The Correlation Between Aminotransferase Enzyme Leves, Neutrophil-to-Lymphocyte Ratio, Absolute Lymphocyte Count and the Severity of COVID-19

by Budi Santosa

ORIGINAL ARTICLE

The Correlation Between Aminotransferase Enzyme Levels, Neutrophil-to-Lymphocyte Ratio, Absolute Lymphocyte Count and the Severity of COVID-19

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Abstract

Background/Aim: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) are indicators that are widely used as a determinant of the prognosis of patients with viral pneumonia. Thus, the study aim was to prove the correlation between AST/ALT, NLR and ALC levels with the severity of COVID-19.
Methods: The research method was carried out by collecting medical record data of positive COVID-19 patients who were hospitalised at the Indramayu Hospital in the period September 2020 - January 2021.
Results: The results showed normal AST levels in 63 and elevated AST levels in 57 patients. Normal and elevated ALT levels were in 68 and 52 patients, respectively. The normal NLR was in 102 patients and the high NLR was in 18 patients. The low and normal ALC was in 19 and 101 patients, respectively. AST levels correlated with the severity of COVID-19 (p = 0.045). Other parameters were without statistical significance (p > 0.05).
Conclusion: AST enzyme levels had a weak positive correlation with the severity of COVID-19. On the other hand, ALT, NLR and ALC had not correlated with the severity of COVID-19.

Key words: The severity of COVID-19; Aspartate aminotransferase; Lymphocytes, Neutrophils.

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Introduction

Coronavirus Disease 2019 (COVID-19) is a new infectious disease caused by SARS-CoV-2. In December 2019, a case of pneumonia of unknown origin was first identified in Wuhan, China's Hubei Province and then quickly spread throughout the country.[1,2] Stage I (mild-mild) – early infection - the initial stage occurs at the time of inoculation and early disease formation. For most people, this involves an incubation period associated with mild and often specific symptoms such as malaise, fever and dry cough.[3] Stage II (moderate-moderate) – during this stage, the patient has a cough, fever and hypoxia (PaO_2/FiO_2 < 300 mmHg).[2,4] Blood tests show increased lymphopenia (< 1500 cells/L). Stage III (severe–severe) – some COVID-19 patients will progress to this stage which is the most severe stage of all stages manifesting as an extrapulmonary systemic hyper-inflammatory syndrome. At this stage, markers of systemic inflammation appear elevated.[3]

Liver dysfunction is common in hospitalised COVID-19 patients. The expression by bile

274

Al Sas et al. Scr Med 2023 Sep;54(3):273-7.

cells is much higher than by liver cells. This suggests that COVID-19 is more associated with bile duct damage than the liver.[5] Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is reported in 16-53 % of COVID-19 patients. Elevated ALT/AST levels in COVID-19 patients may also be due to drug hepatotoxicity, cytokine storm and/or associated hypoxic pneumonia.[6] The impact of SARS-CoV-2 infection in patients with a history of chronic liver disease, such as hepatitis B and/or C virus infection is still unknown. It is also currently unclear whether SARS-CoV-2 infection induces cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis or with a history of cirrhosis.[7] The mortality rate in COVID-19 patients hospitalised is still very high, elevated levels of the transaminase enzyme are one of the risk factors that are significantly associated with death.[8] The higher AST level might correlated with the risk of death.[9]

In addition, the neutrophil-to-lymphocyte ratio (NLR) is an indicator of the presence of a systemic inflammatory response that is widely used as a determinant of the prognosis of patients with viral pneumonia.[10, 11] The human immune response generated by the virus is mainly dependent on lymphocytes, where systemic inflammation significantly suppresses cellular immunity and decreases the number of CD4^{+} T lymphocytes and increases the suppressor CD8^{+} T lymphocytes. Therefore, virally induced inflammation increases the NLR and triggers the progression of COVID-19.[12, 13] An increase in NLR may reflect an increased inflammatory process and is associated with a poor prognosis. Therefore, it can be considered as an independent biomarker in indicating a poor prognosis.[14]

Moreover, absolute lymphocyte count (ALC) is one of the routine haematological examinations in COVID-19 patients. Lymphocytes are an important source of immunoglobulins in the body's humoral immune response.[15] Lymphocytes also have a role as cells that can fight infections caused by viruses or bacteria. It was reported that lymphopenia, defined as ALC < 1500 cells/L, occurring in COVID-19 correlated with increased disease severity.[14, 16] Lymphopenia is a common systemic manifestation in many patients with viral diseases, such as the acute respiratory distress coronavirus syndrome (SARS-CoV), the Middle East coronavirus syndrome (MERS-CoV) and the COVID-19.[2, 17] SARS-CoV-2 has been demonstrated to cause lymphopenia.[11, 18]

