The elevated De Ritis ratio on admission is independently associated with mortality in COVID-19 patients

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Abstract

Background: Besides the respiratory tract infection caused by COVID-19, 14-53% of COVID-19 patients had hepatic dysfunction on admission. Liver damage in COVID-19 patients was witnessed as increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or elevated AST/ALT ratio, known as the De Ritis ratio. However, the prognostic value of the elevated De Ritis ratio in COVID-19 patients is still unknown. The aim of our study was to evaluate the prognostic value of the De Ritis ratio compared to other abnormal laboratory parameters and the relation to mortality.

Methods: 322 COVID-19 patients were selected in this retrospective study between November 2020 and March 2021. Laboratory parameters were measured on admission and followed till discharge or death. Multivariate binary logistic regression and Receiver Operating Characteristic (ROC) curves were performed to evaluate the impact of abnormal laboratory findings to predict mortality. In addition, clinical characteristics and laboratory data of COVID-19 patients were compared by different levels of De Ritis ratio.

Results: Of the 322 COVID-19 patients, 57 (17.7%) had gastrointestinal symptoms on admission. Median age was 66 (54-77) years and 178 were men. The mortality rate was 11.2%. 30 patients (9.3%) had preexisting liver disease; 20 (6.2%) were liver cirrhosis. In COVID-19 recovered patients the De Ritis ratio was significantly smaller ($p<.001$) than in deaths (mean: 1.0 vs. 1.8). Mean values of AST, total bilirubin, albumin, CRP, PCT, IL-6 were significantly higher in COVID-19 deaths compared to survivors ($p<.05$). AST, De Ritis ratio, total bilirubin, IL-6, albumin and age were independently associated with mortality. The De Ritis ratio proved to be an independent risk factor for mortality with an OR of 29.967 (CI 5.266-170.514). In ROC analysis, AUC value of the the De Ritis ratio was 0.85 (95% CI 0.777-0.923, $p<.05$) with sensitivity and specificity 80.6% and 75.2%, respectively. Patients with De Ritis ratio $\geq$ 1.218 were significantly associated with mortality, severity, higher AST and IL-6, however with lower ALT.

Conclusions: The elevated De Ritis ratio on admission is independently associated with mortality in COVID-19 patients. Patients with De Ritis ratio $\geq$1.218 are significantly susceptible to liver damage and cytokine released storm.

Background

Coronavirus disease 2019 (COVID-19) was first isolated in humans in Wuhan, China, in December 2019. The virus has since spread over the world including more than 200 countries and regions [1]. The WHO announced the COVID-19 outbreak a pandemic on March 11, 2020 [2]. As of February, 2022 there have been approximately 376 million confirmed cases and more than 5.5 million death cases worldwide [3]. In Hungary there have been more than 1.5 million confirmed cases of COVID-19 with more than 41 000 death cases, reported to WHO [4]. Previous studies showed that up to 26% of patients with COVID-19 gastrointestinal symptoms were developed mainly with diarrhea, nausea and loss of appetite [5, 6]. COVID-19 could be associated with hepatic dysfunction or liver damage, elevated transaminases (AST,

ALT) and cholestatic parameters (GGT, total bilirubin, ALP) can be present in 14-53% of COVID-19 patients, with more severe outcome [7]. The pathophysiology of liver injury in COVID-19 is multifactorial. COVID-19 may bind to ACE2 positive cholangiocytes and cause direct cytopathic effect through impairing the barrier and bile acid transporting functions of cholangiocytes. Lymphopenia and abnormal inflammatory citokin levels (IL-2, IL-6, IL-10) indicate the dysregulation of innate immune system and may contribute to the life-threatening mechanism of citokin storm. Hypoxic conditions due to sinusoidal microembolisations and ARDS may also induce congestive hepatopathy. Drug-induced liver injury (DILI) has already been registered with the use of tocilizumab because it increases the transaminases significantly [5, 8-10]. Generally, in 2-11% of COVID-19 cases there was an underlying liver disease in the medical history. The clinical outcome of COVID-19 patients may be influenced by the cause of liver disease. Liver cirrhosis is a high risk factor for COVID-19 mortality. Among patients with cirrhosis as measured by Child-Pugh (CP) score, there is a strong association between the severity of cirrhosis and mortality [11]. Cirrhosis-associated immune dysfunction (CAID) is a condition in patients with chronic liver disease, in particular with liver cirrhosis. Upregulation of macrophages, complement system, impaired lymphocytes, neutrophiles as well as intestinal dysbiosis could lead to aberrant inflammatory response during infection [12, 13]. Therefore, CAID makes COVID-19 infected individuals more susceptible to bacterial and fungal infections [14, 15]. Moreover, COVID-19 infection could lead to acut-on-chronic liver failure (ACLF), a syndrome characterised by acute decompensation of chronic liver disease associated with multiple organ failure (MOF) and increased mortality rate [16].

