



Increment de Ritis ratio as a marker factor for worsening Coronavirus disease 2019 patients

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ABSTRACT

Introduction: the coronavirus (Covid-19), identified as the betacoronavirus genus, not only appears in the respiratory tract but can also appear in other organs such as the liver. The ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) activity, known as the de Ritis ratio, can be used as a marker of liver dysfunction.

Objectives: the study aimed to evaluate the increment de Ritis ratio as a predictor of exacerbation of COVID-19.

Methods & Materials: This study was a retrospective cross-sectional study from April to November 2022. Ramelan Naval Hospital Center Surabaya, Dr Mohammad Soewandhie Surabaya Hospital, and Bhakti Rahayu Hospital Surabaya collected samples from 187 people with confirmed COVID-19.

Results: The median age of COVID-19 patients was 45.97 years, the length of hospital stay was 8,67 days, and the de Ritis ratio was 1,57. Spearman's test for increment de Ritis ratio with the length of hospitalization for COVID-10 patients with $r = 0.11$. Conversely, an increment of ratio de Ritis in discharge patients was found with $r = 0.52$.

Conclusion: Higher rates of de Ritis Ratio lead to longer hospital stays and higher mortality for COVID-19 patients.

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INTRODUCTION

Coronavirus disease (Covid-19) has been confirmed as a member of the Betacoronavirus genus. The majority of Covid-19 patients exhibit a range of clinical manifestations ranging from asymptomatic to mild, moderate, and potentially severe death. (Marjot *et al.*, 2021; Zinellu *et al.*, 2021) The primary clinical manifestations of Covid-19 are in the respiratory tract, starting with symptoms like fever, cough, and anosmia and ending with dyspnea. Covid-19 is not only present in the respiratory tract, but also in various organs such as the gastrointestinal tract, liver, and nervous system. (Machhi *et al.*, 2020)

Coronavirus infection infects humans via the angiotensin-converting enzyme 2 (ACE-2) receptor. This receptor is presented in type 2 alveolar cells and ACE-2 is expressed in the lung, heart, ileum, kidney, bladder, gastrointestinal tract, and liver. Liver involvement caused organ dysfunction and exacerbates Covid-19. Liver injury is characterized by slightly increment bilirubin levels. Transaminitis are common in critically ill patients. (Lippi *et al.*, 2020). The ratio of activity between aspartate aminotransferase (AST) and alanine aminotransferase (ALT), known as the de Ritis ratio, is considered one of the markers that characterize liver injury. A de

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Ritis Ratio >1 indicates severe liver damage. (Yazar, Kayacan dan Ozdin, 2020) The purpose of this study was to evaluate the increment de Ritis ratio as a worsening factor in Covid-19 patients, where the de Ritis ratio is easy to use and relatively inexpensive.

METHODS & MATERIALS

It was a cross-sectional study. This study was conducted from April 2022 to November 2022 in Ramelan Naval Hospital Center Surabaya, Dr. Mohammad Soewandhie Surabaya Hospital, and Bhakti Rahayu Hospital Surabaya. The patients recorded data from January 2020 to December 2021 including medical record number, patient identify, age, gender, AST,ALT confirmation of Covid-19 polymerase chain reaction (PCR) results, and length of hospitalization period was include. Patient morbidity and mortality. Covid-19 patient data were collected from a total of 3,385 patients and data were recruited, including 95 male and 92 female. This study received ethical approval from the hospital with ethical approval letter number: 45/EC/KEP/2022.

RESULT

The stational test used in data processing were the mean, standard deviation, Kolmogorov-Smirnov normality test, and Spearman’s test to assess the correlation coefficient.

Table 1. Table of characteristics of patients with Covid-19

Parameters	Mean ± SD
Age (year)	45.97±12.72
Length of Hospitalization (days)	8.67±5.20
AST (U/L)	151.33±107.55
ALT (U/L)	160.11±118.50
Ratio de Ritis	1.57±2.36

Based on Table 1, the average age of Covid-19 patients was 45.97 years with a length of hospitalization of 8.67 days with a de Ritis ratio of 1.57.

Data distribution analysis was performed using Kolmogorov-Smirnov normality tests to determine morbidity and mortality in Covid-19 patients, for a group of independent variables: length of hospitalization and discharge status of the patient (death, improvement, recovery). The results showed that the de Ritis ratio according to the length of hospitalization or discharge status of the patients was normally distributed.

Table 2. The Ratio de Ritis correlation analysis with length of hospitalization and discharge status

	Subject Group	Correlation coefficient (r)	Significance (p)
Ratio de Ritis	Length of hospitalization	0.110	0.134
	Discharge status of the patients	-0.521	0.001

Based on Table 2 Spearman’s results showed a positive correlation of $r=0.11$ between the increment in the de Ritis ratio and length of hospitalization in patients with Covid-19. Conversely, a negative correlation ($r=-0,521$; $p: 0.001$) was observed between the increment in the de Ritis ratio and the discharge status of the patient. The discharge status is divided into three parts: The

patient died, improved, and recovered. The lower the discharge status, the higher the mortality rate.

