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CORRELATION OF NEUTROPHIL LYMPHOCYTE RATIO, ALANINE TRANSAMINASE, AND ASPARTATE TRANSAMINASE WITH DISEASE SEVERITY IN MILD-MODERATE AND SEVERE-CRITICAL CORONAVIRUS DISEASE-19 PATIENTS

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ABSTRACT:

The SARS-CoV-2 pandemic has a very high daily mortality rate. Rapid spread and worsening of clinical manifestations need early intervention. Systemic inflammation in COVID-19 can cause multi-organ damage, thus one of inflammation markers, Neutrophil Lymphocyte Ratio (NLR) can be used as an early predictive factor for COVID-19. Liver is one of the organs affected by COVID-19, which can be seen from increased Alanine Transaminase (ALT) and Aspartate Transaminase (AST). This study aims to analyze the correlation between NLR, ALT, and AST with disease severity of COVID-19 patients. Total of 50 patients with mild-moderate COVID-19 and 50 severe-critical patients, were taken by consecutive sampling from medical records of Primasatya Husada Citra Hospital Surabaya with cross sectional design. The spearman test analysis test on NLR, ALT, and AST with severity of COVID-19 patients, had a significant result, $p = 0.000$ ($p < 0.05$). The correlation coefficient of clinical severity of COVID-19 with NLR had strong correlation ($r=0.746$), and moderate correlation to ALT, and AST ($r=0.653$, $r=0.704$). Immune dysregulation due to COVID-19 triggers a cytokine storm and causes multi-organ damage. Liver damage will increase the release of liver enzymes. It can be concluded that NLR, ALT, and AST have a correlation with severity of COVID-19 patients.

Keywords: COVID-19, severity of illness, liver, alanine transaminase, aspartate aminotransferase, neutrophil-to-lymphocyte ratio.

Correlation of Neutrophil Lymphocyte Ratio, Alanine Transaminase, and Aspartate Transaminase with Disease Severity in Mild-Moderate and Severe-Critical Coronavirus Disease-19 Patients

INTRODUCTION

The World Health Organization (WHO) declared Coronavirus disease (COVID-19), which began with an outbreak in Wuhan, a global pandemic on March 11, 2020, with 118,319 confirmed cases globally on that day (Ma et al., 2020). Indonesia stated on March 10, 2021, that there were 1,398,578 cases in 510 districts throughout 34 provinces, with 5,663 new cases, and a total of 37,932 fatalities (175 new) (Organization, 2020).

SARS-CoV-2 is a ribonucleic acid (RNA) virus that plays a role in this disease; its protein can attach to the human angiotensin converting enzyme-2 (ACE-2) receptor. Because ACE-2 is expressed in practically all human organs, the virus might attack organs other than the lungs and causes multi-organ damage. This condition can affect the prognosis of the patient and increase his mortality (Devaux et al., 2020).

The liver is one organ that is thought to be failing. Increased readings of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) show that this failure has occurred. Patients with more severe clinical degrees had higher ALT and AST levels than patients with low clinical degrees, according to Sun et al (28.1 %, 39.4 % vs. 19.8 %, 18.2 %) (Sun et al., 2020).

COVID-19-induced increased inflammatory response adds to liver damage in addition to being mediated through the ACE-2 receptor. A cytokine storm is defined by an increase in pro-inflammatory cytokines, and these occurrences are common in patients with Acute Respiratory

Distress Syndrome (ARDS) or who are in severe-critical condition (Landecho et al., 2021). COVID-19 must be identified as soon as possible in order to maximize the recovery rate. The Neutrophil Lymphocyte Ratio (NLR), a measure of inflammation, has previously been demonstrated to be a prognostic factor in the early stages of COVID-19 (Selanno et al., 2021) ; (Liu et al., 2020). This study aims to examine the correlation between NLR, ALT, and AST with the disease severity of COVID-19 patients based on understanding of the relationship between COVID-19, inflammatory responses, and multiorgan damage.

