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ORIGINAL ARTICLE

Liver injury predicts overall mortality in severe COVID-19: a prospective multicenter study in Brazil

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Abstract

Background/purpose The relationship between liver injury and mortality remains unclear in patients with COVID-19. We aimed to evaluate the prognostic value of aminotransferases levels at hospital admission to predict mortality in patients with COVID-19.

Methods and results This prospective study included 406 patients [57% male, aged 56 years] with COVID-19 hospitalized in 26 centers in Brazil. Overall, 36.7% (95% CI 32.1–41.5) presented at admission with severe disease requiring respiratory support. The prevalence of elevated ALT and AST levels at admission [$>2\times$ULN] was 14.0% (95% CI 11.0–17.8) and 12.9% (95% CI 10.0–16.6), respectively. Sixty-two patients [15.3% (95% CI 12.1–19.1)] died during hospitalization and the overall mortality rate was 13.4 (10.5–17.2) deaths per 1000 persons-years. The 15-day-overall survival (95% CI) was significantly lower in patients with ALT levels $\geq 2\times$ULN compared to those with ALT $<2\times$ULN [67.1% (48.4–80.2) vs 83.4% (76.1–88.6), $p=0.001$] and in those with AST levels $\geq 2\times$ULN compared to those with AST $<2\times$ULN [61.5% (44.7–74.6) vs 84.2% (76.5–89.5), $p<0.001$]. The presence of elevated aminotransferases levels at hospital admission significantly increased the risk of in-hospital all-cause mortality adjusted for age-and-sex. Those findings were present in the subgroup of critically ill patients already admitted in need of respiratory support ($n=149$), but not in patients without that requirement at admission ($n=257$).

Conclusions Elevated aminotransferases at hospital admission predicted in-hospital all-cause mortality in patients with COVID-19, especially in those with severe disease. Measurement of transaminases levels at hospital admission should be integrated to the care of patients with COVID-19 as an auxiliary strategy to identify patients at higher death risk.

Keywords SARS-CoV-2 infection · Aminotransferases · Death · Hepatic · Coronavirus · Hospitalization · Hospital admission · Prognostic value · Severe disease · Respiratory support

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
IQR	Interquartile range
RR	Relative risk
RT-PCR	Real-time reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ULN	Upper limit of normal

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Background and purpose

Globally, more than 25 million people have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The clinical presentation of Coronavirus disease 2019 (COVID-19) might range from mild symptoms to critical illness requiring respiratory support including invasive mechanical ventilation [2]. Elevation of aminotransferases has been observed in 14–53% patients with COVID-19 [3]. However, the clinical relevance of liver tests abnormalities has been controversial [4, 5]. Although most studies have showed that liver injury is more prevalent in severe cases of COVID-19 cases [6], its relationship with mortality has not been clearly demonstrated [7, 8]. In addition, the prognostic value of aminotransferases in predicting severe clinical outcomes in patients with COVID-19 remains uncertain [9]. Therefore, the aim of this study was to assess the prognostic value of aminotransferases levels at hospital admission to predict all-cause mortality in hospitalized patients with COVID-19.

Materials and methods

Study design and population

This prospective multicenter study included patients with COVID-19 hospitalized in 26 tertiary hospitals from Brazil between March 10th, 2020 and June 6th, 2020. Adult patients hospitalized with confirmed SARS-CoV-2 infection that underwent invasive mechanical ventilation at any point of the hospitalization and had aminotransferases tests available on the first day of hospitalization were included. SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal and/or oropharyngeal swabs. We excluded patients with conditions that led to an increase in aminotransferases unrelated to liver injury, such as rhabdomyolysis, and those without measurement of aminotransferase levels in the first 24 h of hospitalization. Patients on spontaneous breathing or low flow oxygen therapy at admission were classified as mild presentation and those requiring significant respiratory support at admission (high flow oxygen therapy, noninvasive or invasive mechanical ventilation) as severe presentation of COVID-19.

Data collection and follow-up

Demographic, clinical, and biological data were collected by trained investigators using the standardized form International Severe Acute Respiratory and Emerging Infection Consortium/World Health Organization Clinical Characterization Protocol (ISARIC/WHO CCP) [10]. Data were entered in electronic case-report forms at Research Electronic Data Capture (REDCap, https://projectredcap.org/). Clinical records included comorbidities, disease symptoms, duration of symptoms and vital signs at hospital admission. Laboratory tests were performed at hospital admission and included red and white blood-cells count, platelets count, glucose, creatinine, blood urea nitrogen (BUN) test, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and INR levels, sodium, potassium and C-reactive protein (CRP). Significant aminotransferases elevation at hospital admission was defined as ALT and/or AST levels higher or equal than two times the upper limit of normal (ULN). The course of transaminases during hospitalization was assessed. Presence of pulmonary disease was defined as chronic obstructive pulmonary disease or asthma; and heart disease as congestive cardiac failure or coronary arterial disease. All patients included in the study progressed to invasive mechanical ventilation at any point of the hospitalization and they were prospectively followed until hospital discharge or in-hospital death.

