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The De Ritis ratio as prognostic biomarker of in-hospital mortality in COVID-19 patients

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Abstract

Increased concentrations of serum aspartate transaminase (AST) and alanine transaminase (ALT) are common in COVID-19 patients. However, their capacity to predict mortality, particularly the AST/ALT ratio, commonly referred to as the De Ritis ratio, is unknown. We investigated the association between the De Ritis ratio on admission and in-hospital mortality in 105 consecutive patients with coronavirus disease of 2019 (COVID-19) admitted to three COVID-19 referral centres in Sardinia, Italy. The De Ritis ratio was significantly lower in survivors than nonsurvivors (median: 1.25; IQR: 0.91-1.64 vs 1.67; IQR: 1.38-1.97, $P = .002$) whilst there were no significant between-group differences in ALT and AST concentrations. In ROC curve analysis, the AUC value of the De Ritis ratio was 0.701 (95% CI 0.603-0.787, $P = .0006$) with sensitivity and specificity of 74% and 70%, respectively. Kaplan-Meier survival curves showed a significant association between the De Ritis ratio and mortality (logrank test $P = .014$). By contrast, no associations were observed between the ALT and AST concentrations and mortality (logrank test $P = .83$ and $P = .62$, respectively). In multivariate Cox regression analysis, the HR in patients with De Ritis ratios ≥1.63 (upper tertile of this parameter) remained significant after adjusting for age, gender, smoking status, cardiovascular disease, intensity of care, diabetes, respiratory diseases, malignancies and kidney disease (HR: 2.46, 95% CI 1.05-5.73, $P = .037$). Therefore, the De Ritis ratio on admission was significantly associated with in-hospital mortality in COVID-19 patients. Larger studies are required to confirm the capacity of this parameter to independently predict mortality in this group.

KEYWORDS

ALT, AST, COVID-19, De Ritis ratio

1 | INTRODUCTION

Since January 2020, when it was first isolated in China, coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2),[1] has spread throughout the world affecting more than twenty six million individuals and causing more than 870 000 deaths worldwide as of 06 September 2020.[2] The clinical manifestations of COVID-19 range from asymptomatic or mild symptoms to severe illness with respiratory failure and death.[3-8] Older adults and subjects of any age with comorbidities such as hypertension, coronary heart disease and diabetes have a higher risk of adverse outcomes.[9,10] Although pulmonary manifestations such as cough, nasal congestion and shortness of breath are typical of SARS-CoV-2 infection,[11] damage can occur in multiple organs, including the intestine, liver, and central nervous system.[12,13] Liver injury is an emerging concern with COVID-19, as also observed with other highly pathogenic coronaviruses such as the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV).[14] Some studies have reported elevated concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[4,15-19] in SARS-CoV-2 patients. Furthermore, >50% of patients affected by COVID-19 have different degrees of liver injury.[20] Although liver injury is more frequent in severe COVID-19,[21,22] the capacity of routine markers of liver injury to predict survival is uncertain. In addition, to the best of our knowledge, no information is available on the association between the AST/ALT ratio, commonly referred to as the De Ritis ratio, and mortality in COVID-19. We sought to address this issue by investigating the association between AST and ALT on admission and in-hospital mortality in COVID-19 patients and comparing their performance to that of the De Ritis ratio.

