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ABSTRACT

Background: The study aimed to examine some biochemical test parameters and De Ritis ratio in COVID-19 patients, considering age and gender.
Method: The study was performed on patients with real-time polymerase chain reaction and computed tomography lung diagnosis. The relationship between lactate dehydrogenase, creatine kinase (CK), creatine kinase-MB, alanine aminotransferase, aspartate aminotransferase and De Ritis ratio were analysed in the first blood samples of the patients. The difference between gender was also compared with the independent sample t-test. Alpha value was accepted < 0.05.
Results: The De Ritis was significantly higher in females ($p = .040$). The De Ritis ratio was associated with CK in both gender. There was no significant difference in the biochemical parameters according to gender.
Conclusion: The De Ritis ratio appears to be a parameter that can be used in COVID-19 patients. However, more detailed and comprehensive studies including the symptoms of patients are needed.

Introduction

In December 2019, a cluster of pneumonia cases of unknown aetiology was identified in Wuhan, China. Health officials state that these cases may be linked to the city's South China Seafood Market. With ongoing studies, the WHO has revealed that there is a situation called SARS-CoV-2 and also known as COVID-19 disease (Lake 2020). Then, it has been seen that the number of cases has spread rapidly all over the world and it is today stated that the number of cases has exceeded 1.5 million (https://www.jhu.edu/). Various researches on SARS-CoV-2 have continued rapidly and are still ongoing. With various test parameters, scientists are trying to reveal how this new virus has affected people.

The enzymes of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are among the biochemical parameters, are among the most frequently used tests in all laboratories without exception. These two tests, which have been generally accepted among liver function tests for more than 30 years, have taken their places among the first biomarkers in the COVID-19 pandemic (Qian et al. 2020). We would like to discuss some information about ALT and AST, which are among the biochemical parameters in our study, also stated in the kit insert. ALT is an aminotransferase consisting of an enzyme group that catalyses the conversion of α-keto acids into amino acids in a reversible manner by transferring amino groups. Since the specific ALT activity in the liver is approximately 10 times higher than in the heart and skeletal muscle, high serum ALT activity is mainly accepted as an indicator of parenchymal liver disease. ALT is located in the cytosol of hepatocytes, and high serum levels indicate a disruption in the integrity of the hepatocyte plasma membrane. AST is indicated for the diagnosis, differentiation and monitoring of liver-biliary disease, myocardial infarction and skeletal muscle destruction. AST, which exhibits the highest activity in the liver and skeletal muscle, occurs in a wide variety of tissues, including liver, heart muscle, skeletal muscle, brain, kidneys, lungs, pancreas, erythrocytes and leukocytes (Schmidt and Schmidt 1984, Moss et al. 1987, Thomas 1998). Experiencing high levels of AST, increasing up to 20 to 50 times in virus-induced hepatitis and hepatic necrosis-related liver diseases, has also attracted attention in the studies conducted for COVID-19 (Mardani et al. 2020).

The spread of the SARS-CoV-2 virus into the human body and spread by droplet infection has increased the importance of researches conducted especially in the nasopharyngeal region. A study demonstrating that there is a relationship between the De Ritis ratio and non-metastatic nasopharyngeal carcinoma prognosis is considered interesting in this regard. In this study, the relationship between the De Ritis ratio and survival was examined. According to the findings of this study, the prognosis was worse in the patients with a high De Ritis ratio compared to patients with a low De Ritis ratio (Wu et al. 2019). Similar studies suggested that the rate of De Ritis could be an independent prognostic predictor for patients. The De Ritis ratio, which also means the evaluation of AST activity with ALT, was first defined by Fernando De Ritis in 1957 (Botros and Sikaris 2013). In proceeding days, De Ritis was recognised as the ratio between AST and ALT levels (AST/ALT) in the blood serum as a good indicator of liver damage. Studies revealed that rates of De

Ritis < 1.0 indicated moderate to severe liver damage, and rates higher than 1.0 indicated severe liver diseases. If the De Ritis ratio was slightly above 1 or 1.09, it was accepted as an indicator of the progression of cirrhosis due to chronic viral hepatitis (Williams and Hoofnagle 1988, Üstündag et al. 2000).

Creatine kinase (CK) and creatine kinase-MB isoenzyme (CK-MB) measurements are mainly used in the diagnosis and treatment of myocardial infarction and are also the most sensitive indicator of muscle damage. These were also the first test parameters for heart damage laboratory findings in COVID-19 patients (Mishra et al. 2020). In healthy individuals, total serum activity mainly contains creatine kinase-MM isoenzyme (CK-MM), other CK isoenzymes and variants are only found in trace amounts or cannot be detected. CK-MB is found at varied levels in the heart muscle and a very low level in the skeletal muscle. CK activity increases after myocardial destruction, with a noticeable increase in both CK-MM and CK-MB fractions (Stein 1998, Moss and Henderson 1999).