Statistical analysis

Continuous variables were reported as median (interquartile range, IQR) and/or discrete variables were reported as absolute (n) and relative frequency (%). Comparisons between independent groups were assessed by Mann–Whitney and Chi-square test for quantitative and qualitative comparisons, respectively. The duration of COVID-19 was calculated from onset of symptoms to hospital admission. Additionally, duration of follow-up was calculated from the hospital admission to the date of discharge or death until June 30th, 2020. The clinical and laboratory characteristics at the first day of hospitalization (hospital admission) were considered for baseline. The primary outcome analyzed was the in-hospital all-cause mortality. The mortality rates (deaths per 1000 person-years) were reported. Kaplan–Meier curves were plotted and the log-rank test was calculated. We used the time to event Cox proportional model adjusted for age and sex to check the hazard-ratio (HR) risk of in-hospital all-cause mortality related to elevated ALT and/or AST levels at hospital admission. A sensitivity analysis stratified by severity of COVID-19 at admission was performed according to the need of respiratory support. The analysis was performed using STATA package, version 15, 2017 (StataCorp LP, College Station, TX, USA). Significance level was determined when $p \leq 0.05$ assuming two-tailed tests.

Results

During the recruitment period, 936 patients hospitalized with symptoms of COVID-19 were eligible. A total of 126 with negative SARS-CoV-2 RT-PCR in naso or oropharyngeal swabs and 26 with missing COVID-19 test were excluded. From 788 hospitalized patients with confirmed COVID-19, a total of 382 patients were excluded, mostly due to missing ALT or AST levels at hospital admission. Therefore, 406 patients with confirmed diagnosis of COVID-19 were included in this study (Fig. 1). The median age was 56 years (IQR, 45–65) and 57% were male; 68% had hypertension and 29% had type-2 diabetes. Additionally, the prevalence of pulmonary disease and malignant neoplasm was 7% and 3%, respectively. The top leader symptoms were cough (74%), fever (73%) and difficulty breathing (58%) and the median duration symptoms was 7 days (IQR, 5–10) before admission. Demographic and clinical characteristics at hospital admission are described in Table 1. The prevalence of elevated ALT and AST levels [$\geq 2 \times$ ULN] were 14.0% [95% CI 11.0–17.8] and 12.9% [95% CI 10.0–16.6], respectively at admission. A total of 338 patients [83% (95% CI 79–87)] and 332 patients [82% (95% CI 78–85)] had at least a second ALT and AST measure during follow-up, respectively. The maximal aminotransferases levels were measured from the second to the fifth day of hospitalization in 51% ($n = 173$ for ALT and $n = 170$ for AST); from the sixth to the tenth day in 29% ($n = 97$ for ALT and $n = 94$ for AST) and after the tenth day of hospitalization in 20% of cases ($n = 68$ for both). During the follow up, 7% ($n = 25$) of patients had ALT levels $\geq 5 \times$ ULN.

Overall in-hospital all-cause mortality

A total of 62 patients [15.3% (95% CI 12.1–19.1)] died during a median follow-up after hospitalization of 8 days (range, 1–61 days). The overall in-hospital all-cause mortality rate was 13.4 [95% CI 10.5–17.2] deaths per 1000 persons-years. These mortality rates [deaths per 1000 persons-years (95% CI)] were significantly higher in patients with elevated liver enzymes at hospital admission [$\geq 2 \times$ ULN] compared to those with liver enzymes $< 2 \times$ ULN. Patients with elevated