2 | METHODS

We retrospectively studied 105 consecutive COVID-19 patients admitted to the Respiratory Disease and Infectious Disease Units of the University Hospital of Sassari and the Pneumology Unit of the Santissima Trinità Hospital of Cagliari, Sardinia, Italy, between 15 March and 15 May 2020. COVID-19 was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) in all cases. The demographic, clinical and laboratory data were retrieved from individual clinical records and recorded in a dedicated electronic database. In particular, we collected established parameters of comorbidity (Charlson Comorbidity Index) and markers of inflammation and organ dysfunction, including C-reactive protein (CRP), white blood cell count (WBC), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and coagulation (fibrinogen, D-dimer). The upper normal limit for AST and ALT was 34 and 55 UI/L, respectively. We also collected information about the intensity of care received, particularly in terms of respiratory support (oxygen supplementation, noninvasive or invasive respiratory support) during hospitalization. The patients were followed till discharge or in-hospital death. The criteria for discharge were as follows: (a) no fever for at least 3 days; (b) significant improvement on chest CT scan or Xray imaging; and (c) two consecutive negative nucleic acid tests, performed at least 24 hours apart. The study was conducted in accordance with the declaration of Helsinki and was approved by the ethics committee of the University Hospital (AOU) of Cagliari (PG/2020/10915). Data are expressed as mean values (mean ± SD) or median values (median and IQR). The Kolmogorov-Smirnov test was performed to evaluate variables distribution. Between-group differences of continuous variables were compared using unpaired Student's *t* test or Mann-Whitney rank sum test, as appropriate. Differences between categorical variables were evaluated by Fisher test or chi-squared test, as appropriate. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden Index. The DeLong method was utilized to make pairwise comparisons of ROC curves. For survival analysis, time zero was defined as the time of hospital admission. In order to assess survival probability by Kaplan-Meyer method and logrank test, with the end point being death, the study population was divided into tertiles according to continuous AST, ALT and AST/ALT ratio values: AST, tertile I 8-25, tertile II 26-40 and tertile III 41-609 IU/L; ALT, tertile I 6-11, tertile II 12-32 and tertile III 33-409 IU/L; and De Ritis ratio, tertile I 0.56-1.11, tertile II 1.16-1.62 and tertile III 1.63-4.95. The low limit of tertile III of the De Ritis ratio, 1.63, was considered as cut-off value for further analysis.

Cox proportional hazards regression was performed for both univariate and multivariate analyses. Regression analyses were adjusted for age, gender, smoking status, cardiovascular disease, intensity of care, diabetes, respiratory diseases, malignancies and kidney disease. Statistical analyses were performed using MedCalc for Windows, version 19.4.1 64 bit (MedCalc Software, Ostend, Belgium).

3 | RESULTS

A total of 105 COVID-19 patients (70 men and 35 women) were included in the study (Table 1). The median age was 72.0 (59.5-80) years. Seventy-seven patients (73.3%) were discharged alive whereas the remaining 28 (26.7%) died. Of the 105 patients, 71 (67.6%) had one or more pre-existing diseases. Cardiovascular disease (56%), respiratory disease

TABLE 1 Demographic, clinical and laboratory characteristics of the study population

	COVID-19 global cohort (n = 105)	COVID-19 survivors (n = 77)	COVID-19 nonsurvivors (n = 28)	*P*-value
Age, y	72.0 (59.5-80.0)	68.0 (56.8-76.0)	79.5 (73.0-86.0)	**<.001**
Gender (F/M)	35/70	27/50	8/20	.53
Smoking status (no/yes/former)	62/32/11	45/24/8	17/8/3	.97
BMI, (nonobese/obese)	82/23	59/18	23/5	.55
Cardiovascular disease, (no/yes)	46/59	40/37	6/22	**.006**
Respiratory disease, (no/yes)	82/23	62/15	20/8	.32
Kidney disease, (no/yes)	90/15	65/12	25/3	.49
Diabetes, (no/yes)	83/22	62/15	21/7	.54
Cancer, (no/yes)	89/16	65/12	24/4	.87
Autoimmunity, (no/yes)	99/6	72/5	27/1	.71
Charlson Comorbidity Index	5 (2-7)	4 (2-6)	6 (5-8)	**<.001**
Interval between disease onset and admission, (days)	5.0 (3.0-8.0)	6.5 (3.5-9.0)	4.0 (1.0-5.0)	**.003**
ACE inhibitors, (no/yes)	85/20	64/13	21/7	.35
ARBs, (no/yes)	84/21	63/14	21/7	.44
Intensity of care (no, OT, RSni, RSi)	20/45/19/21	19/32/10/16	1/13/9/5	**.047**
Hospital stay, (days)	17 (9-27)	21 (14-36)	6 (3-12)	**<.001**
WBC, ($\times 10^9$ L)	6.7 (5.0-9.4)	6.4 (4.9-8.9)	9.3 (5.8-14.1)	**.005**
CRP, (mg/dL)	10.0 (2.9-22.1)	8.4 (2.5-19.8)	12.9 (8.6-41.3)	**.03**
Albumin, (g/dL)	3.3 (3.1-3.7)	3.5 (3.1-3.8)	3.2 (3.0-3.5)	**.03**
LDH, (IU/L)	282 (232-420)	272 (206-361)	384 (276-504)	**.002**
D-dimer, (μg/mL)	1.49 (0.69-6.58)	1.16 (0.61-2.79)	6.98 (1.24-399)	**.003**
Fibrinogen, (mg/dL)	575 ± 195	547 ± 193	500 ± 194	.40
ALT > UNL, (no, yes)	88/17	63/14	25/3	.36
AST > UNL, (no, yes)	53/51	42/35	11/16	.22

