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Research Article

Correlation between De Ritis Ratio with Severity of Covid-19 Patients Severity

Hubungan antara Rasio *De Ritis* dengan Derajat Klinis Pasien Covid-19

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ABSTRACT

SARS COV-2 is the causative agent of the infectious disease Corona Virus Illness-19 (Covid-19). Covid-19 can cause damage to multiple organs, including the liver. The de Ritis ratio is a ratio between AST and ALT in blood serum, which may be a useful indicator for assessing liver damage in Covid-19 patients. The aim of this study is to determine the association between the severity of liver injury and an increase in the de Ritis ratio in Covid-19. The study population included patients with acute Covid-19 disease whose infection was validated using real-time PCR. A retrospective cross-sectional study was conducted. There were 1.983 subjects included, and 1.123 belonged to the moderate, 673 severe, and 181 to the critical groups. Calculations using Spearman rank revealed a strong significant association between De Ritis ratio and Covid-19 grade severity (rs=0.624, p<0.001). The more severe Covid-19, the higher de Ritis ratio values. The ROC curve of de Ritis ratio with Covid-19 severity shows AUC of 0.771 (P<0.001), sensitivity of 63.5%, specificity of 90.6%, PPV of 98.5% and an NPV of 20.02%. In conclusion, the severity of Covid-19 symptoms increases proportionally with the de Ritis ratio.

Keywords: *ALT, AST, Covid-19, De Ritis ratio*

ABSTRAK

Corona Virus Disease-19 (Covid-19) merupakan penyakit infeksi akibat *Severe Acute Respiratory Syndrome Corona Virus* 2 (SARS-CoV-2) yang diketahui menyebabkan manifestasi klinis multiorgan, teramsuk hepar. Nilai rasio De Ritis merupakan perbandingan kadar enzim AST/ALT yang berguna untuk menilai kerusakan hepar pada pasien Covid-19.Penelitian ini bertujuan untuk mengetahui hubungan antara derajat klinis gangguan fungsi hepar dengan peningkatan rasio *De Ritis* pada pasien infeksi Covid-19. Populasi penelitian adalah pasien Covid-19 rawat inap berdasarkan hasil pemeriksaan *Real Time*-PCR. Desain penelitian merupakan *cross sectional* retrospektif. Penelitian mendapatkan total 1983 subjek. Dengan 1123 Covid-19 derajat sedang, 673 Covid-19 derajat berat, dan 181 Covid-19 derajat kritis. Hasil perhitungan analisis *Spearman-rank* mendapatkan hubungan yang cukup kuat dan bermakna antara rasio *De Ritis* dengan klasifikasi derajat klinis Covid-19 (rs=0.624, p<0.001). Semakin berat derajat Covid-19 maka semakin tinggi rasio *De Ritis*. Kurva ROC rasio *De Ritis* terhadap derajat Covid-19 memiliki AUC 0,771 (P<0,001), sensitivitas 63,5%, spesifisitas 90,6%, PPV 98,5%, dan NPV 20,02%. Sebagai kesimpulan, terdapat hubungan yang cukup kuat bermakna antara rasio *De Ritis* dengan derajat Covid-19.

Kata Kunci: ALT, AST, Covid-19, rasio *De Ritis*

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INTRODUCTION

Coronavirus disease 2019 (Covid-19) is an emerging disease caused by severe acute respiratory syndrome coronavirus 2. (SARS-CoV-2). In January 2022, the World Health Organization (WHO) reported that there were 332,617,707 confirmed positive cases of Covid-19, with 5,551,314 deaths (CFR 1.7%) worldwide and up to 219 countries infected (1). The first case of Covid-19 in Indonesia was identified on March 2, 2020, and the number continues to rise sharply until the end of 2021. As of January 20, 2021, the Ministry of Health reported 4,275,528 confirmed cases of Covid-19, with 144,192 deaths (CFR 3.4%) spread across 34 provinces (2,3).

