

## Relationship between Transaminase Enzyme Levels and Severity of Dengue Fever

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**Abstract:** Since dengue hemorrhagic fever (DHF) can cause liver damage, aminotransferase levels as liver function test may be useful in predicting the severity of dengue hemorrhagic fever. The purpose of this study was to determine the relationship between transaminase enzyme levels and the severity of dengue hemorrhagic fever. This study used analytic observational approach with cross-sectional design. The data used was secondary data, namely medical records of H. Adam Malik Hospital and Hospital of Prof. Dr. Chairuddin P. Lubis University of North Sumatera. From a total of 65 patients included, there were 63.1% (41 patients) with DHF grade 1, 29.2% (19 patients) were DHF grade 2, 6.2% (4 patients) were DHF grade 3 and 1.5% (1 medical record) were DHF grade 4. For aminotransferase level 56.9% (37 records) had elevated SGPT levels and 92.3% (60 records) had elevated SGOT levels, it was found that there was no relationship between increased levels of SGPT and SGOT with the severity of DHF (SGPT  $p = 0.628$  and SGOT  $p = 1.00$ ). There is no association between the elevations of transaminase enzyme levels and the severity of DHF.

**Keywords:** Dengue Hemorrhagic Fever, Serum Glutamic Pyruvic Transaminase, Serum Glutamic Oxaloacetic Transaminase, Liver Damage.

## INTRODUCTION

Dengue infection causes dengue fever (DD), dengue hemorrhagic fever (DHF) and the highest severity of the disease is dengue shock syndrome (SSD). Symptoms and signs of dengue infection are fever, muscle and/or joint pain, thrombocytopenia, leucopenia, hemorrhagic diathesis, and lymphadenopathy, while in DHF, the main pathological symptom is plasma leakage.<sup>1</sup>

According to data from the World Health Organization (WHO), there was an increase in cases from 2000 to 2019, from 505,403 cases to 5.2 million cases so that in 2020, WHO included dengue infection as one of the ten most dangerous diseases in the world. This shows that dengue infection is still a threat and has not been completely overcome. Dengue that has not been immediately solved will lead to the occurrence of extraordinary events, severe dengue and even death.<sup>1,2</sup>

Deaths that occur in patients with dengue infection can be avoided by early detection of the disease and its degree before it gets worse. The severity of dengue hemorrhagic fever can be determined based on the signs, symptoms and laboratory examination results performed when the patient comes to the health service. The severity of dengue infection can also involve organ damage, especially in degrees III and IV of dengue hemorrhagic fever, one of the organ damage that can occur is liver damage. The mechanism of dengue-induced liver damage includes many mechanisms, but immunopathological reactions play the most role in liver damage. Liver damage occurs due to direct cytopathic effects and damage due to immune response.<sup>3,4</sup>

Liver damage can be known through liver function test, which includes examining the levels of SGPT and SGOT which are transaminase enzymes. If there is an increase in liver enzyme levels in dengue patients, this should be a sign of vigilance against liver damage. In liver damage or inflammation, there will be an increase in SGPT and SGOT levels. The SGPT is more specific for liver disease than SGOT, because SGPT is an enzyme made by hepatocyte cells, while SGOT is a mitochondrial enzyme. The SGOT enzyme is not only found in the liver but also in the heart, muscles, and kidneys.<sup>5,6</sup>

Transaminase elevation in dengue infection is more specific in children compared to adults. In adults, although transaminases remain elevated longer than children, the peak point does not correlate with dengue fever severity, but several other studies have shown that dengue patients with more severe symptoms are associated with significantly higher aminotransferase levels.<sup>3,7</sup> From a study conducted by José De Souza in 2004 which said that there was a relationship between increased transaminase enzyme levels and dengue hemorrhagic fever severity,<sup>8</sup> but from a study conducted by Priyangika in 2021 found that there was no relationship between transaminase enzyme levels and dengue hemorrhagic fever severity.<sup>9</sup> Seeing the unclear relationship between transaminase enzyme levels and the severity of dengue infection, new research is needed, especially in adult patients. According to the researchers, this is needed so that transaminase enzyme levels can be one of the warning signs for dengue severity, hopefully it can confirm the theory of the relationship between liver enzyme levels and dengue hemorrhagic fever severity and increase understanding of the effect of dengue hemorrhagic fever on the liver.