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index, COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LDH, lactate dehydrogenase; M, male; OT, oxygen therapy; RSi, invasive respiratory support; RSni, noninvasive respiratory support; UNL: upper normal limit; WBC: white blood cells. Bold values indicate statistical significance at the $p < .05$ level.

(22%), diabetes (21%), malignancies (15%) and kidney disease (14%) were the most common comorbidities. The median (IQR) hospitalization duration was 17 (9-27) days. Nonsurvivors were significantly older [79.5 (73.0-86.0) years vs 68.0 (56.8-76.0) years, $P =< 0.001$], more likely to have cardiovascular disease (79% vs 48%, $P = .006$) and had higher values of Charlson Comorbidity Index [median (IQR) 6 (5-8) vs 4 (2-6), $P < .001$]. A significant difference between survivors and nonsurvivors was observed in intensity of care ($P = .047$). Furthermore, survivors had a longer hospital stay [median (IQR) 6 (3-12) days vs 21 (14-36) days, $P < .0001$]. In addition, laboratory findings demonstrated significantly higher levels of WBC [median (IQR) 9.3 (5.8-14.1) $\times$ 10^9L vs 6.4 (4.8-8.9) $\times$ 10^9L, $P = .005$], CRP [12.9 (8.6-41.3) mg/dL vs 8.4 (2.5-19.8) mg/dL, $P = .03$], LDH [384 (276-504) IU/L vs 272 (206-361) IU/L, $P = .002$], D-dimer [6.98 (1.24-399) μg/mL vs 1.16 (0.61-2.79) μg/mL, $P = .003$] and lower concentrations of albumin [3.2 (3.0-3.5) g/dL vs 3.5 (3.1-3.8) g/dL, $P = .003$] in nonsurvivors. By contrast, there were no significant differences between survivors and nonsurvivors in gender, BMI, smoking status, kidney disease, respiratory disease, diabetes, autoimmunity disease, malignancies, use of ACE inhibitors or ARBs, serum fibrinogen concentration, and frequency of patients with AST and ALT above UNL. Figure 1 shows that the two groups had similar values of serum ALT and AST concentrations [ALT median (IQR) 25 (13-39) IU/L vs 24 (17-38) IU/L, $P = .87$; AST median (IQR) 30 (21-47) IU/L vs 35 (27-69) IU/L, $P = .07$]. By contrast, the De Ritis ratio was significantly lower in survivors than in nonsurvivors [median (IQR) 1.25 (0.91-1.64) vs 1.67 (1.38-1.97), $P = .002$].