Methods

Study population

In the third wave of COVID-19 pandemic, between November 2020 and March 2021, 322 COVID-19 patients were retrospectively recruited at the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University.

COVID-19 was confirmed by a positive reverse transcription-polimerase chain reaction (RT-PCR, SEQONCE qPCR Multi Kit, IVD) test using the protocol by the World Health Organization [17].Oropharyngeal or/and nasopharyngeal swab specimen were collected, and high-resolution computer tomography (HRCT, Phillips Incisive128) was performed on admission and during the hospital stay.

Study design

This analysis of a retrospective study was conducted using data from electronic medical records. All data of confirmed COVID-19 patients regarding epidemiological and clinical characteristics, laboratory findings, imaging features, management and treatment were collected and reviewed. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (IV/5245-1/2021/EKU, Budapest, 06.07.2021). It conforms to the ethical norms and standards in the declaration of Helsinki.

On admission, physical examination was performed, and a detailed, accurate medical history was taken with special emphasis on comorbidities, symptoms (respiratory tract and gastrointestinal manifestations) and underlying liver diseases. We also collected data about pulmonary imaging features and intensive care received, regarding the respiratory support. Hence, patients confirmed with COVID-19 were divided into mild, moderate, severe and critical type in clinical classification. The guidelines for clinical classification and diagnostic criteria of COVID-19 were based on our national protocol published by Ministry of Human Capacities according to the guidelines of the Chinese National Health Commission [18].

Data collection

During hospitalization, follow-up laboratory examinations were performed regularly, including liver enzymes (AST, ALT), cholestatic parameters (GGT, total bilirubin, ALP), inflammatory biomarkers (baseline C-reactive protein, IL-6, PCT) and liver function marker (albumin). Laboratory markers like direct bilirubin, LDH, cell blood counts (erythrocytes, leukocytes, thrombocytes) and INR were excluded from this study because laboratory tests of these markers were not carried out for all patients with COVID-19. Furthermore, at each follow-up, the De Ritis ratio (AST/ALT) was calculated to investigate the clinical outcome. The patient surveillance was managed till discharge or death. Criteria for releasing COVID-19 patients from our hospital were as follows: (1) resolution of fever >48 hours without antipyretics, (2) oxygen saturation ≥ 94%, (3) no signs of increased work of breathing or respiratory distress, (4) improvement in signs and symptoms of illness (cough, shortness of breath, and oxygen requirement) and (5) two negative RT-PCR tests in a row, at least 24 hours apart.

Admitted COVID-19 patients with preexisting liver disease were divided into two groups: patients having chronic liver disease (CLD) with cirrhosis and those having CLD without cirrhosis. Data about the etiology of CLD in both groups were retrieved from individual clinical reports. In addition, we used Child-Pugh (CP) score, based on our local protocol, for the assessment of prognosis in liver cirrhosis. Modified Child-Pugh classification included serum concentrations of total bilirubin and albumin, international normalized ratio (INR), the degree of ascites and the degree of hepatic encephalopathy. A CP score of 5 to 6 is considered CP class A (well-compensated disease), 7 to 9 is CP class B (significant functional compromise), and 10 to 15 is CP class C (decompensated cirrhosis) [19].