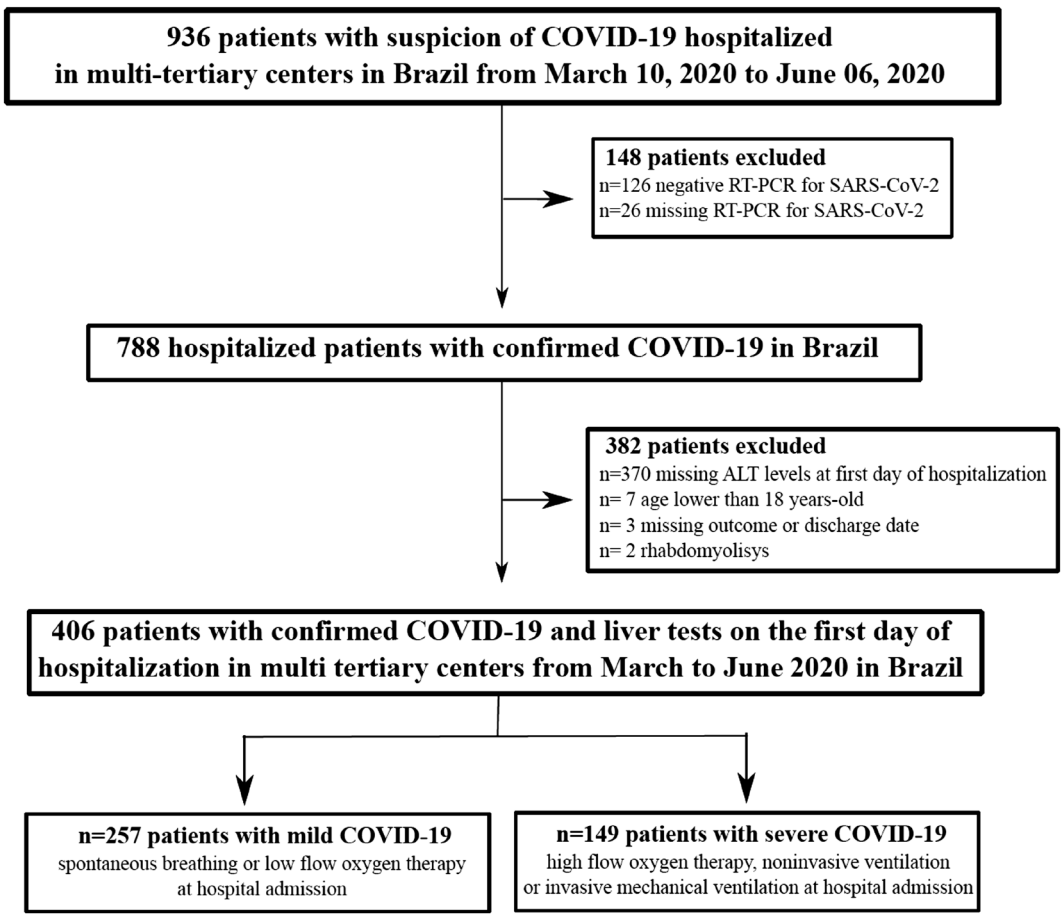

Fig. 1 Study flowchart for inclusion of patients

Table 1 Baseline characteristics of patients according to severity of COVID-19

Clinical and demographical characteristics	All ($n=406$)	Mild presentation ($n=257$)	Severe presentation ($n=149$)	p value
Male sex[a]	231 (57)	143 (56)	88 (59)	0.530
Age, years[b]	56 (45–65)	53 (42–63)	60 (48–68)	< 0.001
Pulmonary disease[a]	28 (7)	21 (8)	7 (5)	0.270
Type-2 diabetes[a]	117 (29)	63 (25)	54 (36)	0.002
Hypertension[a]	277 (68)	174 (68)	103 (69)	0.770
Heart disease[a]	27 (7)	16 (6)	11 (7)	0.650
Malignant neoplasm[a]	13 (3)	7 (3)	6 (4)	0.370
Symptoms				
Fever[a]	296 (73)	182 (71)	114 (77)	0.042
Cough[a]	302 (74)	189 (74)	113 (76)	0.071
Sore throat[a]	54 (13)	31 (12)	23 (15)	0.160
Nasal congestion[a]	55 (14)	40 (16)	15 (10)	0.210
Shortness of breath or difficulty breathing[a]	234 (58)	120 (47)	114 (77)	< 0.001
Digestive symptoms[a]	90 (22)	70 (27)	20 (13)	0.006
Time from onset of symptoms to hospital admission[b]	7 (5–10)	7 (4–8)	8 (5–12)	< 0.001
Vital signs at hospital admission				
Body temperature, Celsius[b]	36.6 (36.1–37.2)	36.6 (36.3–37.3)	36.6 (35.9–37.0)	0.019
Pulse, bpm[b]	89 (79–102)	90 (80–101)	89 (78–106)	0.930
Respiratory rate, rpm[b]	19 (18–22)	19 (18–20)	20 (18–24)	< 0.001
Systolic blood pressure, mmHg[b]	133 (120–147)	135 (120–147)	130 (113–148)	0.067
Diastolic blood pressure, mmHg[b]	79 (70–89)	80 (71–90)	75 (65–86)	< 0.001
Oxygen saturation (SpO2), %[b]	96 (94–98)	96 (95–98)	96 (92–98)	0.002
Biochemistry				
Hemoglobin, mg/dL[b]	13.5 (12.1–14.5)	14.0 (13.0–14.9)	12.3 (11.0–13.6)	< 0.001
White blood cells, $\times 10^9$/L[b]	6.8 (4.8, 12.5)	5.9 (4.5–7.9)	11.6 (6.7–18.6)	< 0.001
Lymphocytes, $\times 10^9$/L[b]	0.97 (0.36–1.44)	0.94 (0.02–1.41)	1.02 (0.55–1.58)	0.050
Platelet count, $\times 10^9$/mm^3[b]	185 (153–238)	188 (158–236)	177 (139–240)	0.220
Glucose, mg/dL[b]	122 (102–158)	116 (98–145)	129 (109–201)	0.003
Creatinine, mg/dL[b]	1.0 (0.8–1.2)	0.90 (0.70–1.10)	1.20 (0.90–2.20)	< 0.001
Blood urea nitrogen (BUN) test, mg/dL[b]	30 (24–45)	28 (21–36)	50 (30–71)	< 0.001
ALT, UI/L[b]	38 (25–62)	35 (24–56)	48 (29–71)	< 0.001
AST, UI/L[b]	37 (27–57)	34 (25–46)	49 (31–76)	< 0.001
Sodium, mEq/L[b]	138 (136–140)	138 (136–140)	138 (136–142)	0.006
Potassium, mEq/L[b]	4.1 (3.8–4.5)	4.0 (3.7–4.3)	4.3 (3.8–4.9)	< 0.001
C-reactive protein (CRP)[b]	8.7 (2.7–54.5)	5.6 (2.0–17)	50.1 (6.5–239.3)	< 0.001