Lactate dehydrogenase (LDH), which is present in all cells of the human body and is invariably present only in the cell cytoplasm, has been one of the enzymes investigated in COVID-19. Zhou et al. (2020) examined the risk factors associated with disease progression in a group of patients infected with the new coronavirus. LDH was among their test parameters. Undoubtedly, the LDH concentration in the tissue is 500 times higher than that in plasma, which means that even minor damage is reflected in the serum. In addition to this feature that makes LDH important, it shows high levels of specific enzyme activities in the liver, heart muscle, skeletal muscle, kidneys and erythrocytes. Besides, the determination of serum LDH is a reliable method for measuring the level of haemolysis, which is an important factor in achieving the correct result in other test parameters.

In our study, patients who were diagnosed with COVID-19 disease were examined at the first admission to the hospital; AST, ALT, CK, CK-MB and LDH test values were examined in their serum. These five test parameters, consisting of the most frequently used tests in all laboratories, were specifically selected. It is aimed to contribute positively to the process by including the AST/ALT ratio in these test parameters at the present days when searching for practical, easy-to-use, reliable biomarkers related to COVID-19. Besides, the lack of a De Ritis ratio study in COVID-19 themed research adds a distinctive originality to our study.

Materials and methods

The study was carried out on patients with a definitive diagnosis between 15 March 2020 and 1 April 2020. COVID-19 diagnoses of the included patients were carried out with real-time polymerase chain reaction and computed tomography lung screening. Blood samples of all patients, whose age and gender were taken into consideration, were taken from the venous blood (first blood sample taken before drug treatment) by phlebotomists. Cooled centrifugation was performed in 5000 rpm for 10 min to obtain serum. All tests (ALT, AST, CK, CK-MB, LDH) were conducted in the biochemistry lab of Sakarya University Training and Research

Hospital, Turkey. The statistical evaluation was performed by calculating the De Ritis ratio as AST/ALT. The patients were examined in two groups as <1 and >1 according to De Ritis ratios. The device used in the study was Beckman Coulter AU5800 Clinical Chemistry Fully Automatic System (The Fastest AU Analyzer Ever. Serial Number: 2016022598. Tokyo, Japan). Ethical approval of the study was given by the Medical School Ethics Committee (Ethical Number: 050.01.04/161).

Statistics

Data were analysed using SPSS v(0).21 (IBM, Armonk, NY, USA). The data which were not normally distributed were transformed into log 10 scale, and then, the data determined to be normally distributed were analysed using an independent t test. The relationship between the data was obtained by the Pearson correlation method using log-converted data (Table 1).

Results

It was determined that the data did not show normal distribution in the Shapiro–Wilk test. According to the findings, the AST/ALT ratio (De Ritis) was found significantly higher in females ($p = .040$). Only ALT was high in male patients. Other parameters (AST, CK, CK-MB and LDH) were observed to be higher in females, but there were no statistical differences in these parameters (Table 2). No relation was found between the age and the parameters measured (Table 3). In the correlation analysis performed on the total data without any gender discrimination, it is seen that the De Ritis ratio has a positive correlation with CK in both genders. A positive correlation was found between CKMB and ALT, CK in total correlation findings. Also, LDH was found to be associated with ALT, AST, CK and CK MB (Tables 3 and 4). LDH was also associated with AST in female patients (Table 5). Figure 1 shows the De Ritis ratio for male and female patients.

Descriptive (raw) data of the groups according to gender were statistically significant. AST/ALT ratio was found significantly higher in women (Log$_{10}$ base). It was observed that only ALT was higher in men. In other parameters, it is observed that women's values are higher.

It was observed that the correlation between parameters in women was less than that of men. No relationship was detected between De Ritis ratio and other chemical parameters (except AST). A positive correlation was observed between LDH and AST.

Discussion

The SARS-CoV-2 outbreak is spreading rapidly worldwide. All clinicians are trying to find a new biomarker for SARS-CoV-2

Table 1. Performance characteristics of biochemical tests.

Parameters (U/L)	Linearity	Sensitivity	Precision (%CV)	Reference range
ALT	3–500	1 U/L	0.80	0–35
AST	3–1000 U/L	1 U/L	%CV 1.22	0–35
CK	10–2000 U/L	3 U/L	%CV 3.28	0–145
CK-MB	10–2000 U/L	5 U/L	%CV 0.90	0–24
LDH	50–3000 U/L	5 U/L	%CV 1.96	0–247

Table 2. Statistical findings of the measured parameters.