Transmission of Covid-19 can occur directly or indirectly through droplets, with an incubation period of 1–14 days. SARS-CoV-2 infection can cause a variety of clinical manifestations, ranging from mild to severe. SARS-CoV-2 infection can also lead to hepatocyte damage. The mechanism of hepatocyte injury in SARS-CoV-2 infection begins with the entry of SARS-CoV-2 into the hepatobiliary system via the ACE2 receptor on cholangiocyte endothelial cells and then replicates in hepatocytes and the biliary system, causing inflammation and resulting in damage to the liver and biliary system (4). Damage to the hepatocytes leads to an increase in the enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST). A study by Kukla et al. reported that liver damage occurs most often in severe cases of SARS-CoV-2 infection and has a poor prognosis (5,6).

The De Ritis Ratio (AST/ALT) is a comparison of AST and ALT values. Fernando De Ritis introduced the De Ritis ratio in 1957 (7,8). The De Ritis ratio is an effective indicator of liver disease (9,10). Hayrullah et al. found that a De Ritis ratio <1.0 indicates moderate to severe liver injury, while a De Ritis ratio > 1.0 indicates severe liver disease (5,11). The SARS-CoV2 virus causes severe liver damage by reaching the liver via the ACE2 receptor and then replicating in hepatocytes, leading to inflammation and liver destruction. Chen et al. hypothesized that an increase in the de ritis ratio correlates with a severe course of Covid-19 (12). However, few studies have been conducted on the relationship of De Ritis ratio in Covid-19 patients in Indonesia. The aim of this study is to find whether there is a relationship between the clinical severity of Covid-19 and an increase in the rate of de ritis ratio in the Dr. Hasan Sadikin Bandung General Hospital.

METHODS

The research was carried out in the Laboratory of Clinical Pathology of Dr. Hasan Sadikin General Hospital (RSHS) in Bandung. The aim of this retrospective cross-sectional analytical study is to find out whether there is an association between the severity of liver function problems in CoviD-19 patients and an increase in the De Ritis ratio in RSHS from January to December 2021. Data on the clinical grade of Covid-19 patients were obtained by tracing the medical records of patients with Covid-19 infection who attended RSHS from January to December 2021.

Medical records of individuals. who met the inclusion and exclusion criteria of this study were used. The inclusion criteria were adults >18 years old, Covid-19 patients with positive RT-PCR results whether moderate, severe, or critical degree according to the Indonesian Ministry of Health guideline (13) (Table 1), and have undergone AST and ALT testing at the time of or within 48 hours of enrolment. The exclusion of this study were incomplete data of patients' characteristics and AST and ALT resulst. Rank-Spearman statistical analysis was used to analyze the correlation between liver enzyme and De Ritis ratio for each of the Covid-19 severity groups. Specifically, the de Ritis ratio and Covid-19 severity were analyzed using the receiver operating characteristic (ROC) curve.

This study used a De Ritis ratio cutoff value based on previous research by Chen *et al.* (6). A de Ritis ratio >1.0 is classified as severe Covid-19.

Table 1. Severity of Covid-19 criteria

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Severity	Clinical Manifestation
Moderate	Clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) and no signs of severe pneumonia
Severe	With fever or under monitoring of respiratory infection, plus one of: respiratory rate >30 x/min, severe shortness of breath, or oxygen saturation (SpO2) <90% on room air.
Critical	**Onset:** new or worsening within a week. Chest imaging (CT scan of the chest or lung ultrasound): bilateral opioids, unexplained pleural effusion, lung collapse, lobular or nodular collapse. **Causes of edema:** Respiratory failure not due to cardiac failure or excess fluid. If no risk factors are found, an objective examination (e.g. echocardiography) is required to exclude that the cause of the edema is non-hydrostatic **ARDS criteria** - Mild ARDS: 200 mmHg <PaO2/FiO2 ≤ 300mmHg (with PEEP or continuous positive airway pressure (CPAP) ≥5cmH2O, or non-ventilated) - Moderate ARDS: 100mmhg <PaO2 / FiO 2 ≤200mmHg with PEEP ≥5cmH2, or non-ventilated; - Severe ARDs: PaO2/FiO2 <100 mmH g with PEep ≥5cmH2O, and not diventilated. If PaO2 is not available, SpO2/FiO2 ≤315 indicates ARDS (including non-ventilated patients)

RESULTS

In 2021, RSHS treated a total of 3259 Covid-19 patients, and up to 1983 subjects met the inclusion and exclusion criteria for this study. In total 56.8% of Covid-19 patients treated in 2021 were in moderate degree. Abnormal ALT and/or AST levels were detected in 22.7% and 51.3% of the total patients, respectively (Table 2).

