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# THE RELATIONSHIP BETWEEN ASPARTATE AMINOTRANSFERASE (AST) AND ALANINE AMINOTRANSFERASE (ALT) WITH DISEASE SEVERITY IN COVID-19 INPATIENTS AT UDAYANA UNIVERSITY HOSPITAL FROM JANUARY 2020 TO DECEMBER 2021

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## **ABSTRACT**

The COVID-19 pandemic had a significant impact on global health. In addition to its high transmission rate, the clinical presentation of the disease varied, ranging from asymptomatic to critical cases. Previous studies found differences in laboratory results between critical and non-critical patients. One of these laboratory results was Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT). However, the relationship between AST and ALT with the disease severity in COVID-19 patients remained unclear. This study aimed to determine the relationship between AST and ALT with the disease severity in COVID-19 patients at Udayana University Hospital. This study used a cross-sectional approach involving 126 COVID-19 patients who were hospitalized at Udayana University Hospital. Data were collected through consecutive sampling from the medical records of COVID-19 patients from January 2020 to December 2021. Among the 126 COVID-19 patients studied, 64 were critical patients and 62 were non-critical patients. The median (min-max) age of critical patients was 59.5 years (18-76), while non-critical patients had a median age of 45.5 years (20-70). Laboratory data showed that 90.6% of critical COVID-19 patients had elevated AST levels and 64.1% had elevated ALT levels. The results of multivariate logistic regression analysis indicated a significant relationship between AST (PR: 3.929, 95% CI: 1.177-13.117) and ALT (PR: 2.881, 95% CI: 1.053-7.883) levels with the disease severity in COVID-19 patients. There was a significant relationship between AST and ALT levels with disease severity in COVID-19 patients at Udayana University Hospital.

**Keywords:** ALT level, AST level, COVID-19

# INTRODUCTION

Coronavirus was a non-segmented RNA virus from the Coronaviridae family. It usually infected humans and other mammals. Generally, coronavirus infections were mild, but this was not the case for Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). These two betacoronavirus infected over 10.000 people, with mortality rates of 10% and 37%. <sup>1</sup>

In December 2019, a pneumonia outbreak occurred in Wuhan, Hubei, China.<sup>2</sup> Analysis showed the presence of 2019 Novel Coronavirus (2019-nCoV). Within months, the virus spread to Thailand, Japan, and Korea.<sup>3</sup> In March 2020, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) as pandemic.<sup>4</sup>

The COVID-19 pandemic had a significant impact on global health. The disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) had a Case Fatality Rate (CFR) of 0,91%, which was lower than SARS-CoV and MERS-CoV.<sup>5</sup> However, the transmission rate of COVID-19 was

much higher than SARS-CoV.<sup>6</sup> As of November 3, 2024, there were 776.798.873 COVID-19 cases, with 7.074.400 deaths. In Indonesia, by November 16, 2024, there were 6.830.113 confirmed cases, with 162.066 deaths.<sup>5</sup>

Acute Respiratory Distress Syndrome (ARDS) was associated with high mortality among COVID-19 patients. This condition was closely related to hypoxia, mechanical ventilation, and vasoconstrictor therapy for hemodynamic instability. However, mortality in COVID-19 patients was also caused by extrapulmonary abnormalities such as myocardial dysfunction, arrhythmias, acute coronary syndrome, liver dysfunction, acute kidney injury, hyperglycemia, ketosis, and skin complications.