RESEACRH METHOD

Study design and participants

This cross-sectional analytical study examined a group of confirmed COVID-19 patients who were admitted to the Primasatya Husada Citra Hospital (PHC) in Surabaya, Indonesia, between January and July 2021. This study employed 100 confirmed COVID-19 patients who were hospitalized and had laboratory findings in the form of NLR, ALT, and AST. Patients with a history of liver disease and suffering from Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) were not included in the study. This study divides clinical grades into mild-moderate, and severe-critical, each of which will need the analysis of 50 cases. COVID-19 Diagnosis the disease severity is classified using real-time polymerase chain reaction (RT-PCR) and the recommendations of the Ministry of Health of the Republic of Indonesia. The

following criteria characterize severe-critical clinical degrees: (1) respiratory distress with a rate of breath higher than 30x/min, (2) oxygen saturation less than 93 %, and (3) ARDS manifestation by aggravation (Kemenkes, 2011).

Data collection

Age, gender, disease severity characterized by clinical symptoms, discharge conditions, and test findings were all extracted from hospital medical records. The levels of neutrophils, lymphocytes, ALT, and AST are all included in the laboratory findings. The NLR value was calculated by dividing the total number of neutrophils by the total number of lymphocytes.

Statistical analysis

Numbers (n) and ages (%) are used to describe categorical variables, whereas mean and standard deviation are used to describe continuous variables (SD). This study employs the Spearman correlation test to examine the link between non-parametric variables, which is considered significant if the p value is less than 0.05. Software statistics product and service solutions (SPSS) version 25.0 was utilized for all statistical analysis tests. SPSS stands for Statistical Package for the Social Sciences; please check and include its manufacturer.

Ethical consideration

This study was approved by name of the IRB (reference 147/WM12/KEPK/MHSW/T/2021).

RESULTS AND DISCUSSION

Result

There was a substantial difference in the distribution of laboratory findings in research that included 100 hospitalized COVID-19 patients, 50 mild-moderate (50%) and 50 severe-critical (50%) patients, as shown in Table 1. The essential differences between mild-moderate and severe-critical symptoms are shown in Table 2. Patients over the age of 50 had the most severe-critical degrees, with as many as 30 patients (60 %), and patients of male sex had the most severe-critical degrees, with 31 (62 %) vs. 24 (48 %) and 46 (92 %) vs. 4 (8 %) patients died at mild to moderate. Table 3 shows the results of statistical test analysis between the relationship between NLR, ALT, and AST with the disease severity of COVID-19 patients using the Spearman correlation test. The table shows that NLR, ALT and AST had significant results and a positive correlation with the disease severity of disease ($p=0.000$). NLR had a strong correlation strength ($r=0.746$), while ALT and AST had a moderate correlation strength ($r=0.653$) vs ($r=0.704$).

Correlation of Neutrophil Lymphocyte Ratio, Alanine Transaminase, and Aspartate Transaminase with Disease Severity in Mild-Moderate and Severe-Critical Coronavirus Disease-19 Patients

Table 1
Laboratory Results For COVID-19 Sufferers are Based On Clinical Grade

Variable	n	Mean (± SD)
Mild-Moderate		
Neutrophil Lymphocyte Ratio	50	2,71 (± 1,51)
Alanine Transaminase	50	33,7 (± 16,29)
Aspartate Transaminase	50	33,16 (± 13,14)
Severe-Critical		
Neutrophil Lymphocyte Ratio	50	9,75 (± 7,74)
Alanine Transaminase	50	83,62 (± 64,63)
Aspartate Transaminase	50	89,40 (± 63,38)

Table 2
Distribution Of COVID-19 Sufferers Based On Age, Gender and Clinical Outcomes

Variable	Frequency (n)		Percentage (%)	
	Mild-Moderate	Severe-Critical	Mild-Moderate	Severe-Critical
Age (years)				
21-30	5	1	10%	2%
31-40	8	7	16%	14%
41-50	9	12	18%	24%
51-60	16	15	32%	30%
>60	12	15	24%	30%
Gender				
Male	24	31	48%	62%
Female	26	19	52%	38%
Clinical Outcomes				
Survive	46	4	92%	8%
Died	4	46	8%	92%