Patients on spontaneous breathing or low flow oxygen therapy at admission were classified as mild admission presentation and those requiring significant respiratory support at admission [high flow oxygen therapy ($n=21$), noninvasive ventilation ($n=40$) or invasive mechanical ventilation ($n=88$)] as severe admission presentation of COVID-19. Pulmonary disease was defined as chronic obstructive pulmonary disease or asthma; heart disease was defined as congestive cardiac failure or coronary arterial disease. Missing data (n): pulmonary disease (18), type 2 diabetes (17), malignant disease (19), fever (14), cough (12), sore throat (28), nasal congestion (25), shortness of breath (5), digestive symptoms (24), body temperature (44), pulse (8), respiratory rate (36), systolic and diastolic blood pressure (9), SpO2 (14), hemoglobin (12), white blood cells (12), lymphocytes (27), platelet count (13) glucose (191), creatinine (12) BUN (20), AST (11), sodium (29), potassium (32) CRP (31)

ALT alanine aminotransferase, AST aspartate aminotransferase

[a]Data expressed as n (%). Comparison between groups were assessed by Chi-square

[b]Data expressed as median (IQR). Comparison between groups were assessed by Mann–Whitney test

ALT levels presented mortality rates of 27.7 (17.2–44.6) in comparison to 11.3 deaths per 1000 persons-years (8.4–15.1) in patients with ALT levels $< 2 \times$ ULN at admission ($p=0.001$). Similarly, higher rates of mortality were found in patients with AST levels at admission $\geq 2 \times$ ULN [30.7 (19.8–47.6) vs 10.6 (7.8–14.4), $p<0.001$] than in patients

with AST levels < 2 × ULN. Additionally, the 15-days overall survival (95% CI) was significantly lower in patients with ALT levels ≥ 2 × ULN compared to those with ALT < 2 × ULN [67.1% (48.4–80.2) vs 83.4% (76.1–88.6), $p = 0.001$] and in those with AST levels ≥ 2 × ULN compared to those with AST < 2 × ULN [61.5% (44.7–74.6) vs 84.2% (76.5–89.5), $p < 0.001$] (Fig. 2). In the time-dependent Cox analysis [HR (95% CI)], the presence of elevated liver enzymes levels (≥ 2 × ULN) at hospital admission significantly increased the risk of in-hospital all-cause mortality adjusted for age-and-sex [ALT ≥ 2 × ULN vs < 2 × ULN, HR = 2.92 (1.65–5.16); AST ≥ 2 × ULN vs < 2 × ULN, HR = 2.79 (1.63–4.79)] ($p < 0.001$ for all).

On the other hand, total bilirubin levels [$n = 236$ and 34 deaths; per mg/dL; HR = 0.98 (95% CI 0.93–1.04), $p = 0.575$] were not associated with in-hospital all-cause mortality in sensitivity analyses. Higher INR levels at admission, however, significantly increased the risk of overall death during hospitalization [$n = 256$ and 57 deaths; per unit; unadjusted HR = 1.27 (95% CI 1.01–1.61), $p = 0.039$; adjusted for age and sex HR = 1.40 (95% CI 1.07–1.82), $p = 0.013$]. In this sensitivity analyses, higher leucocyte count, low hemoglobin levels and low platelet count at admission were associated with higher risk of in-hospital mortality (Supplementary Table 1). In addition, elevated ALT levels at admission remained independently associated with in-hospital all-cause mortality [HR = 2.32 (95% 1.06–5.06), $p = 0.035$] in a Cox model adjusted for clinical characteristics and laboratory parameters.

Regarding serial aminotransferases measures during hospitalization, progression of aminotransferases to levels higher than 2 × ULN during follow-up in patients with ALT or AST < 2 × ULN at admission was not associated with in-hospital mortality in models adjusted for age and sex [for ALT levels: HR = 1.76 (0.88–3.52), $p = 0.108$; for AST levels: HR = 1.51 (0.75–3.06), $p = 0.250$] (Supplementary Table 2).