Statistical analysis

All statistical analyses were performed using SPSS software version 28 (IBM Corporation Armonk, NY, United States). Data were tested for normality using Kolmogorov-Smirnov test, and were found to be non-normally distributed. Therefore, all the continuous data were presented as mean ± standard deviation, categorical variables were presented as frequency and percentage or median with interquartile range (IQR). Mann-Whitney U test was used to compare continuous variables with mortality, chi-square test and cross-tabulation were applied for comparing categorical variables in severity groups and mortality. Furthermore, the remaining 8 valuable factors (7 laboratory parameters and age) were selected and analysed in Multivariate Binary Logistic Regression. Odds Ratios (OR) with 95% Confidence Intervals (CI)

were calculated. The Receiver Operating Characteristic (ROC) curve analysis was also performed to identify the ability of AST, De Ritis ratio, total bilirubin, IL-6 and albumin levels to predict mortality. Cut-off values were calculated using the Youden-index. In addition, survival probabilities were portrayed by Kaplan-Meier plot and compared with a log-rank test. A p-value <0.05 was defined as statistically significant.

Results

Patient characteristics

All 322 laboratory-confirmed COVID-19 patients were enrolled in this study. The median age was 66 (IQR 54-77) years; 178 (55,3%) were men. On admission, according to our national protocol based on WHO guidelines, all patients were categorised into 4 severity groups. Confirmed COVID-19 cases are mostly moderate (56.2%), mild (15.5%) and severe (16.1%) cases were similarly frequent. 36 COVID-19 patients (11.2%) died in the hospital.

Clinical features are summarized in (Table 1). In total, 57 COVID-19 patients (17.7%) had already gastrointestinal (GI) symptoms on admission, the most typical initial GI symptom was diarrhea (9.6%). Among the history of comorbidities, hipertension and diabetes were the most common with 53% (171/322) and 31% (100/322), respectively.

30 COVID-19 patients (9.3%) had preexisting liver disease in the medical history; two-third of patients with liver disease were liver cirrhosis. To assess the prognosis in patients with cirrhosis, we applied the modified Child-Pugh classification. On admission, out of the 20 patients with cirrhosis, 9 CP-A (45%), 7 CP-B (35%) and 4 CP-C (20%) patients were hospitalized. One laboratory-confirmed COVID-19 patient with CP-B had hepatic decompensation and died due to the onset of acute-on-chronic liver failure (ACLF). The etiological agents of liver cirrhosis were as follows (Fig. 1): alcohol 40% (8/20), hepatitis C virus 15% (3/20), nonalcoholic steatohepatitis 10% (2/20), autoimmune hepatitis 5% (1/20), hepatitis B virus 5% (1/20).

Laboratory findings

The laboratory parameters and comparison among COVID-19 recovered patients (n=286) and COVID-19 deaths (n=36) are noted in (Table 2). Considering the laboratory data, mean values of AST, total bilirubin, CRP, PCT and IL-6 were significantly higher in deaths compared to COVID-19 survivors (p<.05). By contrast, mean value of albumin was significantly lower in deaths (p<.05). The calculated De Ritis ratio and age showed a significant difference between the two groups (p<.05), although no differences in comorbidities or GI symptoms were noted.

De Ritis ratio as an independent predictor for in-hospital mortality in COVID-19 patients

As demonstrated (Table 3), AST, De Ritis ratio, total bilirubin, IL-6, albumin and age were independently associated with in-hospital mortality. De Ritis ratio proved to be an independent risk factor for in-hospital

mortality with an OR of 29.967 (CI 5.266-170.514).

Table 1 Epidemiological, clinical characteristics and severity grade of 322 COVID-19 patients admitted to Semmelweis University Department of Surgery, Transplantation and Gastroenterology between November 2020 and March 2021.

Epidemiological, clinical characteristics	Patients (n=322)
*Age (IQR)	66 (54-77)
Gender (male/female), n	178/144
Hospital stay (days)	11 (8-14)
GI symptoms n (%)	57 (17.7)
Diarrhea, n (%)	31 (9.6)
Vomit, n (%)	5 (1.6)
Melaena, n (%)	5 (1.6)
Ascites, n (%)	7 (2.2)
Hipertension, n (%)	171 (53)
Diabetes, n (%)	100 (31)
Cancer, n (%)	21 (6.5)
Anaemia, n (%)	9 (2.8)
Liver disease, n (%)	30 (9.3)
cirrhosis, n	20
Child-Pugh A, n	9
Child-Pugh B, n	7
Child-Pugh C, n	4
without cirrhosis, n	10
Severity grade	
Mild, n (%)	50 (15.5)
Moderate, n (%)	181 (56.2)
Severe, n (%)	52 (16.1)
Critical, n (%)	39 (12.1)
In-hospital mortality rate, n (%)	36(11.2)