Liver test abnormalities were commonly found in COVID-19 patients. They were considered to have liver test abnormalities when there was an increase in several parameters, such as AST >30/34 U/L, ALT >36/44 U/L, Alkaline Phosphatase (ALP) >104/129 U/L,  $\gamma$ -glutamyl Transferase (GGT) >39/66 U/L, or total bilirubin >1,00 mg/dL. Research showed that 50,3% of patients had liver test abnormalities with 41,5% elevated of AST and ALT levels. Elevated of AST and ALT associated with

disease severity.<sup>9</sup> This was supported by other studies that found elevated of AST and ALT levels in 18,2% and 19,8% of mild COVID-19 patients with 39,4% and 28,1% in severe patients.<sup>10</sup> Additionally, the mortality rate was also related to elevated of AST levels.<sup>11</sup>

Since May 5, 2023, the WHO had lifted the status of COVID-19 as a Public Health Emergency of International Concern (PHEIC). August 4, 2023, Kementerian Kesehatan declared the end of the pandemic in Indonesia. However, data from the Ministry of Health showed that there was still a growth in COVID-19 cases through week 46 of 2024. The end of the pandemic did not completely eliminate COVID-19 cases. Understanding of COVID-19 remained necessary, especially in predicting disease severity. This study aimed to investigate the relationship between AST and ALT levels with disease severity in COVID-19 patients at Udayana University Hospital.

# RELATIONSHIP BETWEEN AST AND ALT LEVELS WITH DISEASE SEVERITY IN COVID-19 PATIENTS

In the liver, AST and ALT were found in hepatocyte cells, with AST concentrated in the cytoplasm and ALT in the cytosol. Elevations of AST and ALT occurred in response to events that caused hepatocyte membrane disruption or necrosis. When released from hepatocytes, AST and ALT entered the plasma, and rose within 1-2 hours. The level of increase in AST and ALT was proportional to the number of hepatocytes that were damaged. <sup>13</sup>

Initial observations indicated that SARS-CoV-2 infection was associated with elevated AST and ALT levels. This mechanism occurred through the cytopathic effects of the virus on hepatocytes. Additionally, SARS-CoV-2 infection reduced the expression of mRNA for tight junction cholangiocytes, leading to impaired hepatocyte protection from toxic bile components. Further studies found that hyperactivation of the immune response, drug toxicity, hypoxia, and preexisting liver disease in COVID-19 patients were also associated with hepatocyte damage. Associated with hepatocyte damage.

During the infection process, proinflammatory molecules such as cytokines and chemokines were released. <sup>16</sup> In some cases, excessive production of these inflammatory molecules triggered a cytokine storm and caused multiorgan damage. <sup>14</sup> Laboratory results in COVID-19 patients showed increased levels of eosinophils, immunoglobulin E, IL-5, IL-6, and IL-13. <sup>17</sup> Under normal conditions, IL-6 was involved in liver regeneration and hepatoprotective effects. However, excessive production of IL-6 could disrupt this regenerative process and cause hepatocyte damage. <sup>18</sup> Additionally, patient management could also impact liver function. A study showed that three out of 12 COVID-19 patients treated with remdesivir experienced elevated AST and ALT. <sup>19</sup>

Elevated AST and ALT were associated with disease severity. This was supported by other studies that found elevated of AST and ALT levels in 18,2% and 19,8% of mild COVID-19 patients with 39,4% and 28,1% in severe patients. 10

The severity of COVID-19 varied across different stages, ranging from asymptomatic to critical. The first stage was

asymptomatic, where patients did not exhibit clinical symptoms. Patients with symptoms but no evidence of viral pneumonia or hypoxia and  $\mathrm{SpO_2}$  >95%, were classified as mild. Patients with pneumonia symptoms and  $\mathrm{SpO_2}$  93–95%, were categorized as moderate disease. Severe disease was characterized by pneumonia with respiratory rates >30 breaths per minute or severe respiratory distress. In this stage, the oxygen saturation was <93%. The critical stage was marked by ARDS, sepsis, and septic shock. ARDS in critical COVID-19 patients was associated with hepatocellular hypoxia. Turthermore, the use of mechanical ventilation in critical patients could increase intra-abdominal pressure and impairing hepatic blood flow.

# MATERIALS AND METHOD

This study used a cross-sectional approach with 126 COVID-19 patients who were hospitalized at Udayana University Hospital between January 2020 to December 2021. Data were collected from medical records, which were obtained using consecutive sampling and had received approval from Ethics Commission of the Faculty of Medicine, Udayana University No: 0113/UN14.2.2.VII.14/LT/2024.