Patients with severe COVID-19 symptoms should have laboratory parameters checked for hyperinflammatory markers to reduce mortality rates. Routine haematological examinations and leukocyte counts in patients with COVID-19 can be important supporting data for medication consideration.[19] AST/ALT, NLR and ALC are common assessment with affordable costs and relatively fast processing time in the hospital for COVID-19 patients. The purpose of this study was to analyse the correlation between AST/ALT, NLR and ALC with the severity of COVID-19.

Methods

Study design

A cross-sectional study approach was used to determine the correlation between the independent variables AST/ALT, NLR and ALC with the severity of COVID-19. The research site was at the Indramayu Hospital, Indonesia. The time starts from December 2021 to January 2022.

This study began by taking and collecting research subjects which were data on all medical records of positive COVID-19 patients who were hospitalised at the Indramayu Hospital in the period September 2020 to January 2021. The data taken included data: age, sex, body temperature, state of consciousness, positive PCR examination results, results of aminotransferase enzyme levels (AST and ALT), neutrophil values and absolute lymphocyte counts. Patients with complete data were recruited as respondents of the study. Data obtained were analysed using the IBM SPSS Version 24. The results of this study were described by presenting descriptive analysis and bivariate analysis, namely the Spearman's test.

Ethical consideration

This study was approved by Health Research Ethics Committee Swadaya Gunung Jati, Cirebon, Indonesia (No 79/EC/FKUGJ/XI/2021).

Results

The research was conducted on the relationship between AST/ALT, NLR and ALC with the severity of COVID-19 (Table 1).

■ Al Sas et al. Scr Med 2023 Sep;54(3):273-7.

275

Table 1: *Aspartate aminotransferase (AST), alanine aminotrans-ferase (ALT), neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) related to severity of COVID-19*

Variables	Severity of COVID-19			
	Moderate		Severe	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
AST	34.0 ± 15.7	12.00 - 94.00	34.0 ± 15.7	12.00 - 94.00
ALT	32.9 ± 16.8	6.00 - 93.00	32.9 ± 16.8	6.00 - 93.00
NLR	2.2 ± 1.6	0.12 - 10.50	2.2 ± 1.6	0.12 - 10.50
ALC	2676 ± 1897	830 - 19320	2676 ± 1897	830 - 19320

Characteristics of patients related to severity of COVID-19 is presented in Table 2.

Table 2: *Characteristics of the COVID-19 patients*

Characteristics	COVID-19 [n (%)]		
	Total (n = 120)	Moderate (n = 108)	Severe (n = 12)
Age (year)			
30 - 40	24 (20.0)	23 (21.3)	1 (8.3)
41 - 60	82 (68.3)	74 (68.5)	8 (66.7)
> 60	14 (11.7)	11 (10.2)	3 (25.0)
Gender			
Male	63 (50.8)	54 (50.0)	9 (75.0)
Female	57 (49.2)	54 (50.0)	3 (25.0)
Body temperature			
Fever	120 (100.0)	108 (100.0)	12 (100.0)
No fever	0 (0.0)	0 (0.0)	0 (0.0)
Consciousness			
Conscious	115 (95.8)	108 (100.0)	7 (58.3)
Unconscious/decrease	5 (4.2)	0 (0.0)	5 (41.7)
Comorbidities			
No	106 (88.4)	98 (91.0)	8 (66.7)
Diabetes mellitus	10 (8.3)	8 (7.4)	2 (16.6)
Hypertension	4 (3.3)	2 (1.6)	2 (16.7)
AST (U/L)			
Normal	63 (52.5)	60 (55.6)	3 (25.0)
High	57 (47.5)	48 (44.4)	9 (75.0)
ALT (U/L)			
Normal	68 (56.7)	63 (58.3)	5 (41.7)
High	52 (43.3)	45 (41.7)	7 (58.3)
NLR (%)			
Normal	102 (85)	92 (85.2)	10 (83.3)
High	18 (15)	16 (14.8)	2 (16.7)
ALC (cell/µL)			
Low	19 (15.8)	16 (14.8)	3 (25.0)
Normal	101 (84.2)	92 (85.2)	9 (75.0)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; NLR: Neutro-phil-to-lympocyte ratio; ALC: Absolute lymphocyte count;

There were slightly more male patients (50.8 %), the majority (68.3 %) were 41-60 years old, all had a fever, 95.8 % were conscious, without comorbidities were 88.4 %. Approximately half of patients had normal AST (52.5 %) and ALT levels (56.7 %), the normal NLR levels had 85.0 % and normal ALC levels had 84.2 % of patients.