* This data is median (IQR)

IQR interquartile range

Table 2 Comparison of clinical conditions and laboratory results on admission between COVID-19 recovered patients and COVID-19 deaths

Parameter	COVID-19 recovered patients n=286	COVID-19 deaths n=36	p
AST, mean (SD)	33.1 (26)	74.2 (78)	**< .001**
ALT, mean (SD)	37.4 (29.6)	48.4 (75.3)	.745
De Ritis ratio, mean (SD)	1.0 (.39)	1.8 (.85)	**< .001**
GGT, mean (SD)	91 (123)	125 (169)	.437
ALP, mean (SD)	136.9 (126)	189.7 (172)	.061
Total bilirubin, mean (SD)	33.1 (84.6)	70.8 (154.4)	**.019**
Albumin, mean (SD)	35.7 (7)	27.9 (13.7)	**< .001**
CRP, mean (SD)	148.4 (230.9)	260.3 (397.9)	**.008**
PCT, mean (SD)	6.67 (46.9)	23.1 (92.5)	**< .001**
IL-6, mean (SD)	39.6 (43.3)	86.4 (60.7)	**< .001**
Age, mean (SD)	63 (16)	79 (10)	**< .001**
Hospital days, mean (SD)	11 (5)	13 (5)	.077
Diarrhea, n (%)	30 (10.4)	1 (2.7)	.139
Ascites, n (%)	5 (1.7)	2 (5.5)	.140
Hipertension, n (%)	154 (53.8)	17 (47.2)	.453
Diabetes, n (%)	91 (31.8)	9 (25)	.405
Liver disease, n (%)	26 (9)	4 (11.1)	.694
Cirrhosis, n (%)	17 (5.9)	3	.576

Statistically significant values are presented in bold.

AST aspartate aminotransferase; ALT alanine aminotransferase; GGT gamma-glutamyl transferase; ALP alkaline phosphatase; CRP C-reactive protein; PCT procalcitonin; IL-6 interleukin 6; SD standard deviation

Predictive value of the De Ritis ratio for in-hospital mortality

The ROC lines of AST, total bilirubin, IL-6, albumin and the De Ritis ratio were compared in (Fig. 2). The AUC value of the De Ritis ratio (AUC=0.850, 95% CI 0.777-0.923, p<0.05), with sensitivity of 80.6% and specificity of 75.2% were higher compared to the other parameters. The optimal cut-off value was 1.218 (Table 4).

Table 3 Logistic regression for in-hospital mortality comparing 7 laboratory parameters and age

Variable	ß	S.E	p	OR	CI 95%
AST	.034	.010	**<.001**	1.034	1.015-1.054
De Ritis ratio	3.400	.887	**<.001**	29.967	5.266-170.514
Total bilirubin	.008	.003	**.003**	1.008	1.003-1.013
CRP	-.001	.002	.336	.999	.996-1.002
PCT	.002	.005	.613	1.002	.993-1.012
IL-6	.027	.008	**<.001**	1.027	1.012-1.042
Albumin	-.293	.058	**<.001**	.746	.666-.836
Age	.129	.032	**<.001**	1.138	1.069-1.211

Statistically significant values are presented in bold.

AST aspartate aminotransferase; CRP C-reactive protein; PCT procalcitonin; IL-6 interleukin 6; S.E standard error; OR odds ratio; CI confidence interval

Table 4 Diagnostic accuracy of the 5 laboratory parameters

Prognostic marker	AUC (95% CI)	Cut-off	Sensitivity	Specificity	p
AST	0.723 (0.624-0.821)	29.5	0.722	0.622	**<.05**
De Ritis ratio	0.850 (0.777-0.923)	1.21811	0.806	0.752	**<.05**
Total bilirubin	0.619 (0.519-0.719)	10.1	0.722	0.437	**<.05**
IL-6	0.743 (0.649-0.837)	51.915	0.722	0.748	**<.05**
Albumin	0.133 (0.057-0.208)	29.4	0.361	0.126	**<.05**

Statistically significant values are presented in bold.