Tabel 2. Research subject characteristics

Characteristics	Degree of Severity of Covid-19		
	Moderate	Severe	Critical
	Number (%)	Number (%)	Number (%)
Total	1123(56.8)	673(34)	181(9.2)
Gender:			
Male	559(28.3)	279(14.1)	77(3.9)
Female	564(28.5)	394(1.9)	104(5.3)
Age (year)			
18-25	121(6.1)	83(4.2)	36(1.8)
26-35	141(7.2)	88(4.5)	23(1.2)
36-45	207(10.5)	108(5.5)	22(1.1)

Tabel 2. Research subject characteristics

Characteristics	Degree of Severity of Covid-19		
	Moderate	Severe	Critical
	Number (%)	Number (%)	Number (%)
Age (year)			
46-55	259(13.1)	124(6.3)	24(1.2)
56-65	248(12.6)	142(7.2)	31(1.6)
>65	146(7.4)	127(6.4)	41(2.1)
ALT			
Normal	912(46.1)	504(25.5)	93(4.7)
Abnormal (>59)	211(10.7)	169(8.5)	88(4.5)
AST			
Normal	446(22.6)	407(20.6)	109(5.5)
Abnormal (>37)	677(34.2)	266(13.5)	72(3.6)

Statistical analyses using Spearman rank revealed a weak but significant association between both ALT and AST levels and the Covid-19 severity (rs =0.209, p<0.001, and rs =-0.232, p<0.001, respectively). The more severe the clinical course of Covid-19, the higher ALT, but lower AST values (Table 3). Spearman rank analyses also showed that that there is a fairly strong and significant relationship between the De Ritis ratio and the severity of Covid-19 degrees (rs =0.624, p<0.001). The more severe the clinical course of Covid-19, the higher the de Ritis ratio (Table 3). As the De Ritis Ratio equal to or greater than 1.0 classified as critical Covid-19, there were 17 (0.9%) cases identified in the present study (Table 4). Further analyses using the Receiver Operating Curve (ROC) between de Ritis ratio and Covid-19 severity showed that AUC was 0.771 (p<0.001), sensitivity value 63.5%, and specificity 90.6%, with. a positive predictive value (PPV) of 98.5% and a negative predictive value (NPV) of 20.2% (Figure 1).

Tabel 4. De Ritis ratio vs Covid-19 degrees

	Covid-19 degrees	
	Moderate-Severe (n)	Critical (n)
De Ritis Ratio <1,0	1141(57.7%)	17(0.9%)
De Ritis Ratio ≥1,0	655(33.1%)	164(8.3%)

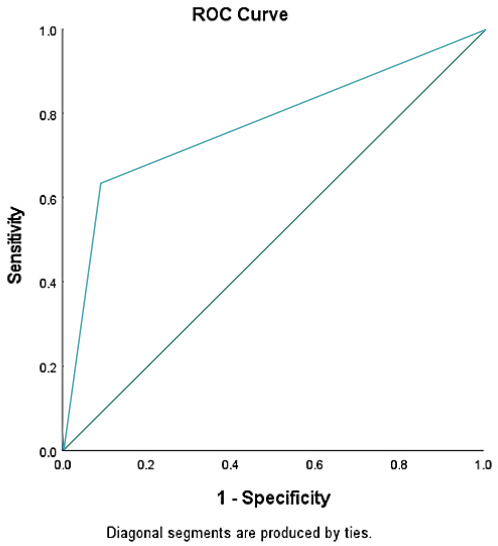

Figure 1. ROC curve

DISCUSSION

The results of this study revealed that both moderate and severe Covid-19 infections were found more on patients with age 46 yo or above (33.1% and 20%) than the younger ones (23.8% and 14.2%, respectively), whereas interestingly the critical patients were not so different among all age groups (Table 1). Immunosenescence which involve all cell types including those of adaptive and innate immune responses plays significant roles, at least in part, in susceptibility and severity of clinical manifestations of Covid-19 in the elderly (14).