Sample size calculation was carried out using a sample size formula for analytical research with a cross-sectional approach. The  $\alpha$  and  $Z\alpha$  values were 0,05 and 1,96. Meanwhile, the prevalence in the population, difference of clinical proportion, and q values were 0,415, 0,1, and 0,585. The minimum sample size was 93,26, which was rounded up to 94 samples.

COVID-19 diagnosis was made through nasopharyngeal/oropharyngeal swab using the RT-PCR method. Both male and female of COVID-19 patients included in this study were at least 18 years old. Patients whose medical records were incomplete or missing, those who had not undergone liver function tests upon hospital admission, or those with pre-existing liver diseases were excluded from this study. These conditions included hepatitis, cirrhosis, Alcoholic Fatty Liver Disease (AFLD), Non-alcoholic Fatty Liver Disease (NAFLD), and Hepatocellular Carcinoma (HCC).

This study used AST and ALT levels as independent variables and disease severity as dependent variables. Covariates in this study included age, sex, hypertension, diabetes, heart disease, and obesity.

AST and ALT levels were recorded and grouped into two categories based on the laboratory results at hospital admission. AST was considered normal when the level  $\leq$ 34 U/L for males and  $\leq$ 30 U/L for females. Increased when >34 U/L for males and  $\leq$ 30 U/L for females. ALT was considered normal when the level  $\leq$ 44 U/L for males and  $\leq$ 36 U/L for females. Increased when >44 U/L for males and  $\leq$ 36 U/L for females.

The disease severity was grouped into two categories, critical and non-critical. Patients were classified as critical if they experienced ARDS, sepsis, or septic shock according to the Kementerian Kesehatan criteria. Non-critical patients were those who did not experience any of these three conditions.

Data analysis was conducted in several stages, including descriptive, bivariate, and multivariate analyses. Descriptive analysis began with a normality test for the numerical variable (age) using the Kolmogorov-Smirnov method. Normality test revealed that age was not normally distributed, so it was reported as the median and minimum-maximum. Meanwhile, categorical variables (sex, comorbidities, AST, and ALT levels) were reported as frequencies and percentages.

Bivariate analysis was conducted on the numerical variable (age) and categorical variables (sex, comorbidities, AST, and ALT levels). Mann Whitney test was used for numerical variables and the categorical variables were analyzed with Chi-Square test. Statistical significance was considered when p <0,05 with 95% Confidence Interval (CI). Variable that statistical significance in bivariate analysis then analyzed with multivariate logistic regression. Statistical significance was considered when p <0,05 with 95% CI. IBM SPSS Statistics 26 software was used for analysis.

#### RESULT

Analysis showed the study population consisted of 64 critical patients and 62 non-critical patients. The median (range) age of critical patients was 59,5 (18-76) years, while non-critical patients was 45,5 (20-70) years. Additionally, 71,9% of the critical patients were male, and 28,1% were female. Among the critical patients, 37,5% had comorbid hypertension, 31,3% had diabetes, 46,9% had heart disease, and 54,7% had obesity. Laboratory data showed that 90,6% of the critical patients had elevated AST levels and 64,1% had elevated ALT levels. Only 46,8% of non-critical patients had elevated AST levels and 22,6% had elevated ALT levels. Characteristics of this study population were presented in Table 1.

Table 1. Characteristics of the study population

Variables	Critical	Non-critical	
Variables	(N = 64)	(N = 62)	
Age median (min-max)	59,5 (18-76)	45,5 (20-70)	
Sex N (%)			
Male	46 (71,9)	36 (58,1)	
Female	18 (28,1)	26 (41,9)	
Comorbidities N (%)			
Hypertension			
Yes	24 (37,5)	8 (12,9)	
No	40 (62,5)	54 (87,1)	
Diabetes			
Yes	20 (31,3)	9 (14,5)	
No	44 (68,8)	53 (85,5)	
Heart disease			
Yes	30 (46,9)	3 (4,8)	
No	34 (53,1)	59 (95,2)	
Obesity			
Yes	35 (54,7)	40 (64,5)	
No	29 (45,3)	22 (35,5)	
AST level N (%)			
Increased	58 (90,6)	29 (46,8)	
Not increased	6 (9,4)	33 (53,2)	
ALT level N (%)	* * /	,	
Increased	41 (64,1)	14 (22,6)	
Not increased	23 (35,9)	48 (77,4)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; maks: maximum; min: minimum