AST aspartate aminotransferase; IL-6 interleukin 6; AUC area under curve; CI confidence interval

We conducted a Kaplan-Meier analysis of length for survival between COVID-19 patients stratified by different levels of the De Ritis ratio (Fig. 3). Comparing the estimated survival time of patients with De Ritis ratio ≥ 1.218 to those with De Ritis ratio **<**1.218, the De Ritis ratio was significantly associated with in-hospital mortality (log-rank test: p**<.**001).

As demonstrated (Table 5), patients with higher levels of the De Ritis ratio were significantly associated with severity grade (Fig. 4), were significantly older, and had an increased occurence of ascites. In addition, we found AST and IL-6 were significantly higher, however ALT was significantly lower compared to patients with lower levels of the De Ritis ratio.

Discussion

Initial identification of prognostic biomarkers for progression in hospitalized COVID-19 patients is high priority during the pandemic. Therefore, we conducted a retrospective study analysing patient characteristics and laboratory parameters in assessing the prognosis of COVID-19 patients. We present a single-center cohort of 322 patients with COVID-19, which is one of the largest analysed on this matter in the Central European region that we are aware of. On admission, slight majority of the patients were male and classified as moderate.

Out of the 322 cases, 16.1% were severe, which is similar to international studies [20, 21].

39 critically ill patients were treated in an intensive care unit due to an inadequate proinflammatory response with multiorgan failure, known as cytokine release syndrome [22, 23].

A recent prospective study of 20,133 UK patients and a cohort study of 192,550 US patients reported that hospital mortality rates were 26% and 13.6%, respectively [24, 25]. By contrast, the death rate in our study was 11.2%. Previous studies showed that 11.3-50.5% of COVID-19 patients presented with gastrointestinal symptoms, similar to our findings [26-28]. 57 patients (17.7%) presented with a digestive symptom, including predominantly diarrhea. Decreased appetite was excluded from the study, because it is not a concrete gastrointestinal symptom.

Table 5 Demographics, clinical and laboratory characteristics of COVID-19 patients grouped by the optimal cut-off value of the De Ritis ratio

Variable	De Ritis ratio ≥ 1.218 n=101	De Ritis ratio< 1.218 n=221	p
Mortality rate, n (%)	29 (28.7)	7 (3.1)	**<.001**
Severity grade			**<.001**
Mild, n (%)	13 (12.9)	37 (16.7)	
Moderate, n (%)	45 (44.5)	136 (61.5)	
Severe, n (%)	13 (12.9)	39 (17.7)	
Critical, n (%)	30 (29.7)	9 (4.1)	
Gender (male/female), n	50/51	128/93	.159
GI symptoms n (%)	19 (18.8)	38 (17.2)	.724
Diarrhea, n (%)	7 (6.9)	24 (10.9)	.267
Ascites, n (%)	5 (5)	2 (0.9)	**.021**
Hipertension, n (%)	51 (50.5)	120 (54.3)	.526
Diabetes, n (%)	30 (29.7)	70 (31.7)	.723
Liver disease, n (%)	9 (8.9)	21 (9.5)	.865
cirrhosis, n	6 (5.9)	14 (6.3)	
AST, mean (SD)	45.9 (39)	34 (36.8)	**<.001**
ALT, mean (SD)	27.9 (19.8)	43.5 (42.4)	**<.001**
Total bilirubin, mean (SD)	41 (98.3)	35.6 (94.1)	.133
Albumin, mean (SD)	34 (9.6)	35.2 (7.7)	.088
CRP, mean (SD)	158.5 (256)	162 (257.4)	.539
PCT, mean (SD)	13.2 (68)	6.3 (46.2)	.449
IL-6, mean (SD)	56.9 (55.7)	39.4 (42.8)	**.006**
Age, mean (SD)	70 (16)	63 (16)	**<.001**

Statistically significant values are presented in bold.

AST aspartate aminotransferase; ALT alanine aminotransferase; CRP C-reactive protein; PCT procalcitonin; IL-6 interleukin 6; SD standard deviation; GI gastrointestinal

Singh and colleagues reported, patients with preexisting liver disease, remarkably cirrhosis, were more susceptible to poor outcome compared to patients without liver injury [29].