Parameter (U/L)	Gender	N	Mean	SEM	STDev	Min	Max	p (Log₁₀)
Age (Year)	Male	69	57.390	18.493	2.226	6	91	.799
	Female	23	54.300	15.131	3.155	21	79	
ALT	Male	69	154.480	226.257	27.238	51	1723	.714
	Female	23	123.610	86.634	18.065	51	393	
AST	Male	69	178.120	251.952	30.331	52	1791	.275
	Female	23	210.000	237.052	49.429	58	1151	
CK	Male	19	1793.160	2049.780	470.252	160	7939	.811
	Female	9	3894.330	6358.258	2119.419	180	16,542	
CK-MB	Male	19	78.905	73.428	16.846	26	316	.854
	Female	9	78.244	66.866	22.289	28	251	
LDH	Male	19	729.790	311.596	71.485	280	1599	.401
	Female	9	791.222	457.212	152.404	349	1767	
AST/ALT	Male	69	1.266	0.728	0.088	0.290	3.608	.040
	Female	23	1.629	0.898	0.187	0.697	3.938	

Table 3. Total correlation findings of measured parameters[a].

Parameters (U/L)	Age (Year)	ALT	AST	CK	CK-MB	LDH
ALT	−0.021					
	0.843					
	92					
AST	0.109	0.735				
	0.299	**0.001**				
	92	92				
CK	0.113	−0.268	0.032			
	0.372	0.168	0.872			
	64	28	28			
CK-MB	−0.003	0.375	0.351	0.362		
	0.979	**0.049**	0.067	**0.003**		
	64	28	28	64		
LDH	0.212	0.387	0.528	0.268	0.430	
	0.092	**0.042**	**0.004**	**0.032**	**0.00**	
	64	28	28	64	64	
AST/ALT	0.185	−0.179	0.535	0.532	0.008	0.325
	0.078	0.088	**0.001**	**0.004**	0.969	0.092
	92	92	92	28	28	28

Values written in bold in the table represent statistically significant correlations. In the total analysis without any gender discrimination, it is seen that the De Ritis ratio has a positive correlation with CK. Also, it was determined that the measured biochemical parameters were related to each other. No relation was found between the age and the parameters measured.
[a]The first line represents the values of *r*, the second line indicates the values of *p* and the third line indicates the number of patients in all correlation findings.

Table 4. Correlation findings detected in the male patients.

Parameters (U/L)	Age (Year)	ALT	AST	CK	CK-MB	LDH
ALT	−0.021	1				
	0.866					
	69	69				
AST	0.102	0.742				
	0.405	**0.001**				
	69	69				
CK	0.149	−0.078	0.201			
	0.323	0.751	0.408			
	46	19	19			
CK-MB	0.016	0.425	0.415	0.408		
	0.917	**0.07**	0.077	**0.005**		
	46	19	19	46		
LDH	0.161	0.329	0.468	0.382	0.519	
	0.284	0.17	**0.043**	**0.009**	**0.001**	
	46	19	19	46	46	
AST/ALT	0.175	−0.23	0.481	0.535	0.049	0.326
	0.15	0.057	**0.001**	**0.018**	0.842	0.173
	69	69	69	19	19	19

As determined in the total correlation, the De Ritis ratio in males has a positive correlation with CK. It was observed that LDH had a positive correlation with AST, CK, and CK-MB.
The Bold values represent statistically significant findings (<0.05).

Table 5. Correlation findings detected in the female patients.

Parameters (U/L)	Age (Year)	ALT	AST	CK	CK-MB	LDH
ALT	−0.027					
	0.901					
	23					
AST	0.166	0.766**				
	0.449	**0.001**				
	23	23				
CK	0.027	−0.63	−0.278			
	0.915	0.069	0.47			
	18	9	9			
CK-MB	−0.089	0.229	0.158	0.281		
	0.726	0.553	0.685	0.258		
	18	9	9	18		
LDH	0.433	0.517	0.672*	0.072	0.214	
	0.073	0.154	**0.047**	0.775	0.395	
	18	9	9	18	18	
AST/ALT	0.29	0.03	0.665**	0.551	−0.1	0.33
	0.18	0.893	**0.001**	0.124	0.798	0.386
	23	23	23	9	9	9

*=< 0.05; **=< 0.01.
The Bold values represent statistically significant findings (<0.05).

infection by conducting intensive research. Liver function tests, especially AST and ALT measurements, are undoubtedly the first tests that come to mind. On the other hand, despite the examination of these two test parameters, there is no study where AST activity is evaluated together with ALT, and the relationship between the De Ritis ratio and COVID-19 is examined together. This topic is specifically addressed in our study, because De Ritis ratio, which was first introduced by Fernando De Ritis in 1957, is still accepted as a good indicator of liver destruction (Botros and Sikaris 2013). On the other hand, research on the De Ritis ratio is of course not only limited to liver damage. There are also many studies conducted in different patient groups for the use of AST/ALT ratio as prognostics (Gorgel *et al.* 2017 , Ha *et al.* 2019, Ikeda *et al.* 2020).