The severity of Covid-19 will lead to an increase in de Ritis ratio. Our results support such a notion. Others also reports similar observation (6,15), and that De Ritis ratio was associated with Covid-19 severity and mortality rate (16). The more severe the Covid-19 disease, the more severe the degree of liver dysfunction in Covid-19 patients (6). Our results were in line with to those of Medetalibeyoglu *et al.,* that an AST/ALT ratio >1 was associated with worsening disease progression and may also increase Covid-19 mortality (15).

An increase in the De Ritis ratio occurs because the liver can be directly and indirectly damaged by the SARS-CoV-2 virus, causing an increase in transaminase enzymes. Also

Table 3. Relationship between Covid-19 severity and De Ritis ratio

Variabel (Median)	Covid-19 Degree			P Value	Coefficien r (95% CI)
	Moderate 1123 (56,8)	Severe 673 (34)	Critical 181 (9,2)		
ALT					
Median	31	36	59	<0.001	0.209
SD - Range	82.272(7-1516)	160.426(5-2129)	956.298(9-12306)		
AST					
Median	45	31	30	<0.001	-0.232
SD - Range	104.257(2-1662)	154.118(2-2783)	105.805(2-1036)		
De Ritis ratio					
Median	0.7273	0.2034	2.1786	<0.001	0.624
SD - Range	0.45919(0.04-6.63)	0.54474(0.19-5.13)	4.05728(0.43-52.59)		

known,SARS-CoV-2 infection can cause hepatocyte damage (17). The mechanism of hepatocyte damage in SARS-CoV-2 infection begins with the entry of SARS-CoV-2 into the hepatobiliary system via the ACE2 receptor on cholangiocyte endothelium cells and then replicates in hepatocytes and the biliary system, causing inflammation and resulting in damage to the liver and biliary system (17). Damage to hepatocyte cells will cause an increase in the enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST) (18). A study conducted by Kukla et al. reported that liver damage was most often found in severe SARS-CoV infections and carries a poor prognosis (5,6,19). An increase in the De Ritis ratio is related to the degree of Covid-19 and multiorgan failure, such as heart, skeletal muscle, kidney, and brain (4). This is also supported by the theory, which states that ALT is more concentrated in the liver while AST is found in organs other than the liver, such as heart muscle, lungs, and kidneys (20). As Covid-19 inflammation is systemic so the AST parameter as a hepar function marker may also indicate other or multi-organ failures. This is also demonstrated by the findings that the De Ritis ratio ≥1 is greater (8.3%) compared to the De Ritis ratio <1(0.9%) in the critical patient group (Table 4), approximately 9 fold liver enzyme abnormalities.

The results of ROC curve calculation give an AUC of De Ritis ratio of 0.771, indicating that De Ritis ratio has moderate diagnostic ability. In this study, the de ritis ratio had significance with a p value <0.000, a sensitivity value of 63.5%, a specificity of 90.6%, a positive predictive value (PPV) of 98.5% and a negative one Predictive value (NPV) of 20.2% compared to a study by Zinelu et al., which showed lower sensitivity and specificity values of 45% and 70% with an AUC value of 0.708 This shows that the De Ritis ratio has a better diagnostic value for liver injury in Covid-19 patients than the AST or ALT parameter alone, and the De Ritis ratio can be used as additional information for liver injury in Covid-19 patients. Thus, to conclude, this study showed that there is a strong and significant relationship between the de Ritis ratio and the degree of Covid-19 disease. The more severe Covid-19, the higher the de Ritis ratio.

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