Two-thirds of patients with liver disease were liver cirrhosis. The possible reason for higher proportion of cirrhosis was as follows: the department is the largest hepatology center in Hungary, thus most of the patients with cirrhosis, in particular Child-B and Child-C, were treated in our department. The overall prevalence of chronic liver disease in patients with COVID-19 was 9.3%, also in line with previously published numbers [30, 31]. Relevant to cirrhosis, patients with alcohol use disorder are particularly vulnerable and might be among the populations that are the most seriously influenced due to disordered immune system, alcohol relapse and postponed medical checkups during the pandemic.

Previous studies reported that significantly higher levels of liver transaminases (AST, ALT), total bilirubin, cholestatic liver enzymes (GGT, ALP), inflammatory markers (CRP, IL-6, PCT) and lower albumin were associated with poor outcome [32-34]. We found significant differences in serum concentrations of laboratory parameters including AST, total bilirubin, albumin, CRP, PCT, IL-6 in relation to mortality. However, ALT was not significantly higher in deaths, the AST/ALT ratio was found to be significantly associated with in-hospital mortality. Elevated AST is less specific for liver injury but may indicate multiple organ dysfunction compared to ALT [35]. The De Ritis ratio proved to be a valuable warning indicator of liver damage. In a meta-analysis with 4,606 patients, the elevated De Ritis ratio was found to be associated with poor prognosis in COVID-19 with a sensitivity of 55% (95% CI 36-73), specificity of 71% (95% CI 52-85) and AUC of 0.67 (95% CI 0.63-0.71) [36]. In our findings, the De Ritis ratio on admission could predict with above-average sensitivity and specificity the fatal outcome. However, the cut-off value in our study is smaller than in previously published international cohorts [37, 38]. In a survival analysis, the survival probability of patients with De Ritis ratio ≥1.218 was significantly worse and had a 2.3-fold higher risk of poor outcome (Fig. 5). In addition, in contrast to patients with De Ritis ratio <1.218, patients with De Ritis ratio ≥1.218 were associated with significantly higher AST and IL-6 levels. Raised IL-6 levels occur with excessive immune response, hyperinflammation and associate with poor prognosis in COVID-19 patients [39]. A prospective study with 153 patients reported, among immune-inflammatory biomarkers IL-6 was concluded as the most accurate and highly predictive inflammatory biomarker for mortality in patients with COVID-19 [40]. In our analysis, elevated De Ritis ratio on admission was independently associated with a more than 29-fold higher chance for in-hospital mortality.

Our data are the first to show that De Ritis ratio ≥1.218 proved to be a highly sensitive prognostic marker to predict in-hospital mortality. The elevated De Ritis ratio with higher IL-6 may indicate both liver injury and dysregulation of immune response and might serve as a red flag that COVID-19 infection may exacerbate.

Conclusion

In conclusion, elevated De Ritis ratio on admission is independently associated with mortality in COVID-19 patients. Patients with De Ritis ratio ≥1.218 are more susceptible to liver damage and cytokine release syndrome. We also gave proof that De Ritis ratio and IL-6 are proposed to be employed in guidelines for risk stratification of COVID-19 patients, which promotes medical providers to make good decisions.

Limitations

The main limitations of the study include the retrospective single-center design and smaller sample size. The number of enrolled COVID-19 patients with liver disease, in particular with liver cirrhosis, was limited. Hence, further prospective studies are needed to evaluate the diagnostic advantage of the elevated De Ritis ratio in this subgroup. In addition, laboratory parameters including INR, LDH, WBC, CK, direct bilirubin or hemoglobin were excluded by the absence of laboratory tests. Therefore, further prospective studies are expected monitoring these laboratory markers for the whole study population.

Abbreviations

COVID-19: Coronavirus disease 2019; OR: odds ratio; IQR: interquartile range; ROC: Receiver Operating Characteristic; MOF: multiple organ failure; CAID: cirrhosis-associated immune dysfunction; ACLF: acut-on-chronic liver failure; HRCT: high-resolution computer tomography; RT-PCR: reverse transcription-polimerase chain reaction; WHO: World Health Organization; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; DILI: Drug-induced liver injury

Declarations

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Authors' contributions

BD and KW contributed to the concept and design of the study. Sample preparation was contributed by all authors. Data collection, reference selection, statistical analysis and writing were performed by BD. KW guided the study and made critical revisions to the manuscript. KH commented on the latest version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Accessible upon reasonable request from the corresponding author.