In ROC curve analysis (Figure 2), the AUC value of De Ritis ratio (AUC = 0.701, 95% CI 0.603-0.78, $P = .0006$) was significantly higher than the AUC values of AST and

ALT and showed higher combined sensitivity and specificity values (Table 2). Kaplan-Meier survival curves were used to evaluate in-hospital mortality in COVID-19 patients with different levels of ALT, AST and De Ritis ratio (Figure 3). ALT and AST concentrations were not associated with mortality (logrank test $P = .83$ and $P = .62$, respectively). By contrast, a significant association between the De Ritis ratio and mortality was observed (logrank test $P = .014$). Compared with patients with De Ritis ratios in the first tertile (<1.11), the risks of death increased by 3.6-fold (95% CI, 1.43-9.08, $P = .006$) in patients with values in the third tertile (≥1.63). Median hospital stay was, respectively, 17 (13-29) days, 20

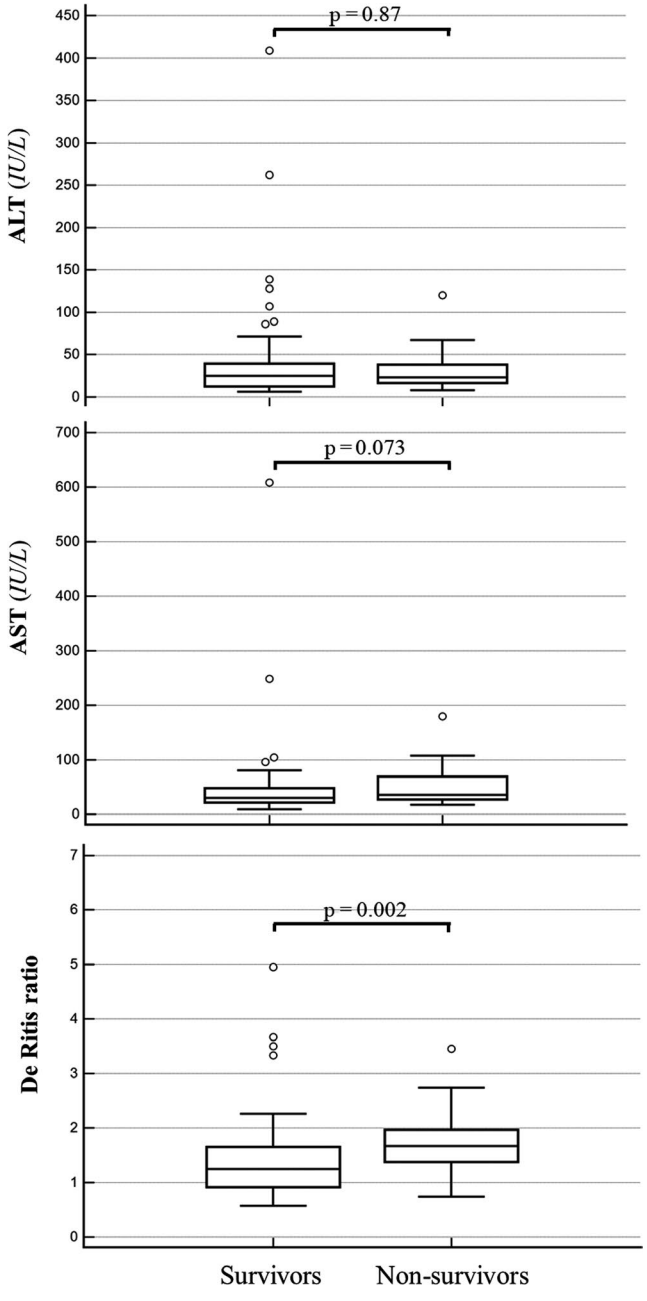

FIGURE 1 Serum concentration of ALT, AST and De Ritis ratio values in survivors and nonsurvivors. The central horizontal line on each box represents the median, the ends of the boxes represent the 25 and 75 percentiles and the error bars are the 5 and 95%