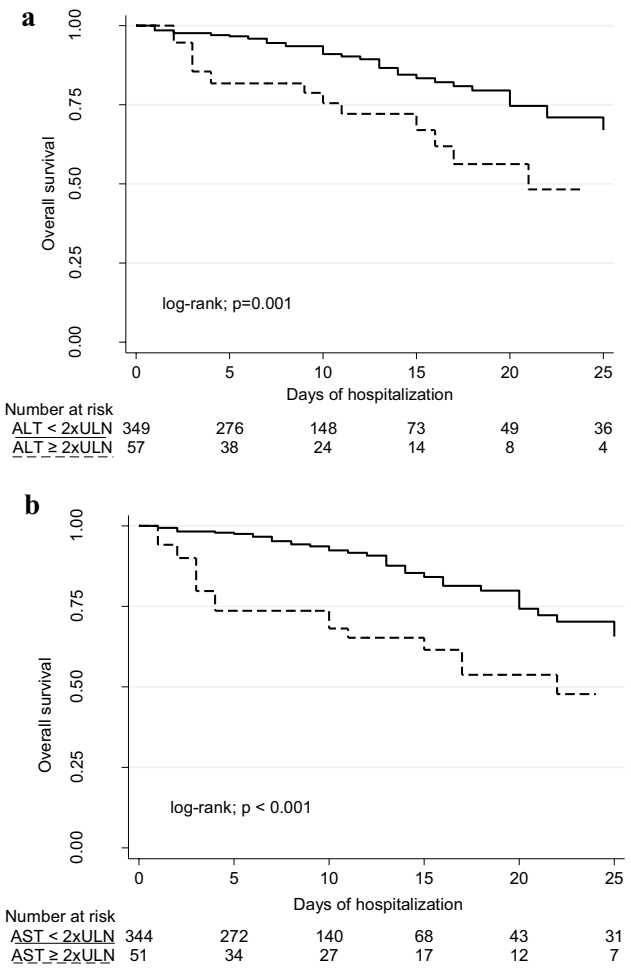

Fig. 2 Kaplan–Meier curves of overall survival of hospitalized patients with confirmed Coronavirus disease 2019 (COVID-19) according to: **a** alanine aminotransferase (ALT) levels [in times of upper limit of normal (ULN)] at first day of hospitalization and **b** aspartate aminotransferase (AST) levels [in times of upper limit of normal (ULN)] at first day of hospitalization [all log-rank test]

In-hospital all-cause mortality stratified by severity of COVID-19 at admission

Severity of disease at admission was classified according to the need of respiratory support. A total of 257 patients [63.3% (95% CI 58.4–67.9)] was admitted on spontaneous breathing or low flow oxygen therapy at admission (mild presentation) and 149 patients [36.7% (95% CI 32.1–41.5)] presented respiratory distress requiring respiratory support such as high flow oxygen therapy, noninvasive or invasive mechanical ventilation at admission (severe presentation). (Table 1). The relative risk (RR) of death was significantly higher in severe respiratory impairment compared to mild presentation at admission [RR = 16.6 (95% CI 5.2–53.2), $p < 0.001$].

Considering the group of patients requiring respiratory support at admission ($n = 149$), the mortality rate [deaths per 1000 persons-years (95%CI)] was significantly higher in patients with ALT levels ≥ 2 × ULN [43.2 (26.5–70.6)] compared to those with ALT < 2 × ULN [20.2 (15.0–27.3)] ($p = 0.008$) and in those with AST levels ≥ 2 × ULN [42.6 (27.2–66.8)] compared to those with AST < 2 × ULN [19.8 (14.4–27.2)] ($p = 0.005$). In this group, the 15-days overall survival (95% CI) was significantly lower in patients with ALT levels ≥ 2 × ULN compared to those with ALT < 2 × ULN [52.1% (31.5–69.1) vs 70.0% (59.6–78.2), $p = 0.016$] and in patients with AST levels ≥ 2 × ULN compared to those with AST < 2 × ULN [49.7% (31.2–65.7) vs 71.2% (60.3–79.7), $p = 0.009$] (Fig. 3). Additionally, the presence of elevated ALT levels at hospital admission significantly increased the risk of in-hospital