Ethics approval

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (IV/5245-1/2021/EKU, Budapest, 06.07.2021). It conforms to the ethical norms and standards in the declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

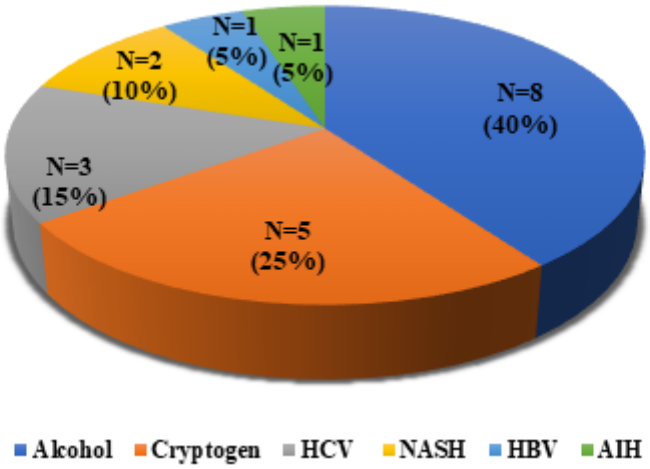

Figure 1

Distribution of etiological agents in COVID-19 patients with liver cirrhosis

HCV hepatitis C virus; NASH nonalcoholic steatohepatitis; HBV hepatitis B virus; AIH autoimmune hepatitis

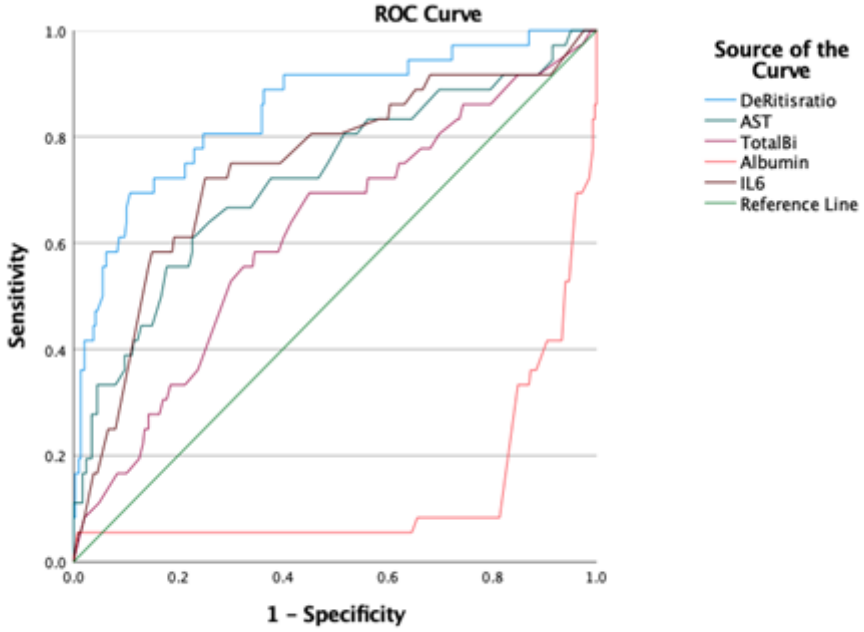

Figure 2

ROC-line of De Ritis ratio, AST, total bilirubin, albumin and IL-6

ROC Receiver Operating Characteristic; AST aspartate aminotransferase; IL-6 interleukin 6