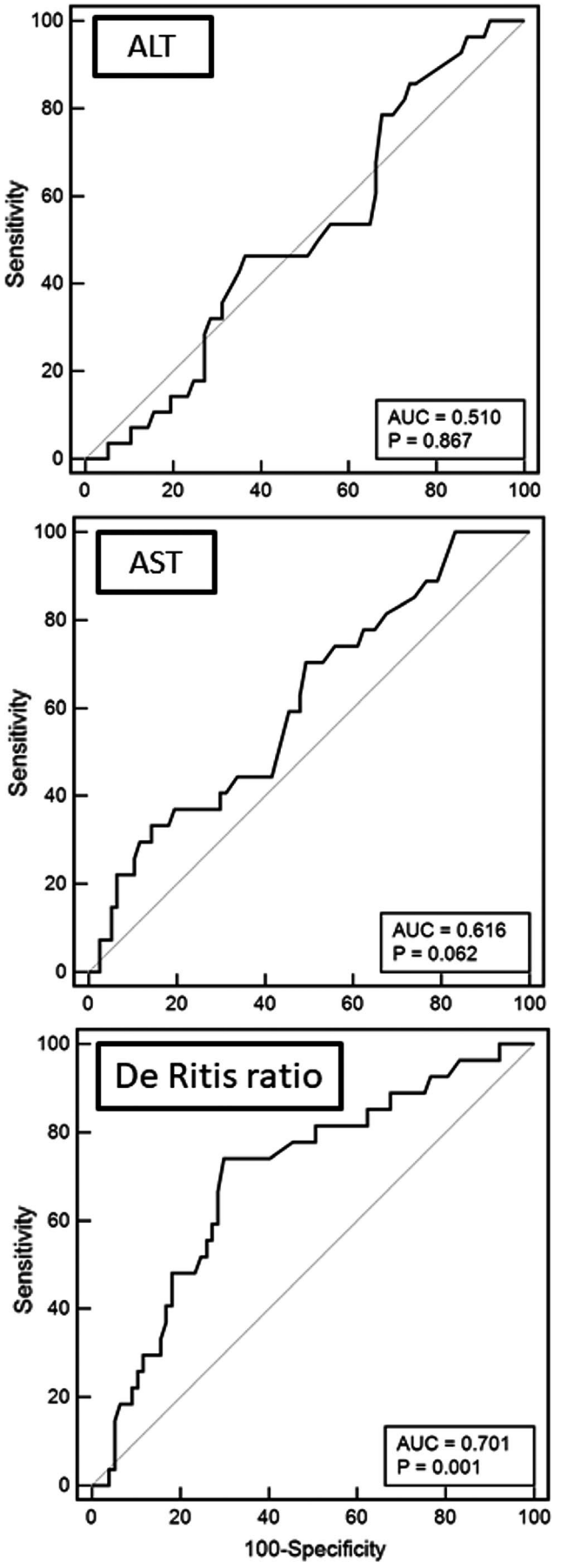

FIGURE 2 Receiver operating characteristics (ROC) curves for ALT, AST and the De Ritis ratio

TABLE 2 Receiver operating characteristics (ROC) curves and prognostic accuracy of ALT, AST and the De Ritis ratio

	AUC	95% CI	*P*-value	Cut-off	Sensitivity (%)	Specificity (%)	DBA vs De Ritis index	SE	*P*-value
ALT	0.519	0.418-0.618	.867	>13	86	26	0.182	0.102	.073
AST	0.616	0.515-0.710	.062	>30	70	51	0.097	0.04	**.015**
De Ritis ratio	0.701	0.603-0.787	**.0006**	>1.49	74	70	-	-	-

Abbreviations: DBA, differences between areas; SE, standard error of DBA. Bold values indicate statistical significance at the $p < .05$ level.

(8-27) days and 13 (6-28) days in De Ritis ratio tertiles I (0.56-11), II (1.12-1.62) and III (1.63-4.95). Death rate was 14% in the De Ritis ratio tertile I, 21% in tertile II and 43% in tertile III. In multivariate Cox regression analysis, the HR for patients with De Ritis ratio > 1.63 (tertile III) remained significant after adjusting for age, gender, smoking status, cardiovascular disease, intensity of care, diabetes, respiratory diseases, malignancies and kidney disease (HR: 2.46, 95% CI 1.05-5.73, $P = .037$; Table 3).