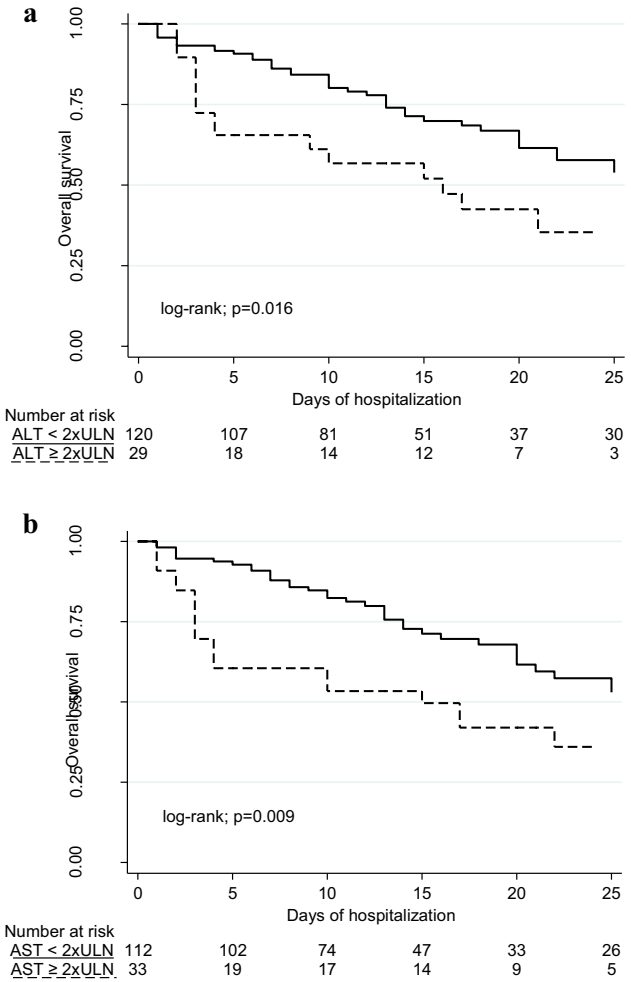

Fig. 3 Kaplan–Meier curves of overall survival of hospitalized patients with confirmed severe Coronavirus disease 2019 (severe COVID-19) according to: **a** alanine aminotransferase (ALT) levels [in times of upper limit of normal (ULN)] at first day of hospitalization ($n=149$) and **b** aspartate aminotransferase (AST) levels [in times of upper limit of normal (ULN)] at first day of hospitalization ($n=145$) [all log-rank test]

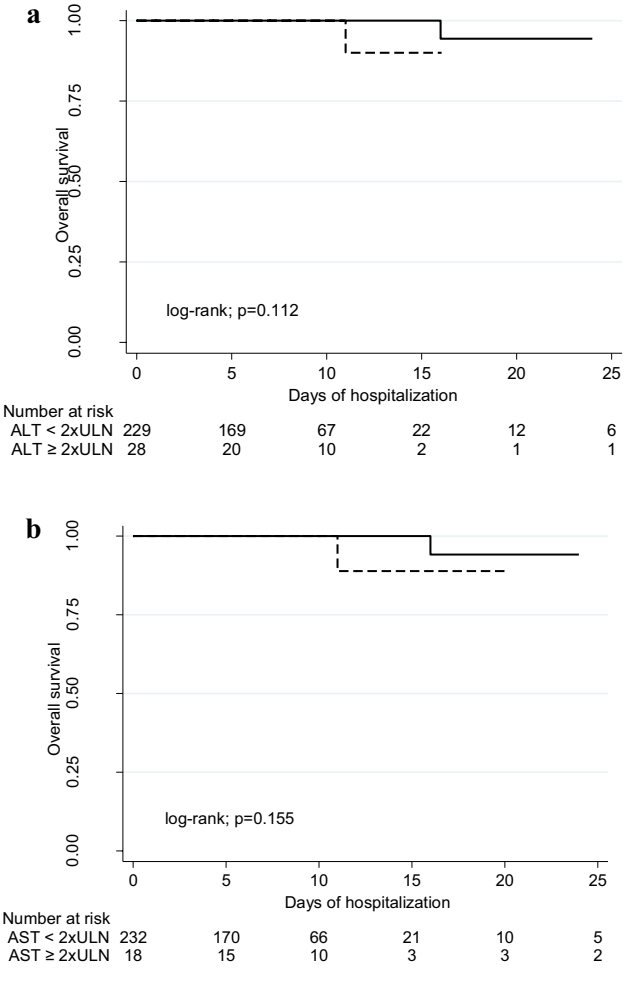

Fig. 4 Kaplan–Meier curves of overall survival of hospitalized patients with confirmed mild Coronavirus disease 2019 (mild COVID-19) according to: **a** alanine aminotransferase (ALT) levels [in times of upper limit of normal (ULN)] at first day of hospitalization ($n=257$) and **b** aspartate aminotransferase (AST) levels [in times of upper limit of normal (ULN)] at first day of hospitalization ($n=250$) [all log-rank test]

all-cause mortality adjusted for age-and-sex [$\geq 2\times$ULN) vs $<2\times$ULN, HR = 2.67 (95% CI 1.47–4.87); $p=0.001$]. Likewise, the presence of elevated AST levels ($\geq 2\times$ULN) significantly increased the risk of in-hospital all-cause mortality adjusted for age-and-sex [HR = 2.18 (95% CI 1.25–3.80); $p=0.006$] in patients with severe presentation at admission.