In the study presented, De Ritis ratio of all patients with COVID-19 was higher than healthy individuals. Besides, this ratio was significantly higher in females than in male patients. In support of this finding, Mera *et al.* (2008) observed that females with different liver diseases (*n* = 154) had higher serum AST/ALT ratios than males, and this was

more apparent in hyperbilirubinemia patients. This made us think that De Ritis ratio may be an important prognostic factor in the new Coronavirus disease type. Of course, there is no definitive answer to this question yet. However, it seems that this question will be the subject of many

The Mean of De Ritis ratio (±SEM*)

P= 0.040
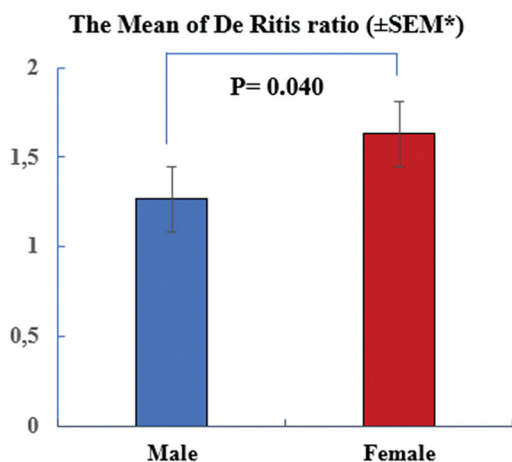
*: The standard error of the mean

Figure 1. ALT/AST (De Ritis ratio). The AST/ALT ratio is generally well below 1.0 and typically ranges from 0.5 to 0.7. However, it is seen that this ratio is above 1 in both patient groups. However, this rate was found to be significantly higher in women than in men.

studies, and biomarker studies with prognostic features will continue for COVID-19.

When the literature is analysed, it is seen that studies on liver enzymes are limited in this patient population, since the COVID-19 virus is new. Guan et al. (2020) investigated liver enzymes in patients with COVID-19 related pneumonia. According to their data, ALT and AST were abnormally higher in some patients with new coronavirus infections. In addition to the overactive inflammatory response due to COVID-19, this situation was interpreted as the possible mechanism of liver tissue damage due to the compensatory proliferation of hepatocytes derived from bile duct epithelial cells. However, contrary to these findings, Zhang et al. (2020) stated that although abnormalities in liver function indices are common in COVID-19 patients ($n = 115$), liver dysfunction was not seen as a prominent feature of COVID-19. However, Zhao et al. (2020) conducted a comparative study of COVID-19 pneumonia compared to other pneumonia. They reported that liver damage was more common in COVID-19 pneumonia. According to them, the evaluation of the LDH test parameter was one of the important markers for this disease. In our study, the LDH test parameter was examined in COVID-19 patients. According to our findings, LDH showed a positive correlation with other parameters in total correlation findings. These findings support the view that tests used in liver function are parameters that can be used in the evaluation of COVID-19 patients.

In our study, the AST/ALT ratio had a significant correlation with AST and CK ($p < .01$). However, CK-MB also had a positive correlation with ALT and CK. In a study, Han et al. (2020) found that CK-MB values were higher in venous blood of COVID-19 patients in China. At the end of their study, they stated that careful monitoring of myocardial enzyme profiles is of great importance in reducing complications and mortality in COVID-19 patients. Similarly, Mishra et al. (2020) studied COVID-19 patterns of heart damage and its relationship to outcome. In their retrospective study, the importance of evaluating the cardiovascular damage marker was emphasised.

One of these markers was shown as the CK-MB test parameter. In our study, CK-MB strengthened this knowledge for COVID-19 disease by showing a positive correlation with other biochemical test parameters.

Conclusion

The De Ritis ratio was examined for the first time in COVID-19 patients in the study. De Ritis ratio can be considered as a parameter possible to be a prognostic biomarker for females with COVID-19. But, the inability to obtain parameters such as morbidity, mortality, length of hospital stay, intubation or dialysis data shows the limitation of the study. Therefore, more research is needed to examine the relationship between De Ritis ratio and gender. Also, the uncertainty of other biomarkers of this disease, which has not yet been fully elucidated, reveals the fact that the validity of this conclusion in our study should also be supported by more extensive long-term research. Besides, according to other results revealed in our study, the AST, CK, CK-MB and LDH test parameters were higher in females and brought about the necessity to think more about the relationship between De Ritis and female gender.

Disclosure statement

The authors report no declarations of interest.

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