Table 4 shows demographic, clinical and haematological characteristics of COVID-19 patients stratified on the basis of the De Ritis ratios. Patients in tertile III of the De Ritis ratio were significantly older [median (IQR): 77 (72-84) years vs 66 (56-77) years, $P < .001$], had increased rate of mortality (43% vs 17%, $P = .008$), a higher frequency of respiratory diseases (34% vs 16%, $P = .03$) and higher values of Charlson Comorbidity Index [median (IQR): 6 (4-7) vs 4 (2-6), $P = .003$] than patients with De Ritis ratio values <1.63. No significant differences were observed in other variables.

4 | DISCUSSION

We retrospectively studied a consecutive series of 105 COVID-19 patients admitted to dedicated referral centres in Sardinia (Italy), with clinical and demographic characteristics similar to those recently described in other COVID-19 cohorts.[4,6,15,16,23-25,28-31] The lag time between the onset of symptoms and hospital admission is a crucial factor in the spreading of SARS-CoV2 across the community. The lag time period in our study (5 days, IQR 3-8) was similar to that reported in previous studies, between 4 and 12 days.[4,15,16,24-27,30] The median length of hospital stay (17 days, IQR 9-27) was also within the range of that described in recent reports (between 12 and 22 days).[4,6,25,27] As previously reported, we found that adverse outcomes is significantly associated with age,[10,25,28-31] cardiovascular disease,[10,29] interval between disease onset and admission,[31] CRP,[6,28-31] LDH,[6,10,28,30,31] D-dimer,[3,10,28,30,31] WBC[3,10,29] and albumin concentrations.[3,10,31] Several studies have also described elevated liver test markers in COVID-19 patients, mainly ALT, AST, gamma-glutamyl transferase (GGT) and total bilirubin levels.[3,4,15-19,28-33] However, in line with other studies we did not find significant differences in AST and ALT serum concentrations in relation to mortality.[34-38] By contrast, the De Ritis ratio was significantly increased in nonsurvivors when compared to survivors. In ROC curve analysis, the De Ritis ratio on admission was able to significantly discriminate between survivors and nonsurvivors (AUC > 0.7) with a sensitivity of 74% and specificity of 70%. These data agree with our previous observation of an increased De Ritis ratio in patients with COVID-19 when compared with non-COVID-19 interstitial pneumonia patients[39] and with the findings of Yazar H et al of elevated De Ritis ratios in COVID-19 patients, without notwithstanding performing a specific prognostic evaluation of this parameter.[40] In addition, we found, by Kaplan-Meier survival analysis, that higher values of the De Ritis ratio, but not of AST and ALT alone, were significantly associated with poor survival in COVID-19 disease. The association remained significant by Cox regression analysis after correction for age, gender, smoking status, cardiovascular disease, intensity of care, diabetes, respiratory diseases, malignancies and kidney disease. The rate of AST and ALT serum concentration was first described by Fernando De Ritis in 1957 and it is commonly known as the De Ritis ratio.[41] ALT and AST are usually requested when there is suspicion of liver disease and their release from liver cells to the circulation may indicate hepatocellular damage or death. These enzymes are normally and constantly released from hepatic cells and their normal levels in health represent the equilibrium between the usual turnover of hepatocytes, due to programmed cell death, and their clearance from serum. By transferring amino groups, the aminotransferase ALT catalyses the conversion of α-keto acids into amino acids in a reversible manner. Liver ALT activity is roughly 10 times higher when compared to the heart or skeletal muscle, thus high serum ALT activity is widely accepted as a good indicator of parenchymal liver disease. Since ALT is located in the cytosol of hepatocytes, its increased serum levels normally indicate an impairment in the integrity of the hepatocyte membrane. By contrast, AST is present in both the hepatocyte cytoplasm and mitochondria with mAST being the more prevalent isoenzyme with approximately 80% of total AST activity in human liver.[42] AST displays the highest activity in the liver and skeletal muscle but also occurs in several tissues, including heart muscle, brain, kidneys, lungs, pancreas, erythrocytes and leucocyte