The bivariate analysis was conducted on the numerical variable (age) and disease severity using the Mann Whitney test to assess differences between the critical and non-critical groups. The analysis revealed a significant difference in age between the

critical and non-critical patients (p = <0.001), as shown in Table 2

**Table 2.** Bivariate analysis of numerical variables

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Variable	Disease severity	Disease severity		
	Critical	Non-critical	_	
Age	59,5 (18-76)	45,5 (20-70)	<0,001*	

<sup>\*</sup>Mann Whitney test (p < 0,05)

Bivariate analysis was also conducted on categorical variables (sex, comorbidities, AST, and ALT levels) with disease severity using the Chi-Square test to assess differences between the variables. The results of the analysis were presented in Table 3.

The bivariate analysis of categorical variables indicated significant differences in the number of patients with and without hypertension (p = 0.002) with PR: 4,050 (95% CI: 1,649-9,947). Significant differences were also observed in the number of

patients with and without diabetes (p = 0,026) and heart disease (p = <0,001) with PR: 2,677 (95% CI: 1,108-6,469) for diabetes and PR: 17,353 (95% CI: 4,924-61,153) for heart disease. Other variables showing significant differences were the number of patients with and without elevated AST levels (p = <0,001) and elevated ALT levels (p = <0,001). The number of patients with elevated AST levels had a PR: 11,000 (95% CI: 4,139-29,233), while PR: 6,112 (95% CI: 2,790-13,390) for patients with elevated ALT levels.

**Table 3.** Bivariate analysis of categorical variables

Variables —	Disease severity		PR	050/ CI	1
	Critical	Non-critical		95% CI	p value
Sex N (%)			1,846	0,878-3,878	0,104
Male	46 (71,9)	36 (58,1)			
Female	18 (28,1)	26 (41,9)			
Comorbidities N (%)					
Hypertension			4,050	1,649-9,947	0,002*
Yes	24 (37,5)	8 (12,9)			
No	40 (62,5)	54 (87,1)			
Diabetes			2,677	1,108-6,469	0,026*
Yes	20 (31,3)	9 (14,5)			
No	44 (68,8)	53 (85,5)			
Heart disease			17,353	4,924-61,153	<0,001*
Yes	30 (46,9)	3 (4,8)			
No	34 (53,1)	59 (95,2)			
Obesity			0,664	0,324-1,358	0,261
Yes	35 (54,7)	40 (64,5)			
No	29 (45,3)	22 (35,5)			
AST level N (%)			11,000	4,139-29,233	<0,001*
Increased	58 (90,6)	29 (46,8)			
Not increased	6 (9,4)	33 (53,2)			
ALT level N (%)			6,112	2,790-13,390	<0,001*
Increased	41 (64,1)	14 (22,6)			
Not increased	23 (35,9)	48 (77,4)			

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval. \*Chi-Square test (p <0,05)

Multivariate logistic regression analysis revealed significant association between age and disease severity in COVID-19 patients (p = 0,036) with PR: 1,034 (95% CI: 1,002-1,066). Additionally, heart disease also associated with disease severity (p = <0,001) with PR: 12,214 (95% CI: 3,126-47,730). Similar

results were observed for elevated AST (p = 0.026) and ALT (p = 0.039) levels, both of which were associated with disease severity. Elevated AST levels had PR: 3,929 (95% CI: 1,177-13,117), while elevated ALT levels had PR: 2,881 (95% CI: 1,053-7,883) (Table 4).

