Transaminase Level of Severity and Mortality of COVID-19 Patients at RSUD Dr. Saiful Anwar Malang

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ABSTRACT

Background: Extend of lung injury, inflammation due to SARS COV-2 can also cause liver injury. Liver injury in COVID-19 patients can be caused by the direct effect on the liver, cholangiocyte role, activation of the immune system, drug-induced liver injury, and hypoxic injury. Hepatocyte necrosis could increase the transaminase. Therefore, transaminase increase may reveal the inflammation severity.

Aim: This study aims to know the relationship of transaminase to the severity and mortality of COVID-19 patients.

Method: A retrospective study of 177 COVID-19 patients hospitalized at Saiful Anwar Hospital Malang. The data were taken from the medical record of COVID-19 patients. The level of transaminase was taken on admission. The severity criteria of COVID-19 was taken from the Indonesian COVID-19 Guidelines. Chi-Square Test and Pearson Correlation Test were used as the statistical analysis with a significance of 0.05 (p=0.05) and a confidence interval of 95% (CI=95%).

Results: From the correlation test, the AST had R=0.42 (p<0.001) for severity and R=0.17 (p<0.001) for mortality. The ALT had R=0.33 (p<0.001) for severity and R=0.28 (p<0.001) of mortality.

Conclusion: There was a significant relationship between AST and ALT in the severity and mortality.

Keywords: COVID-19, Transaminase

INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) was reported and identified in Wuhan, China, in December 2019. Since then, there has been a very rapid increase in the number of cases and WHO declared COVID-19 a global pandemic on March 11, 2020. Indonesia, as a developing country and the fourth most populous country in the world, has also been heavily affected by the COVID-19 pandemic situation. As of December 3, 2020, the total global confirmed cases of COVID-19 in Indonesia were 577,877 cases with 17,355 deaths and a case fatality rate of 3.1%.1,2
One of the most common extrapulmonary manifestations is liver involvement, with one of the manifestations being an increase in the transaminase enzyme. Studies show that Angiotensin Converting Enzyme-2 (ACE-2) is the entry receptor for Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV2). ACE-2 receptors are twenty times more commonly found in the bile duct than in hepatocytes. SARS-CoV2 is thought to infect hepatocytes and bile cells and cause liver dysfunction.\(^{3-6}\)

This study aims to see the profiles of liver enzymes of COVID-19 patients treated at the Department of Internal Medicine at RSUD Dr. Saiful Anwar Malang and to determine the relationship between the severity of COVID-19 and the risk of mortality.

**METHODS**

A retrospective study was conducted and the Pearson correlations test was used as the statistical test. This study aims to determine the relationship between transaminase, CRP, albumin and the disease severity, mortality, and length of stay in COVID-19 patients treated by the Internal Medicine Department, dr. Saiful Anwar Malang.

The study was conducted in the inpatient ward of RSUD Dr. Saiful Anwar Malang by taking data from the medical records of COVID-19 patients cared by the Department of Internal Medicine from August 1, 2020, to October 31, 2020.

**RESULTS**

There was a total of 180 people who were treated in the COVID-19 inpatient ward of dr. RSUD Dr. Saiful Anwar Malang and treated by the Department of Internal Medicine from August 1st, 2020, to October 31st, 2020. Of the 180 patients, 3 patients were excluded because they had a history of liver disease, (hepatitis B and hepatitis C). The characteristics of the subjects show in Table 1.

Chi-square test and Pearson correlation were carried out to see the relationship between increased levels of transaminases and the severity and mortality in COVID-19 patients.

**Table 1.** Demographic Data of COVID-19 Patients Treated at Saiful Anwar Hospital by the Department of Internal Medicine from 1 August to 31 October 2020.

| Characteristic      | Frequency (%) |
|---------------------|---------------|
| **Sex**             |               |
| Male                | 96 (54.2)     |
| Female              | 81 (45.8)     |
| **Age**             |               |
| <30                 | 15 (8.5)      |
| 31-50               | 58 (32.8)     |
| 51-70               | 80 (45.2)     |
| ≥71                 | 24 (13.6)     |
| **Severity**        |               |
| Mild                | 28 (15.8)     |
| Moderate            | 74 (41.8)     |
| Severe              | 29 (16.4)     |
| Critical            | 46 (26)       |
| **Mortality during care** | 66 (37.3) |
Table 2. Relationship of Increased AST on Severity and Mortality.

| Variables | AST (U/L) | Average AST (U/L) | Chi-Square | p-value |
|-----------|-----------|-------------------|------------|---------|
|           | Normal    | Elevated          |            |         |
| Severity  |           |                   |            |         |
| Mild      | 22        | 6                 | 47.21      | < 0.001 |
| Moderate  | 45        | 29                | 51.10      | 31.35   |
| Severe    | 9         | 20                | 78.86      |         |
| Critical  | 10        | 36                | 71.76      |         |
| Mortality |           |                   |            |         |
| Outpatient| 68        | 43                | 47.51      | < 0.001 |
| Death     | 18        | 48                | 82.09      |         |

*: AST, aspartate aminotransferase

Table 3. Relationship of Increased ALT on Severity and Mortality.

| Variables | AST (U/L) | Average ALT (U/L) | Chi-Square | p-value |
|-----------|-----------|-------------------|------------|---------|
|           | Normal    | Elevated          |            |         |
| Severity  |           |                   |            |         |
| Mild      | 22        | 6                 | 42.43      |         |
| Moderate  | 49        | 25                | 46.14      | 14.78   | 0.002   |
| Severe    | 14        | 15                | 72.28      |         |
| Critical  | 18        | 28                | 54.72      |         |
| Mortality |           |                   |            |         |
| Discharged| 72        | 39                | 48.61      | 5.45    | 0.020   |
| Death     | 31        | 35                | 57.86      |         |

*: AST, aspartate aminotransferase.