## MATERIALS AND METHOD

This study is a retrospective study, with an analytical observational approach using the cross-sectional method in dengue fever patients admitted to H. Adam Malik Hospital Medan and Prof. Dr. Chairuddin P. Lubis University of North Sumatera Hospital, to determine whether there is a relationship between the value of transaminase enzyme variables and the severity of dengue hemorrhagic fever. This research received ethical clearance from the Research Ethics Committee for Health Research of Universitas Sumatera Utara with Number: 764/KEPK/USU/2023.

The population of this study were patients who came to H. Adam Malik Hospital during the period 2021-2023 and Prof. Dr. Chairuddin P. Lubis University of North Sumatera Hospital during the period 2018-2023 who had met the inclusion criteria. Sampling was carried out using the non-probability sampling method through purposive sampling, namely by selecting samples from among the population based on the criteria according to the inclusion and exclusion criteria, and due to the unknown population size, sample size calculation was performed using the Lemeshow formula.

The criteria inclusion was dengue hemorrhagic fever patients aged  $\geq 18$  years who had been diagnosed and had complete medical record data, and had passed the exclusion criteria, namely patients with increased transaminase enzyme levels induced by other reasons, patients with hepatitis, fatty liver, alcoholic hepatitis, drug-induced liver damage and hemolysis. Data were analyzed using the chi-square test.

## RESULT

In this study, sampling was carried out using consecutive sampling technique, and 65 dengue fever patient data were obtained, all patient data were taken from the patient's medical record, with the data period at H. Adam Malik Hospital, namely 2021-2023 and Prof. Dr. Chairuddin P. Lubis University of North Sumatera Hospital for the period 2018-2023.

Table 1 shows that most subjects were male (56.9%), with the highest incidence occurring in 2022 and 2023 (41.5%). Grade 1 DHF was most common (63.1%) and the majority of patients experienced cure (96.9%).

**Table 1.** Characteristics of patients

Variable	n	%
<b>Gender</b>		
Male	37	56.9
Female	28	43.1
<b>Incidence (year)</b>		
2018	4	6.2
2019	5	7.7
2021	2	3.1
2022	27	41.5
2023	27	41.5
<b>Severity</b>		
DHF grade 1	41	63.1
DHF grade 2	19	29.2
DHF grade 3	4	6.2
DHF grade 4	1	1.5
<b>Morbidity and Mortality</b>		
Recover	63	96.9
Death	2	3.1

Table 2 shows that the subjects who recovered were mostly diagnosed with grade 1 DHF (61.9%), and all subjects who died were diagnosed with grade 1 DHF (100%).

**Table 2.** Morbidity and mortality at each degree of severity

Morbidity and Mortality		Severity of DHF			
		DHF 1	DHF 2	DHF 3	DHF 4
Recover	n (%)	39 (61.9)	19 (30.2)	4 (6.3)	1 (1.6)
Death	n (%)	2 (100)	0 (0)	0 (0)	0 (0)

Table 3 shows that the majority of subjects were patients without comorbidities (81.5%), and in subjects with comorbidities, it was found that the highest comorbidity was hypertension (10.7%).

**Table 3.** Types of comorbidities in samples

Types of comorbidities	n	%
<b>Without Comorbid</b>	53	81.5
<b>With Comorbid</b>	12	18.5
Pulmonary TB	2	3.1
Hypertension	7	10.7
Only Hypertension	5	7.7
Hypertension and Stroke	1	1.5
Hypertension and AKI	1	1.5
Pleural Effusion	1	1.5
Pneumonia	1	1.5
AKI	1	1.5

In table 4 there is an increase in both transaminase enzyme levels, in elevated SGPT was found in 37 subjects (56.9%) and elevated SGOT in 60 subjects (92.3), with mean level of SGPT is 135.75 and 226.65 in SGOT.