DISCUSSION

The Covid-19 pandemic has become a global health problem with enormous impact. Covid-19 is an RNA virus belonging to the betacoronavirus genus group. (Qin *et al.*, 2020) Covid-19 virus quickly infected the respiratory tract, leading to massive alveolar damage and respiratory failure. In addition to the clinical manifestations of the respiratory system, which is the main complaint of Covid-19, the gastrointestinal and hepatobiliary systems may also be affected. Hepatobiliary involvement in Covid-19 is often characterized by increment AST and ALT activity. (Anirvan *et al.*, 2020)

Elevated levels of AST, ALT, bilirubin, gamma-glutamyltransferase, and ALT activity are basic parameters to assess liver function. The liver is not the primary target organ of damage in Covid-19. However, alterations in organ function may indicate worsening symptoms in Covid-19. Liver involvement in Covid-19 occurs in a heterogeneity way. Covid-19 can penetrate the liver directly through the angiotensin-converting enzyme 2 (ACE-2) receptor. Expression levels of the ACE-2 gene differ throughout the body. The highest expression of ACE-2 was observed in the small intestine, terminal ileus, testis, kidney, myocardium, and thyroid. ACE expression was low in the liver and lungs. Choleduct cells within the bile ducts are the main emplacement of the highest concentration s of ACE-2 receptors. Viral replication in the hepatocyte cell area can directly damage this area through direct cytotoxic mechanism. Additionally, expression of the ACE-2 transmembrane serine protease 2 gene, which pairs with a basic amino acid-cleaving enzyme in cholangiocytes and hepatocytes, cause cytopathic effects. These condition cause cell lysis and induce necrosis and apoptosis as well as, the inflammatory processes of Covid-19, such as the cytokine storm. Hypoxic was associated with pneumonia will increase liver function. (Cichoż-Lach dan Michalak, 2021; Nardo *et al.*, 2021)

The damage various organs specifically skeletal and cardiac muscle can lead to raised AST activity of non-hepatic origin. High AST activity augments the AST clearance in liver sinusoids. However, high AST clearance activity was less detrimental to sinusoidal endothelial cells. Therefore, AST activity is elevated without increment ALT activity in patients proficiency a cytokine storm. (Fu *et al.*, 2022) Liver dysfunction can also be exacerbated by the treatment given to the patient, leading to drug-induced liver injury. (Zhao, Fan dan Wu, 2020; Pranata *et al.*, 2021) Various drugs were given as part of the treatment of patients with Covid-19 are also considered sophisticated factors for liver function. This is because many anthelmintics, anticoagulants, steroids, and herbal medicines used in patients with Covid-19 contribute to transaminitis. (Anirvan *et al.*, 2020; Yang, Zheng dan Fan, 2020)

Covid-19 affects people of all ages. The mean age of Covid-19 patients carried in the study was 45.97 years, and the majority were male. This is similar to the findings of Guan et al. At the beginning of the Covid-19 pandemic, the median age was 47 and the prevalence was predominantly male. (Guan *et al.*, 2019; Łykowska-Szuber *et al.*, 2021) Separately, mean AST and ALT reached a significant increment of 151.33 and 160.11. Drącz's study establish an increment of AST and ALT was significantly correlated with mortality in Covid-19 patients. (Drącz, 2022) Elevated levels of AST and ALT are routinely used to asses liver dysfunction. ALT is found in the cytosol of hepatocytes and AST is found in the cytoplasm and mitochondria. ALT is a more specific

biomarker than AST for liver dysfunction. This was because ALT activity in the liver is 10 times higher than that in the heart and skeletal muscle, and AST activity is found not only in the liver but also in various organs such as the heart, skeletal muscle, lung, kidney, brain, pancreas, leucocytes, and erythrocytes.(Pranata *et al.*, 2021)

The de Ritis ratio is a simple ratio used to determine the severity of the liver in fulminant hepatitis and fibrosis in viral hepatitis.(Fu *et al.*, 2022) The de Ritis ratio can also be used to determine the prognosis of Covid-19 patients. However, it is possible to determine the limits of the delicacy ratio. The mean in the de Ritis ratio determined in this study was 1.57, similar to that of several studies. It can be seen that the de Ritis ratio and length of hospitalization showed a positive correlation with a value of 0.11, signifying that the longer the length of hospitalization, the higher of de Ritis ratio. Conversely, The higher de Ritis ratio will be followed by the lower the patient's discharge. Implicit for elevated patients mortality and morbidity. Results of a meta-analysis by Pranata *et al.* stated that a 3-fold increase in the de Ritis ratio correlated with poor prognosis.(Pranata *et al.*, 2021) Research by Qin *et al* increased the ratio in the de Ritis ≥ 1.38 with an increment AST has a poor outcome in the treatment of patients with Covid-19. (Qin *et al.*, 2020) Zinnellu's research states that de Ritis ratio can be used as a prognostic of mortality in patients with Covid-19 who are treated with a cut-off value of 1.63. (Zinellu *et al.*, 2021)

CONCLUSION

Based on the result of the analysis and discussion above, the correlation between the increment in the de Ritis ratio and length of hospitalization in Covid-19 patients. Additionally, there is a negative correlation between the increment in the de Ritis ratio length of hospitalization. Therefore, the de Ritis ratio can be used as a marker of disease progression in covid-19 patients.

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