**Table 4.** Results of multivariate logistic regression analysis

Variables	В	SE	PR	p value	95% CI
First step					
Age	0,022	0,018	1,022	0,226	0,986-1,060
Hypertension	0,685	0,614	1,983	0,265	0,596-6,604
Diabetes	0,317	0,597	1,373	0,595	0,426-4,425
Heart disease	2,515	0,701	12,369	<0,001*	3,133-48,829
Elevated AST level	1,366	0,626	3,921	0,029*	1,149-13,384
Elevated AST level	0,974	0,523	2,648	0,062	0,951-7,377
Constant	-3,227	0,931	0,040	0,001	=
Second step					
Age	0,033	0,016	1,034	0,036*	1,002-1,066

Heart disease	2,503	0,695	12,214	<0,001*	3,126-47,730
Elevated AST level	1,368	0,615	3,929	0,026*	1,177-13,117
Elevated AST level	1,058	0,513	2,881	0,039*	1,053-7,883
Constant	-3,571	0,896	0,028	<0,001	-

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval. \*Multivariate logistic regression (p <0,05). Nagelkerke R Square 0,513

#### DISCUSSION

The analysis demonstrated an association between age and disease severity. This finding was supported by another study that reported an increased risk of ARDS in older age groups.<sup>23</sup> As age increased, the likelihood of immune system dysregulation, comorbidities, and dysfunction of organ reserve also increased.<sup>2</sup> There was no difference in number of patients between different sex. This result contradicted other studies that had found an association between sex with disease severity in COVID-19 patients. Such an association might have arisen through lifestyle factors and hormonal differences. Lifestyle factors, including smoking, alcohol consumption, and noncompliance with mask wearing were more commonly observed in males. Additionally, the male hormone testosterone might have impaired immune response, whereas estrogen was shown to enhance it.<sup>25</sup> The discrepancy between the findings of these two studies might have been attributed to differences in sampling methods, which were not random.

Hypertension was one common comorbidities observed in COVID-19 patients. Analysis in this study revealed no association between hypertension with disease severity. Similar results were reported in studies conducted at Palu and Surabaya.<sup>26</sup> Longterm use of medications that affected the activity of Angiotensin Converting Enzyme 2 (ACE2) was suspected to be a risk factor for increased disease severity. These medications include ACE inhibitors and ARBs, which required monitoring during use.<sup>27</sup> In addition to hypertension, another comorbidity analyzed in this study was diabetes. The analysis revealed no significant association between diabetes with disease severity. In contrast, analysis in another study found an association between diabetes with disease severity in COVID-19 patients.<sup>28</sup> The discrepancy between the results of these studies might have been attributed to differences in sampling methods, which were not random. Diabetic patients commonly had immune dysfunction and an increase in proinflammatory cytokine production, which heightens the risk of severe disease.<sup>29</sup> Obesity was also analyzed in this study. The analysis found no difference between number of patients with and without obesity. In contrast, multivariate analysis in another study found an association between obesity and disease severity. Similar to diabetes, the differences in results might have been due to non-random sampling methods. The relationship between obesity and disease severity occurred independently through several mechanisms. First, obesity could cause low-grade inflammation, increasing the risk of cytokine storms during COVID-19 infection. Second, adipocytes were among the cells that express the ACE2 receptor, which serves as both an entry point and a reservoir for the SARS-CoV-2 virus. obesity affected ventilation including hypoventilation syndrome that increased the risk of respiratory

failure. Obesity was often accompanied by other comorbidities, such as hypertension, diabetes, and heart disease.<sup>30</sup>

The only comorbidity that showed a significant association in this study was a history of heart disease. This finding was supported by another study that reported patients with heart disease had an increased risk of critical COVID-19. Studies had indicated that SARS-CoV-2 infection triggered systemic inflammation. During this process, macrophage activation could produce collagenase, which degraded the fibrous cap and led to plaque rupture. Additionally, SARS-CoV-2 infection directly damaged the endothelium, increasing the risk of thrombosis, and coronary vasoconstriction. This mechanism was supported by laboratory findings in COVID-19 patients, which typically showed elevated d-dimer, prolonged prothrombin time, and decreased of platelet counts that suggested coagulation abnormalities.