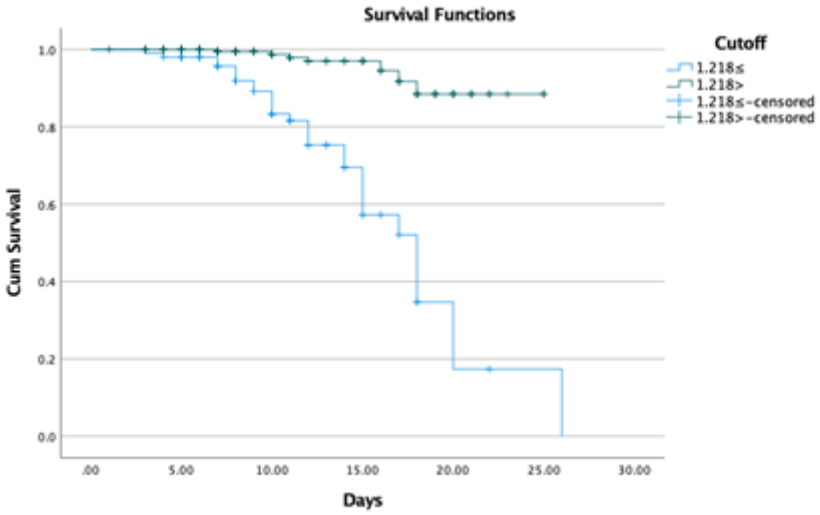

Figure 3

Kaplan-Meier analysis for survival of COVID-19 patients with De Ritis ratio ≥ 1.218

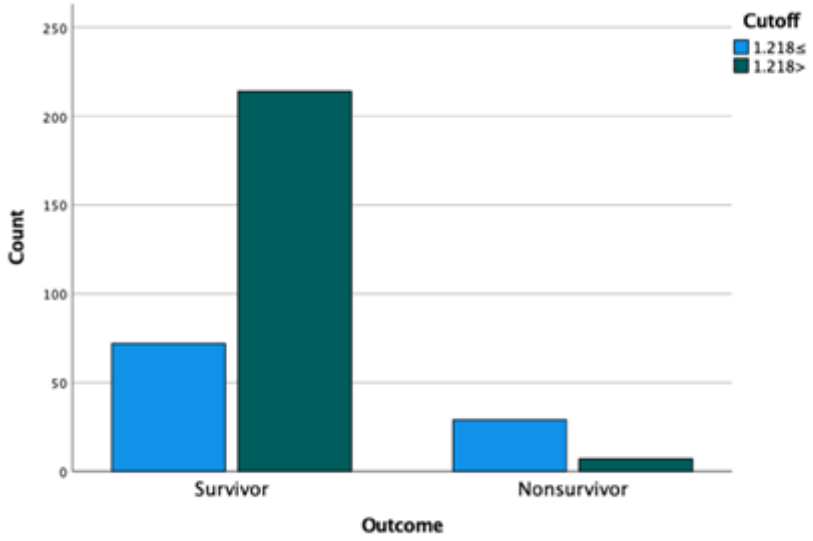

Figure 4

Relation between different levels of the De Ritis ratio and mortality in COVID-19 patients

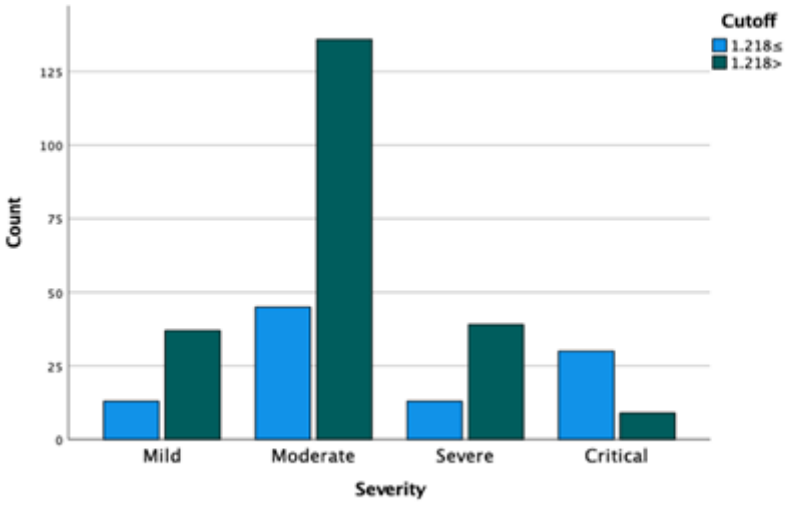

Figure 5

Relation between different levels of the De Ritis ratio and severity grades in COVID-19 patients