an increased risk of complications and mortality[46,47]. We found that ALE on admission was associated with SC-19 despite having less diabetes, hypertension and chronic kidney disease, supporting the prognostic role of liver enzymes. In addition, ALE patients had longer hospital stay, as we demonstrated here in agreement some studies[48]. A multicenter retrospective study with 1765 patients in Hubei province, in China, reported an increased mortality risk in cases of elevated AST (above 34 U/L)[49], although we did not find it, in line with some other studies[43,15]. In the present study, 23.6% of patients died, and patient aged above 60 years had a higher risk of death[40] These findings are consistent with several studies[14,50,51] including a Brazilian one[45]. This finding may be related to the physiological changes of aging. Furthermore, patients with abnormal coagulation with increased INR and elevated D-dimer at admission also have an increased risk of mortality[37]. Coagulation disorders might be related to inflammatory storm as well[52].

This study has some strengths and limitations that should be considered. So far, this is the largest single centered study in Brazil, conducted at a high-volume University tertiary hospital, and it is the first solely reporting results from the South Brazil. On the other hand, it was retrospective, and some data could be incomplete or not recorded, such as medications, alcohol consumption, body mass index, and canalicular enzymes at admission. An additional limitation is that transferred patients, who represented 11.1% of the sample, were considered alive in the final analysis, and this may have impacted the results. Likewise, medications used before admission may have had an influence on liver enzymes.

In conclusion, we demonstrated in a large Brazilian cohort that prevalence of abnormal AST and/or ALT on admission is high (more than 50%) and that mild AST and/or ALT abnormalities are predictors of high-risk severe COVID-19. Thus, AST and ALT should be determined on admission, and in case of abnormalities, a careful observation of clinical curse is advocate.

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Authors' contribution

Joveleviths D and Alvares-da-Silva MR: conceptualized the protocol, obtained REB approval, supported supervision of all stages, production and revision of the manuscript. Picon Y: collected and interpreted data and drafted the initial manuscript. All authors approved the final version as submitted.

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Picon Y, Joveleviths D, Alvares-da-Silva MR. Alterações mínimas em enzimas hepáticas à admissão hospitalar correlacionam-se à gravidade da COVID-19 em uma grande coorte no Brasil. Arq Gastroenterol. 2023;60(1):11-20.

RESUMO – Contexto – COVID-19 é uma doença sistêmica que afeta primariamente o sistema respiratório. O comprometimento hepático é frequente, mas seu impacto no curso clínico da doença ainda é controverso. **Objetivo –** Avaliar na admissão hospitalar a função hepática de pacientes com COVID-19 e correlacioná-la à gravidade e mortalidade da doença. **Métodos –** Estudo retrospectivo de pacientes admitidos a um hospital terciário no Brasil, com infecção confirmada por SARS-CoV-2 entre abril e outubro de 2020. A coorte foi dividida em pacientes com enzimas normais ou alterada, e avaliados dados demográficos, clínicos, laboratoriais e de imagem, bem como a gravidade clínica e a mortalidade. Os pacientes foram seguidos até a alta ou óbito. **Resultados –** 1080 de 1229 pacientes tiveram enzimas hepáticas na admissão. A mediana de idade foi de 60 anos e 51,5% eram homens. As comorbidades mais comuns foram hipertensão (51,2%) e diabetes mellitus (31,6%). Doença hepática crônica ou cirrose estiveram presentes em 8,6% e 2,3%, respectivamente. Enzimas normais ou alterada (aminotransferases >40 IU/L) esteve presente em 56,9% [leve (1–2 vezes o normal): 63,9%; moderada (2–5 vezes): 29,8%; acentuada (>5 vezes): 6,3%]. Homens [RR 1,49; *P*=0,007], bilirubina total elevada [RR 1,18; *P*<0,001] e doença hepática crônica [RR 1,47, *P*=0,015] foram preditores de enzimas normais ou alterada na admissão. Pacientes com enzimas normais ou alterada tiveram maior risco de COVID-19 grave [RR 1,19; *P*=0,004]. Não houve associação entre enzimas normais ou alterada e mortalidade. **Conclusão –** Enzimas normais ou alterada é comum em pacientes hospitalizados com COVID-19. Mesmo alterações mínimas correlacionam-se de forma independente com a gravidade da doença e podem ser úteis como marcador prognóstico.

Palavras-chave – Fígado; COVID-19; gravidade; aminotransferases anormais; SARS-COV-2.

REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. [Internet]. February 01. 2022. Available from: https://covid19.who.int/10gclid=EAIaIQobChMIqqrtlK2C7QIVGxwrCh3LcQm2EAAYASAAEgKaefD_BwE
2. Martines RB, Ritter JM, Matkovic E, Gary J, Bollweg BC, Bullock H, et al. Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. Emerg Infect Dis. 2020;26:2005-15.
3. Thakur V, Ratho RK, Kumar P, Bhatia SK, Bora I, Mohi GK, et al. Multiorgan involvement in covid-19: Beyond pulmonary manifestations. J Clin Med. 2021;10:446.
4. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428-30.
5. Harapan H, Fajar JK, Supriono S, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta-analysis. Rev Med Virol. 2021;1-8.
6. Mendizabal M, Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, et al. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. Ann Hepatol. 2021;21:100298.
7. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol Elsevier BV. 2020;73:566-74.
8. Medetalibeyoglu A, Catma Y, Senkal N, Ormeci A, Cavus B, Kose M, et al. The effect of liver test abnormalities on the prognosis of COVID-19. Ann Hepatol. 2020;19:614-21.
9. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020;72:807-17.
10. Marjot T, Webb GJ, Barritt AS, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol. 2021;18:348-64.
11. Lagana SM, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. Mod Pathol. 2020;33:2147-55.
12. Vishwajeet V, Purohit A, Kumar D, Vijayvergia P, Tripathi S, Kanchan T, et al. Evaluation of liver histopathological findings of COVID-19 by minimally invasive autopsies. J Lab Physicians. 2021;13:97-106.
13. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients – A systematic review and meta-analysis. Ann Hepatol. Fundación Clínica Médica Sur, A.C. 2021;21:100273.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. Elsevier Ltd; 2020;395:1054-62.
15. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92:797-806.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395:497-506.
17. Yip TCF, Lui GCY, Wong VWS, Chow VCY, Ho THY, Li TCM, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut. 2021;70:733-42.
18. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1-98.
19. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020;72:807-17.
20. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [Internet]. 2020. Available from: https://www.covid19treatmentguidelines.nih.gov/.
21. Andrassy KM. Comments on "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease." Kidney Int. 2013;84:622-3.
22. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. Elsevier Ltd; 2020;5:428-30.
23. Harapan H, Karunia J, Supriono F, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta - analysis. 2021;1-8.
24. Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. Hepatology. 2021;73:1509-20.
25. Hao S-R, Zhang S-Y, Lian J-S, Jin X, Ye C-Y, Cai H, et al. Liver Enzyme Elevation in Coronavirus Disease 2019. American Journal of Gastroenterology. 2020:1075-83.
26. Yip TCF, Lui GCY, Wong VWS, Chow VCY, Ho THY, Li TCM, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut. 2021;70:733-42.
27. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.

28. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395:507-13.
29. Hamid S, Alvares Da Silva MR, Burak KW, Chen T, Drenth JPH, Esmat G, et al. WGO Guidance for the Care of Patients with COVID-19 and Liver Disease. J Clin Gastroenterol. 2021;55:1-11.
30. Marín Dueñas I, Vega J, Carrillo-Ng H, Veramendi-Schult I, Zavaleta Alva R, Vásquez L, et al. P-27 Alteration in Liver Function Tests Among Patients Hospitalized for Covid-19: a Multicentric Study in Peru. Ann Hepatol. 2021;24:100391.
31. Piano S, Dalbeni A, Vettore E, Benfaremo D, Mattioli M, Gambino CG, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int. 2020;40:2394-406.
32. Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients With Severe COVID-19: Systematic Review and Meta-analysis. Hepatology. 2021;73:1521-30.
33. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ. 2020;369.
34. Pozzobon FM, Perazzo H, Bozza FA, Rodrigues RS, de Mello Perez R, Chindamo MC. Liver injury predicts overall mortality in severe COVID-19: a prospective multicenter study in Brazil. Hepatol Int. 2021;15:493-501.
35. Balderramo D, Mattos AZ, Mulqui V, Chiesa T, Plácido-Damián Z, Abarca J, et al. Abnormal Liver Tests during Hospitalization Predict Mortality in Patients with COVID-19: A Multicenter Study from South America. Can J Gastroenterol Hepatol. 2021;2021:1622533.
36. Del Valle DM, Kim-Schulze S, Huang H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26:1636-43.
37. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care. 2020;8:1-11.
38. Ibañez C, Perdomo J, Calvo A, Ferrando C, Reverter JC, Tassies D, et al. High D dimers and low global fibrinolysis coexist in COVID19 patients: what is going on in there? J Thromb Thrombolysis. 2021;51:308-12.
39. Harapan H, Fajar JK, Supriono S, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta-analysis. Rev Med Virol. 2021;1-8.
40. Xu G, Ye M, Zhao J, Liu F, Ma W. New view on older adults with COVID-19: comments on "SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes." Geroscience. 2020;42:1225-7.
41. Hariyanto TI, Japar KV, Kwenandar F, Damay V, Siregar JI, Lugito NPH, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. American Journal of Emergency Medicine. Elsevier Inc. 2021;41:110-9.
42. Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther. 2020;52:584-99.
43. Hao S-R, Zhang S-Y, Lian J-S, Jin X, Ye C-Y, Cai H, et al. Liver Enzyme Elevation in Coronavirus Disease 2019. Am J Gastroenterol. 2020:1075-83.
44. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. Ann Hepatol. 2021;21:100273.
45. Konstantyner TCRO, Martins CB, Luppi CG, Yashiro SM, Sanches NAP, Cohrs FM, et al. Baseline factors associated with death in a COVID-19 hospital cohort, Sao Paulo, 2020. Rev Saude Publica. 2021;55:76.
46. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. Clin Gastroenterol Hepatol. 2021;19:1469-79.e19.
47. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol. 2021;74:567-77.
48. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020;18:1561-6.
49. Liu X, Zhu L, Lu T, Liu X, Jiao D, Tang X, et al. Epidemiologic Characteristics of and Prognostic Factors for COVID-19 Among Hospitalized Patients: Updated Implications From Hubei Province, China. Front Public Health. 2021;9:1-10.
50. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80:639-45.
51. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA. 2020;180:934-43.
52. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020. p. e46-7.