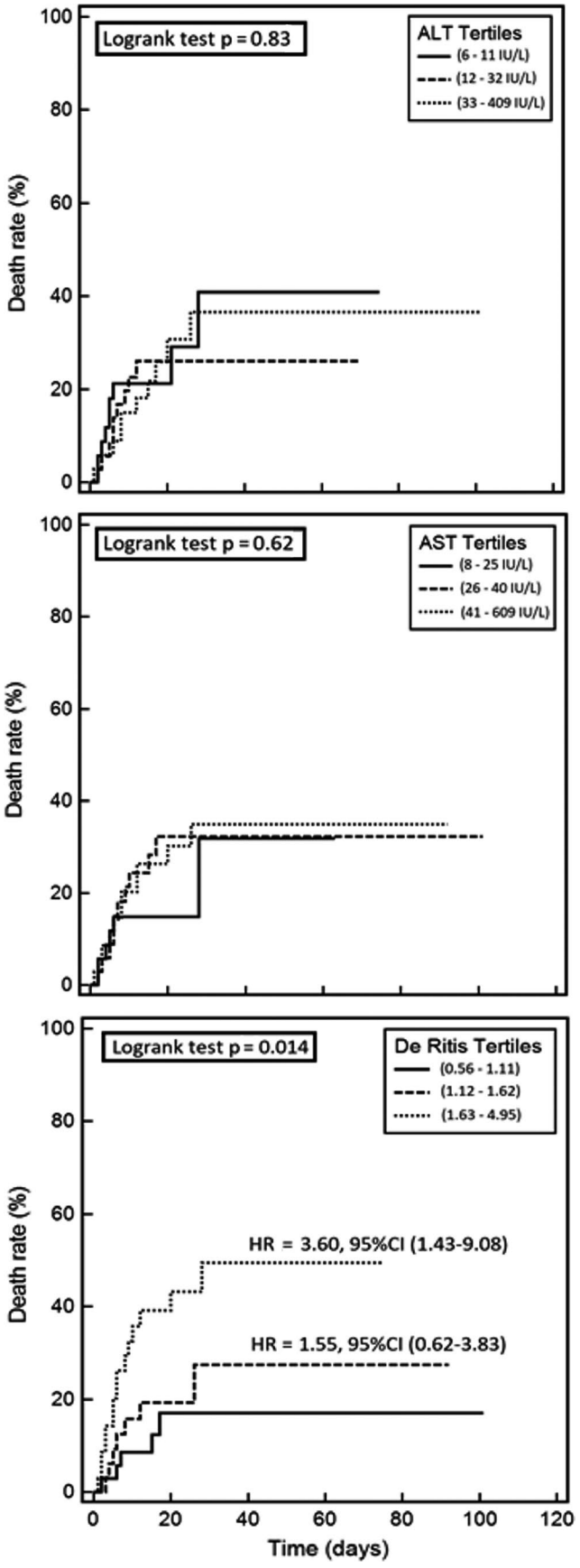

FIGURE 3 Kaplan-Meier curves for survival probability of COVID-19 during hospitalisation in patients with different levels of ALT, AST and the De Ritis ratio

TABLE 3 Multivariate Cox regression model showing hazard ratios for the studied variables

	HR (95%CI)	*P*-value
Age, *(per year increase)*	1.04 (0.99-1.09)	.057
Gender, (*female vs male)*	2.03 (0.76-5.47)	.16
Smoking status, (*nonsmoker vs smoker)*	0.73 (0.49-1.64)	.90
Intensity of care, (*no, OT, RSni, RSi)*	1.20 (0.78-1.87)	.40
Cardiovascular disease	2.53 (0.80-7.99)	.11
Respiratory disease	1.16 (0.43-3.13)	.76
Kidney disease	0.54 (0.14-2.01)	.36
Diabetes	0.52 (0.18-1.50)	.23
Cancer	0.75 (0.23-2.54)	.65
De Ritis index ≥ 1.63	2.46 (1.05-5.73)	**.037**

Abbreviations: OT, oxygen therapy; RSi, invasive respiratory support; RSni, noninvasive. Bold values indicate statistical significance at the $p < .05$ level.