Liver function tests were routine examinations for COVID-19 patients. Two enzymes measured in these tests were AST and ALT. These enzymes were relatively specific markers of liver function and frequently used in clinical management.<sup>9</sup>

In the liver, AST and ALT enzymes were found in hepatocyte cells, with AST concentrated in the cytoplasm and ALT in the cytosol. Elevations of AST and ALT occurred in response to events that caused hepatocyte membrane disruption or necrosis. When released from hepatocytes, AST and ALT entered the plasma, and rose within 1-2 hours. <sup>13</sup>

Studies had reported that hepatocyte damage in COVID-19 patients was mediated by five main mechanisms, such as SARS-CoV-2 infection, hyperactivation of the immune response, hypoxia, drug toxicity, and pre-existing liver disease. He had the ACE2 receptor was known to facilitate SARS-CoV-2 infection. This receptor was expressed in several human cells, including hepatocytes and cholangiocytes. Although ACE2 expression in hepatocytes (2,6%) was lower than in cholangiocytes (59,7%), but one study found SARS-CoV-2 particles in the cytoplasm of hepatocytes. This condition was associated with the presence of trypsin in hepatocyte epithelium. In vitro studies had shown that affinity of the viral spike protein for receptors increased when incubated with trypsin.

SARS-CoV-2 virus could directly damage hepatocytes by the cytopathic effects during infection. <sup>14</sup> Additionally, infection of this virus decreased the expression of mRNA for tight junction cholangiocytes that impaired the protective function of hepatocytes against toxic bile components. <sup>15</sup>

During the infection process, the patient's immune system responded by releasing proinflammatory cytokines. <sup>16</sup> In some cases, excessive production of proinflammatory cytokines could lead to a cytokine storm, which affected multiple organs. <sup>14</sup> Laboratory findings in COVID-19 patients had shown elevated levels of eosinophils, immunoglobulin E, IL-5, IL-6, and IL-13. <sup>17</sup> Under normal conditions, IL-6 was involved in liver regeneration and hepatoprotective effects. However, excessive production of

# THE RELATIONSHIP BETWEEN ASPARTATE AMINOTRANSFERASE (AST) AND ALANINE AMINOTRANSFERASE (ALT)..

IL-6 could disrupt this regenerative process and cause hepatocyte damage.  $^{18}$ 

Multivariate analysis in this study revealed a significant association between AST and ALT levels with disease severity in COVID-19 patients. This was supported by other studies that found elevated of AST and ALT levels in 18,2% and 19,8% of mild COVID-19 patients with 39,4% and 28,1% in severe patients. <sup>10</sup>

COVID-19 patients were classified as critical when they developed ARDS, sepsis, or septic shock. In both ARDS and septic shock, there was a reduction in oxygen supply and systemic arterial pressure, which led to hepatocellular hypoxia.<sup>39</sup> Additionally, the use of mechanical ventilation in COVID-19 patients with ARDS could exacerbate this condition by increasing intra-abdominal pressure and impairing hepatic blood flow. Patients with hepatocellular hypoxia typically exhibited elevated AST and ALT levels.<sup>21</sup> In hypoxic conditions, AST levels tended to rise earlier and more significantly than ALT levels. 40 This study also found that, upon hospital admission, critical patients were more likely have elevated AST than ALT level. Furthermore, patients COVID-19 with elevated AST had a 3,9 fold higher risk of progressing to critical COVID-19 compared to those with elevated ALT, who had a 2,8 fold higher risk. The multivariate analysis in this study showed Nagelkerke R Square value of 0,513, suggesting that other factors contributed to 48,7% of the variability in disease severity among COVID-19 patients.

#### 1. CONCLUSION

Multivariate analysis in this study revealed a significant association between AST and ALT levels with disease severity in COVID-19 patients at Udayana University Hospital. This study had several limitations. Therefore, the authors recommended including additional potential confounding variables in future studies to better understand the factors influencing the outcomes.

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