Table 3
Relationship Of NLR, ALT, And AST With Clinical Grade

	Variable		Disease Severity
Neutrophil Lymphocyte Ratio	Correlation	Coefficient	0,746
	(r)		0,000
	Significance (p)		100
	N		
Alanine Transaminase	Correlation	Coefficient	0,653
	(r)		0,00
	Significance (p)		100
	N		
Aspartate Transaminase	Correlation	Coefficient	0,704
	(r)		0,000
	Significance (p)		100
	N		

Discussion

The fundamental features of respondents, the results of the analysis of the link between NLR and disease severity, and the findings of the analysis of the relationship between ALT and AST with disease severity will all be discussed in this section. Mild-moderate patients (32 %) predominate in the 51-60 years old age group, whereas severe-critical patients predominate in the above 50 years old age group (60 %). These findings are consistent with early study at Germany (Benedikt et al., 2021).

This finding is supported by the theory from Liu et al, that the occurrence of decreased immunity and the severity of comorbidities tends to be at an older age or aged over 50 years so that older people are more susceptible to clinical deterioration (Liu et al., 2020). This study found that

gender was the most affected by COVID-19 were male (55% vs. 45%), and tended to be more clinically severe (62%). These results are supported by research conducted by Li X et al, that men are more susceptible to COVID-19 infection and experience worsening of symptoms because men have higher levels of ACE-2 receptors than women (Li et al., 2020).

Clinical outcomes of patients with COVID-19 in this study had a poor outcome or poor prognosis at the severe-critical grade compared to the mild-moderate grade. A total of 46 (92%) severe-critical patients died and 4 (8%) in the mild-moderate degree. This study is consistent with research by Li X et al. According to this study, patients with male sex, having an older age, having cardiovascular comorbidities and diabetes, and having an increase in leukocytes tend to experience more severe clinical symptoms

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Correlation of Neutrophil Lymphocyte Ratio, Alanine Transaminase, and Aspartate Transaminase with Disease Severity in Mild-Moderate and Severe-Critical Coronavirus Disease-19 Patients

and have a higher mortality rate (Li et al., 2020).

The correlation between NLR and disease severity was shown to have a good correlation ($p = 0.000$, $r = 0.746$) in the findings of the investigation. This is in line with the findings of Qin et al. and Yang et al (Yang et al., 2020). An increased inflammatory response is the cause of ARDS symptoms in patients with a severe-critical clinical grade. This notion is based on the body's defensive mechanism, which involves neutrophils and macrophages releasing interleukin-6 (IL-6) while phagocytosing viral antigens. Viral proteins generate a rush of proinflammatory cytokines and chemokines in the lung tissue, resulting in multi-organ damage and death (Susilo et al., 2020).

Lymphopenia is caused by systemic inflammation that lowers cellular immunity, activation of genes that drive lymphocyte death, and the nature of SARS-CoV-2, which can directly assault the progenitors in the marrow, producing hematopoietic system abnormalities (Yang et al., 2020). According to the findings of the correlation test between liver enzyme parameters and clinical grade, ALT and AST exhibited a significant connection with clinical grade ($p=0.000$) and a moderate correlation strength ($r=0.653$ versus $r=0.704$). These findings are consistent with those previous studies. ($p 0.001$) (Ali & Hossain, 2020), (Sun et al., 2020), (Zhang et al., 2020).

The results of this investigation support the idea that the ACE-2 receptor mediates a direct viral pathogenic action infecting liver cells and bile ducts. SARS-CoV-

2 causes apoptosis in hepatocyte cells. Excessive inflammatory reactions induced by COVID-19, also known as cytokine storms, may harm several organs, one of which is the liver, and COVID-19 problems can cause hypoxia and ischemia in the hepatic circulation, as well as hepatocyte cell destruction (Lei et al., 2020).

CONCLUSION

We concluded that there is a significant correlation between NLR, ALT, and AST with the disease severity of COVID-19 patients, based on the values of NLR, ALT, and AST in the severe-critically symptoms have a higher number than those with mild-moderate indicating. Viral activity, immune dysregulation, and ischemia that occur due to COVID-19 can affect the NLR value and disease severity of the patient, as well as being a factor in the occurrence of multi-organ damage. The study's weaknesses were that it was cross-sectional and relied on medical record data, so some cases didn't have a comprehensive disease history and there were just a few samples.

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