On the other hand, considering patients with mild admission presentation ($n=257$), a low overall mortality rate was observed [1.4 (95% CI 0.5–4.4) deaths per 1000 persons-years]. There was no significant difference in those rates [deaths per 1000 persons-years (95% CI)] according to aminotransferases levels [$\geq 2\times$ULN vs $<2\times$ULN] at admission. According to ALT levels, mortality rates were 4.1 (0.6–29.2) vs 1.1 (0.3–4.3), $p=0.235$ respectively, and considering AST levels, 4.9 (0.7–34.6) vs 1.1 (0.3–4.3), $p=0.174$. Additionally, there was no difference on in-hospital survival according to aminotransferases levels [$\geq 2\times$ULN vs $<2\times$ULN] in patients admitted on spontaneous breathing or low flow oxygen therapy [according to ALT levels = 90% (47.3–98.5) vs 100% (–), $p=0.112$; according to AST levels = 88.9% (43.3–98.4) vs 100% (–), $p=0.155$] (Fig. 4).

Discussion

The current study highlighted that elevated aminotransferases levels at admission predicted in-hospital all-cause mortality in patients with severe COVID-19. Our findings

have implications for optimizing management of hospitalized patients with COVID-19 since measurement of ALT and AST levels could be useful simple parameters to identify patients at high risk of mortality.

Several studies suggested that SARS-CoV-2 infection might cause acute liver injury in mild and critically ill patients with COVID-19 [11–14]. In general, patients with COVID-19 have mild aminotransferases elevation (1–2 × ULN), although more severe liver injury (2–5 × or > 5 × ULN) might be observed in few patients, especially in those with more severe disease [15]. The prevalence of significant elevated aminotransferases (≥ 2 × ULN) at hospital admission reported in the present study was similar to those previously described [16, 17].

Despite the pathways for liver injury in COVID-19 remains unclear, this might be explained by direct viral infection, high expression of liver angiotensin-converting enzyme-2 (ACE-2) receptor, muscular injury, presence of steatosis, microthrombosis, and the use of hepatotoxic drugs [18]. Elevation of aminotransferases, especially at hospital admission, seems to be the liver expression of severe SARS-CoV-2 infection. In the present study, patients with elevated ALT and/or AST levels have a significantly higher proportion of signs of COVID-19 severity at baseline (Supplementary Tables 3 and 4). Overall, our findings reinforced the relationship between elevated aminotransferases and severity of COVID-19 from previous studies that evaluated severe and non-severe hospitalized patients [2, 6, 12, 14, 16]. However, few studies have described the correlation between liver injury and mortality, especially in low-to-middle income countries. A recent longitudinal large sample study described the dynamic patterns of aminotransferases levels during hospitalization in patients with COVID-19 and reported the relationship between peak values of liver enzymes and mortality adjusted for age, sex and comorbidities [12]. Similarly, Hundt et al. identified an association between mortality and peak AST but not ALT levels [15]. However, these authors did not observe any association between admission aminotransferases and mortality.

A low incidence of severe flare of aminotransferases (≥ 5 × ULN) during follow-up was observed in our sample. The peak of ALT or AST levels were not associated with in-hospital mortality in patients with maximal aminotransferases measurement after the fifth day of hospitalization and in those who progressed from aminotransferases levels < 2 × ULN to ≥ 2 × ULN during hospitalization (Supplementary Table 2). However, the low sample size and relatively small number of outcomes in those sub-analysis limited the interpretation of these findings. Similarly, Zhou et al. described higher proportion of deaths in patients with abnormal ALT levels at hospital admission compared to those with ALT < 40 UI/L [48% vs 24%; $p = 0.002$]. This study included 191 hospitalized patients, mostly with severe/critical COVID-19, very similar to our group. However, this was a retrospective study and the authors did not perform a time-dependent analysis [19].

Blood sample parameters, such as CRP, D-dimer, interleukin-6 and procalcitonin levels or lymphocyte count have been used to predict severe outcomes in hospitalized patients with COVID-19 [15, 16]. However, these tests are costly and might not be available in limited-resource settings. Our study confirmed that simple and worldwide available parameters, such as aminotransferases, could be useful to predict all-cause mortality in severe patients with COVID-19, especially in low-to-middle income countries.

We acknowledge that elevation of aminotransferases did not predict in-hospital all-cause mortality in the sub-group of patients with mild respiratory presentation at admission. This finding might be explained by the delay between measurement of aminotransferases at admission and necessity of significant respiratory support during hospitalization in this sub-sample of patients. In the present study, all patients progressed to invasive mechanical ventilation during the hospitalization. However, we only evaluated the prognostic value of aminotransferases levels at hospital admission (day 1) to predict all-cause mortality. Thus, the prognostic value of aminotransferases levels measured closer to progression to significant respiratory support in this sub-sample of mild admission presentation cannot be ruled out.

In our study, higher INR levels at admission correlated significantly with increased risk of overall death during hospitalization, as already reported in the literature [20, 21], but this finding was evaluated in a smaller number of patients and may be influenced by coagulation disorders, so common in patients with COVID-19.