**Table 4.** Distribution of transaminase enzyme level measurement results

Transaminase Enzyme	n	%	Mean
<b>SGPT</b>			
Normal	28	43.1	135.75
Increased	37	56.9	
<b>SGOT</b>			
Normal	5	7.7	226.65
Increased	60	92.3	

Table 5 shows that in the results of the chi-square test, the p value > 0.05 was obtained for SGPT and SGOT, which means that there is no relationship between transaminase enzyme levels and the severity of dengue hemorrhagic fever.

**Table 5.** The distribution and the relationship between transaminase enzyme levels and DHF severity

Transaminase Enzyme		Severity of DHF				P value
		Grade 1	Grade 2	Grade 3	Grade 4	
SGPT	Normal n (%)	20 (71.4)	7 (25)	1 (3.6)	0 (0)	0.6
	Increased n (%)	21 (56.8)	12 (32.4)	3 (8.1)	1 (2.7)	
SGOT	Normal n (%)	4 (80)	1 (20)	0 (0)	0 (0)	1.0
	Increased n (%)	37 (61.7)	18 (30)	4 (6.7)	1 (1.7)	

## DISCUSSION

Cases of dengue infection can occur at any time of the year, during the period 2018 to 2023, the highest incidence of dengue infection occurred in 2022 and 2023, with the frequency of incidence occurring more in men (56.9%) than women (43.1%), this is in line with Made Susila Utama's research in 2019, which found the frequency of dengue infection was greater in men than women. In dengue infection, the high number of cases reported in men can occur due to differences in types of work between men and women, differences in time between men and women outside the home, and can also occur due to differences in treatment-seeking behavior.<sup>10,11</sup>

According to research by Anker & Arima, in 2011, Singapore found that exposure to dengue fever-carrying mosquitoes occurred during the day, both at work and elsewhere, contributing to the increase in dengue fever cases in males among adolescents and adults in Asia reported in this study,<sup>11,12</sup> this is also in line with Indonesia which has the number of male workers at 83.98%, which is more than women at 54.42%,<sup>13</sup> as well as the province of North Sumatera with the percentage of male workers at 83.83% and women 57.42% with the majority of workers are laborers or employees who work in the agriculture, forestry and fisheries sectors.<sup>14</sup> Due to the need for medical certification for absenteeism, working individuals (more likely to be male) are more likely to seek medical assistance and report illnesses to health care facilities.<sup>11</sup>

In the severity level, it was found that DHF degree 1 had the highest frequency of data at 63.1% and DHF degree 4 was the severity level with the lowest frequency at only 1.5% of the total data. This proves that DHF degrees I and II are more common than DHF degrees III and IV or SSD, as a study conducted by Bano in 2023 found that the incidence of DHF degrees I and II was higher than SSD.<sup>15</sup>

The cure rate in dengue infection is greater than the mortality rate. Mortality due to dengue infection in this study was only 3.1%, out of a total of 65 patients there were only 2 patients who died, the two patients who died were middle age patients, 41 years old who were diagnosed with DHF degree 1, and 51 years old with a previous history of acute kidney injury (AKI) who was also clinically diagnosed with DHF degree 1. Acute kidney injury is known to be closely related to mortality in cases of dengue infection. In a case series it was found that 80% of DHF patients with AKI died.<sup>16</sup>

In this study, it was found that the comorbid disease with the highest frequency was hypertension with a total of 5 (7.7%) patients and there was also hypertension accompanied by stroke as much as 1 (1.5%) data and hypertension accompanied by AKI as much as 1 (1.5%) data, in line with research conducted by Ashraf in 2023, which suggested that hypertension is the most common comorbid in DHF patients and has a relationship with the severity of dengue infection.<sup>17</sup>