Bivariate analysis was intended to determine the relationship between each independent and dependent variable (Table 3).

Table 3: *The relationship between aspartate aminotransferase (AST), alanine aminotransferase (ALT), neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) and the severity of COVID-19*

Variables	p	r
Aspartate aminotransferase (AST)	0.045	0.184
Alanine aminotransferase (ALT)	0.273	0.101
Neutrophil-to-lympocyte ratio (NLR)	0.866	0.016
Absolute lymphocyte count (ALC)	0.343	- 0.087

Spearman test;

A bivariate test using Spearman's test indicated that there was a weak positive correlation between AST levels and the severity of COVID-19 (p = 0.045 and r = 0.184). Other parameters were without statistical significance.

Discussion

Most of patients in this study was 41-60 years. The age factor is closely related to COVID-19 because elderly patients have a degenerative process of anatomy and physiology of the body and the body's immunity decreases so they are vulnerable to COVID-19 infection. The number of male COVID-19 patients is more than female. This is because there are fundamental differences in the immunological systems of men and women, differences in lifestyle and smoking prevalence.[20,21] Men experience more severe conditions to death than women. Higher severity is associated with higher comorbidities in men, eg hypertension and diabetes mellitus.[22] All of the COVID-19 patients in this study had a fever with a body temperature of 38.1 – 39 °C.[23, 24]

A bivariate test using Spearman's test indicated that there was a weak positive correlation between AST levels and the severity of COVID-19 (p = 0.045 and r = 0.184). Other parameters were without statistical significance. Elevated AST enzymes indicate liver damage or liver injury caused by several factors.[22] In a recent study, it was found that cholangiocytes can specifically express ACE-2, whereas ACE-2 expression in hepatocytes was 20-fold lower than the level of cholangiocyte expression. The ACE-2 expression pattern revealed that SARS-CoV-2 can directly

infect multifunctional cholangiocytes and play an important role in liver regeneration and immune response.[4, 12] This suggests that viral immunological injury plays a role in liver injury in COVID-19.[25]

The results of statistical tests showed that there is no correlation between ALT enzyme and the severity of COVID-19 with a p-value of 0.273. COVID-19 patients experienced severe symptoms as ALT levels increased and were not significant in statistical testing. An increase in ALT levels is high enough to cause chronic liver disease conditions.[22] Improved liver function was more common in men and in severe cases of COVID-19.[5, 26] This statement is not relevant to the study which stated that more than a third of patients hospitalised with COVID-19 infection had an abnormal liver function and were hospitalised for longer with severity in hospital.[5]

There was no correlation between the number of NLRs and the severity of COVID-19. COVID-19 patients experienced severe symptoms as NLR values increased but were not statistically significant in the test. An increased of NLR value indicates the presence of neutrophilia or immune system disorders.[27] Other researchers found that there was an increase in the NLR value in 191 ICU and non-ICU inpatients.[28] This is because SARS-CoV-2 infection is not only limited to the respiratory tract, but can affect other organ systems such as cardiovascular, renal, gastrointestinal and haematopoietic system.[5] Elderly patients, with obesity, having chronic comorbidities such as diabetes, hypertension, chronic lung disease have a worse prognosis.[29] In statistical test data for ALC, there was no correlation with the severity of the disease (p = 0.343). A low of ALC value indicates the presence of lymphopenia.[2, 4] Lymphocytes also have a role as cells that can fight infections caused by viruses or bacteria.[30] It was reported that lymphopenia, defined ALC < 1500 cells/µL, occurring in COVID-19 correlated with an increase in disease severity.[14, 30]

Conclusion

AST enzyme levels had a weak positive correlation with the severity of COVID-19. On the other hand, ALT enzyme levels, NLR and ALC have not correlated with the severity of COVID-19. Suggestions for further research is to pay more attention to the impact of liver disease due to hepatotoxic drugs should be controlled again. It is necessary to measure the examination of proinflammatory cytokines such as TNF- examination, IL-1 examination and IL-6 examination. It is necessary to carry out other examinations related to the severity of COVID-19 such as blood gas analysis.

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Conflict of interest

None.

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277

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