The main limitations of the study remain the lack of prior history of chronic liver disease or use of hepatotoxic medications and the relatively high number of patients excluded due to missing aminotransferases levels at hospital admission. Viral hepatitis serologies, history of alcohol intake or co-medications use prior to hospital admission were not available. However, the prevalence rates of chronic hepatitis B and C are low in Brazil [22, 23] and only four patients (1%) included in the present study reported any liver disease at admission. In addition, we considered aminotransferases levels collected at the first day of hospitalization to minimize the impact of long term COVID-19 or any hepatic drug induced toxicity during hospital stay. Another limitation is the absence of body mass index (BMI) information mainly due to poor clinical condition of most patients at admission [304 patients (75%) were admitted on intensive care unit and 29% of them ($n = 88$) were under mechanical ventilation] leading it difficult for measuring weight and height. To minimize the influence of muscle injury, another cause of

aminotransferases elevation, and to avoid misclassification of liver injury in these patients, we excluded persons with rhabdomyolysis ($n = 2$).

The main strengths of the present study rely on the longitudinal study design and the relatively high sample size recruited in multi-tertiary centers in Brazil. To the best of our knowledge, this is the first study that confirmed the relationship between abnormal liver tests and severe outcomes in Latin America, the current epicenter of COVID-19 pandemic.

In conclusion, elevated aminotransferases levels at hospital admission could predict in-hospital all-cause mortality in patients with COVID-19, especially in those with severe disease at hospital admission. The use of these simple and worldwide available parameters can help identify patients with severe COVID-19 at high risk of worse prognosis during hospitalization. The measurement of aminotransferases levels at hospital admission should be integrated into the care of patients with COVID-19.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12072-021-10141-6.

Author contributions FMP: analysis and interpretation of data; drafting and critical revision of the manuscript. HP: study concept and design, statistical analysis; analysis and interpretation of data; drafting and critical revision of the manuscript. FAB: study supervision; data collection; analysis and interpretation of data; critical revision of the manuscript. RSR: data collection; analysis and interpretation of data; critical revision of the manuscript. RdMP: study concept and design; study supervision; analysis and interpretation of data; critical revision of the manuscript. MCC: study concept and design; study supervision; analysis and interpretation of data; critical revision of the manuscript.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Compliance with ethical standards

Conflict of interest The authors report no disclosures on this topic.

Ethical approval The study was approved by the Brazilian National Ethical Committee (CONEP) and Local Ethics Committees (IDOR Institute IRB—reference number 29496920.8.0000.5262).

Informed consent Written informed consent was waived due to its observational design and de-identified data collection to preserve the privacy of research participants.

Consent to publish The authors authorized the publication.

References

1. Center JHCR. https://coronavirus.jhu.edu/map.html. Accessed 30 Aug 2020.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
3. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428–30.
4. 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(10):2394–406.
5. Labenz C, Toenges G, Worns MA, Sprinzl MF, Galle PR, Schattenberg JM. Liver injury in patients with severe acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2020.
6. Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: a meta-analysis. Liver Int. 2020;40(6):1316–20.
7. Bertolini A, van de Peppel IP, Bodewes F, Moshage H, Fantin A, Farinati F, et al. Abnormal liver function tests in patients with COVID-19: relevance and potential pathogenesis. Hepatology. 2020;72(5):1864–72.
8. 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(5):475–81.
9. Kunutsor SK, Laukkanen JA. Markers of liver injury and clinical outcomes in COVID-19 patients: a systematic review and meta-analysis. J Infect. 2020;82(1):159–98.
10. Group Icc. Global outbreak research: harmony not hegemony. Lancet Infect Dis. 2020;20(7):770–2.
11. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998–1004.
12. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology. 2020;72(2):389–98.
13. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. Liver Int. 2020;40(6):1321–6.
14. 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. Lancet. 2020;395(10223):497–506.
15. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1827 patients in a major U.S. Hospital Network. Hepatology. 2020. https://doi.org/10.1002/hep.31487
16. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: abnormal liver function tests. J Hepatol. 2020;73(3):566–74.
17. 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(4):584–99.
18. Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and laboratory predictors of in-hospital mortality in patients with coronavirus disease-2019: a cohort study in Wuhan, China. Clin Infect Dis. 2020;71(16):2079–88.
19. 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. Lancet. 2020;395(10229):1054–62.

20. Miesbach W, Makris M. COVID-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149.
21. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.
22. da Motta LR, Adami AG, Sperhacke RD, Kato SK, Paganella MP, Pereira GFM, et al. Hepatitis B and C prevalence and risk factors among young men presenting to the Brazilian Army: a STROBE-compliant national survey-based cross-sectional observational study. Medicine. 2019;98(32):e16401.
23. Carvalho-Louro DM, Soares EB, Trevizoli JE, Marra TMG, da Cunha ALR, Rodrigues MP, et al. Hepatitis C screening, diagnosis, and cascade of care among people aged > 40 years in Brasilia, Brazil. BMC Infect Dis. 2020;20(1):114.