Table 4. Pearson Correlation Test for Increased Transaminase.

| Variables | R  | p-value |
|-----------|----|---------|
| AST Correlation |    |         |
| Elevated AST and Severity | 0.42 | < 0.001 |
| Elevated AST and Mortality | 0.33 | < 0.001 |
| ALT Correlation |    |         |
| Elevated ALT and Severity | 0.18 | < 0.001 |
| Elevated ALT and Mortality | 0.28 | < 0.001 |

*: AST, aspartate aminotransferase; ALT, alanine transaminase.

From Table 2, the probability value (p-value) of the severity was <0.050. This means that there was a significant relationship between increased levels of AST and severity. From the cross-tabulation, it can be seen that in patients with normal AST levels, the severity was mostly mild and moderate, whereas, in patients with elevated AST levels, the severity was most severe and critical. Conforming to from the average AST value, patients with mild severity had the lowest AST average value of 47.21, while the highest AST average was seen in the severe patients, which was 78.87.

Table 2 above shows that the probability value (p-value) of the mortality was <0.050, This means that there was a significant relationship between increased levels of AST and mortality. From the cross-tabulation, it can be seen that most patients with normal AST levels were able to be discharged, while most patients with elevated AST levels deteriorated and passed away. Judging from the average AST level,
discharged patients had an average AST level of 47.51, lower than the average AST in patients who passed away, which was 82.09.

**Table 3.** above shows that the probability value (p-value) of the severity was $0.002 < 0.05$, This means that there was a significant relationship between increased ALT levels and severity. From the cross-tabulation, it can be seen that in patients with normal ALT levels, the severity categories were mostly mild and moderate, whereas, in patients with elevated ALT levels, the severity categories were mostly severe and critical. Conforming to from the average ALT value, patients with mild severity had the lowest ALT average value, which was 42.429, while the highest ALT average was seen in severe patients, which was 72.276.

**Table 3.** above shows that the probability value (p-value) of the mortality variable was $0.02 < 0.05$, so $H_0$ is rejected and $H_1$ is accepted. This means that there was a significant relationship between the ALT increase variable and mortality. From the cross-tabulation, it can be seen that most patients with normal ALT levels were able to be discharged, while most patients with elevated ALT levels deteriorated and passed away. Judging from the average ALT value, patients who went home and outpatients had an average ALT value of 48.613, lower than the average ALT in patients who passed away, which was 57.864.

**Table 4.** shows the result of the Pearson correlation test. It was found that there was a relationship between the increased transaminases and the severity and mortality of COVID-19 patients.
DISCUSSIONS

Based on the results of studies on COVID-19 patients from August to October 2020, it was found that at initial admission, 51.4% and 41.8% of patients experienced increased AST and ALT respectively. There was a significant relationship between increased transaminases levels and the severity of COVID-19, where the lowest mean AST (47.21 U/L) and ALT (42.43 U/L) were found in mild and moderate COVID-19, while the average AST (78.86 U/L) and the highest ALT (72.28 U/L) were found in severe or severe COVID-19.

The results of this study are supported by a retrospective study conducted on 138 COVID-19 patients, in which higher AST and ALT levels were found in severe and critical COVID-19 patients admitted to the ICU. The study by Cai, et al also mentioned an increase in AST and ALT levels in COVID-19 patients, and higher transaminase levels were found more in patients with severe COVID-19 compared to mild degrees. Hajifathalian, et al stated that the presence of liver injury at the beginning of admission was associated with 2.3 times greater risk of patients progressing to severe conditions, needing admission to the ICU, and even death. The three studies above are also supported by a meta-analysis study conducted by Kumar P, et al which involved 128 studies that concluded that liver disorders, in the form of elevated transaminases, are often found in COVID-19 patients, especially with severe manifestations.\(^4,7,8\)

However, the evidence regarding the effect of transaminase levels on the severity of COVID-19 still varies. Several studies, such as those conducted by Papadopoulos, et al and Ramachandran et al, showed that, although elevated transaminases were more often found in patients with COVID-19 with severe symptoms, there was no statistically significant association found.\(^6\)

Based on the results of this study on COVID-19 patients from August to October 2020, there was a significant relationship between increased transaminase levels and the risk of COVID-19 mortality. The lowest mean AST (47.50) and ALT (48.61) levels were found in patients with mild and moderate COVID-19, while the highest average levels of AST (82.09) and ALT (57.86) were found in COVID-19 patients who worsened and passed away.

The results of this study are consistent with a meta-analysis conducted by Boregowda, et al involving 22 studies in their research, of which 17 studies compared liver function levels for severe and mild COVID-19, while 5 other studies compared liver enzyme levels with survival. It was found that the presence of impaired liver function indicates a severe degree of COVID-19 and can predict mortality risk. The study conducted by Lei, et al, which was a retrospective cohort study involving 7,029 patients, stated that an increase in AST was associated with the highest risk of mortality compared to other parameters of liver injury. When compared with patients with normal AST levels, the risk of mortality was significantly increased by 4.81-fold (95% CI, 3.38-6.86; P<0.001) in
patients with an AST between 40 U/L to 120 U/L, and increased by 14.87-fold (95% CI, 9.64-22.93; P<0.001) in patients with AST>120 U/L. [9,10]

**CONCLUSION**

There was a significant relationship between AST and ALT in the severity and mortality.

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