and thus is less specific for liver damage compared to ALT.[43] Generally, AST serum evaluation is indicated for the diagnosis and monitoring of liver-biliary disease, myocardial infarction and skeletal muscle destruction. Therefore, albeit sporadically used, the De Ritis ratio is recognized as a good indicator of liver damage.[44] Experimental evidence suggests that moderate to severe liver damage are characterized by De Ritis ratios < 1.0 whilst severe liver diseases were associated to values above 1.0.[40] Our COVID-19 disease patients had a median De Ritis ratio of 1.33, similar to that reported by Yazar H et al in their cohort.[40] However, we also observed that values in nonsurvivors were significantly higher than those of survivors (1.67 vs 1.25). This suggests the presence of liver damage in hospitalized COVID-19 patients, particularly in nonsurvivors. In particular, patients in the upper tertile of De Ritis ratios (≥1.63) had a 2.46-fold risk of dying when compared to patients in tertile I and II.

The mechanisms involved in liver impairment in COVID-19 patients are unclear. It has been speculated that liver injury in patients with SARS-CoV-2 infection may be directly due to the virus itself.[45] It has been demonstrated that SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell[4] and another study reported that cholangiocytes abundantly express the ACE2 receptor,[46] thus suggesting that SARS-CoV-2 might directly enter cholangiocytes and cause liver dysfunction. However, it cannot be ruled out that antiviral drugs used for treatment might be responsible, at least in part, for liver damage in COVID-19 patients. It needs to be emphasized that in our cohort serum biomarker assessment was performed on the first day of hospitalization, before antiviral drugs administration.

In conclusion, even considering the retrospective nature and the relatively small sample size of this study, our data

TABLE 4 Demographic, clinical and laboratory characteristics of COVID-19 patients stratified by the De Ritis ratio

	De Ritis ratio <1.63 (n = 70)	De Ritis ratio ≥1.63 (n = 35)	*P*-value
Age, years	66 (56-77)	77 (72-84)	**<.001**
Gender (F/M)	21/49	14/21	.31
Smoking status (no/yes/former)	43/23/4	19/9/7	.08
BMI, (nonobese/obese)	58/12	24/11	.10
Cardiovascular disease, (no/yes)	34/36	12/23	.17
Respiratory disease, (no/yes)	59/11	23/12	**.03**
Kidney disease, (no/yes)	62/8	28/7	.24
Diabetes, (no/yes)	58/12	25/10	.18
Cancer, (no/yes)	62/8	27/8	.13
Autoimmunity, (no/yes)	65/5	34/1	.37
Charlson Comorbidity Index	4 (2-6)	6 (4-7)	**.003**
Interval between disease onset and admission, (days)	6.0 (3.0-9.0)	5.0 (1.5-7.0)	.08
Intensity of care (no, OT, RSni, RSi)	14/32/11/13	6/13/8/8	.71
Hospital stay, (days)	18 (11-28)	13 (6-28)	.16
Survivors, (no/yes)	13/57	15/20	**.008**
WBC, ($x10^9$ L)	7.5 (5.2-9.4)	6.3 (4.7-10.8)	.89
CRP, (mg/dL)	10.1 (2.5-21.0)	10.0 (3.7-24.5)	.26
Albumin, (g/dL)	3.4 (3.1-3.8)	3.3 (3.0-3.7)	.84
LDH, (IU/L)	271 (209-401)	296 (261-443)	.11
D-dimer, (μg/mL)	1.25 (0.67-7.17)	1.78 (0.68-6.29)	.69
Fibrinogen, (mg/dL)	549 ± 207	527 ± 163	.63

Abbreviations: BMI, body mass index, COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LDH, lactate dehydrogenase; M, male; OT, oxygen therapy; RSi, invasive respiratory support; RSni, noninvasive respiratory support; WBC, white blood cells. Bold values indicate statistical significance at the $p < .05$ level.

show for the first time that elevated De Ritis ratios on admission are independently associated with in-hospital mortality in SARS-CoV-2 disease. Prospective studies in larger cohorts are needed to confirm our results and to further evaluate whether the De Ritis ratio may represent a useful tool for risk stratification in hospitalized COVID-19 patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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