Hypertension can aggravate dengue infection, with mechanisms not yet fully understood, hypertension causes endothelial dysfunction and vascular damage, increasing endothelial inflammatory activation, altering vascular tone and flow. There is evidence that the vascular wall may be negatively affected by C-reactive protein (CRP), which is often elevated in hypertension. This can lead to endothelial dysfunction and decreased bioavailability of nitric oxide, which is important for tissue clotting. Increased vascular permeability and coagulopathy, as well as fluid loss can lead to hypovolemic shock which is a hallmark of DHF and SSD.<sup>17</sup> In a study conducted by Pauletto and Rattazzi in 2006 with an animal model of hypertension, administration of Angiotensin-II Receptor Blockers (ARBs) reduced the level of inflammatory activation in arteries due to the ability of these drugs to reduce blood levels of CRP and other inflammatory mediators.<sup>18,19</sup> This is in line with the results of a study conducted by Teixeira in 2015, which showed that the incidence of

DHF was lower in patients who received treatment for arterial hypertension compared to those who did not.<sup>17,19</sup>

The mean SGPT level was 135.75 and SGOT was 226.65 obtained in this study, with the mean SGOT level higher than the SGPT level, as well as the percentage of elevation in SGOT which is greater than SGPT, namely SGOT by 92.3% and SGPT by 56.9%, the increase in SGOT levels which is higher than SGPT is also in line with the results of research conducted by Tiwari in 2021. this can occur as a result of myocyte damage due to dengue infection that occurs thereby increasing the release of SGOT, this event is different from hepatitis or liver infection. In hepatitis A, B, and C there was a corresponding increase in both transaminase enzymes.<sup>20</sup>

In amino acid metabolism and gluconeogenesis, SGPT is essential. The reductive transfer of amino groups from aspartate or alanine to alpha-ketoglutarate, which produces glutamate and pyruvate or oxaloacetate, is catalyzed by SGPT and SGOT, respectively. Damaged hepatocytes will release enzymes such as SGPT and SGOT into the extracellular space, the released enzymes eventually enter the bloodstream and increase serum levels of SGPT and SGOT. The heart, brain, skeletal muscle, and liver tissues are locations where SGOT is found. Skeletal muscle and cardiac tissue have lower enzymatic activity than the liver, which is the main location of SGPT, so injury outside the liver, especially to skeletal muscle, can cause an increase in serum ALT and AST enzyme levels.<sup>3</sup>

The results of this study did not show a relationship between the two types of transaminase enzyme levels with the severity of dengue fever (SGPT p-value=0.6 and SGOT p-value=1.0), this is in line with Fernando's research in 2016 which states that there is no relationship between transaminase enzyme levels, namely SGPT and SGOT with dengue severity, especially at the beginning of admission, with SGPT p-value 0.731 and SGOT p-value 0.067.<sup>9,21</sup> The unrelatedness of the results of this study could be due to liver function tests, especially on transaminase enzymes SGPT and SGOT, which were carried out at the beginning of the patient's admission, which is usually in the febrile phase, it is known that transaminase enzymes do not express liver involvement at the beginning of dengue hemorrhagic fever infection.<sup>9</sup> The peak value of the increase in transaminase enzymes of SGPT is known to occur on day 7 of the disease course and on day 6 of the disease for SGOT, after peaking on days 6 and 7, transaminase enzyme levels will drop rapidly, the pattern of changes in transaminase enzyme levels in infection.<sup>9,21</sup> After the increase in transaminase enzymes due to infection occurs, transaminase enzymes will return to normal after 21 days of illness, with an increase in SGPT levels will be longer than SGOT, this longer increase is likely due to the longer half-life of SGPT which is around 32-43 hours while the SGOT is shorter, around 12.5-22 hours.<sup>3</sup>

In a study by Fernando in 2016 and Priyngika in 2021, which was conducted in the febrile phase, it was found that elevated levels of transaminase enzymes did not show predictive value for dengue severity in the examination of baseline values of SGPT and SGOT levels as was done in this study.<sup>9,21</sup> while in a study conducted by Swamy in 2021 and Asim Ahmed in 2014, suggested that there was a relationship between transaminase enzyme levels, namely SGPT and SGOT, and the severity of dengue fever, patients with shock had significantly higher mean values of SGPT and SGOT, and good or bad results correlated with an increase in liver function examination. Elevated liver function test results such as SGPT and SGOT were associated with more complications, higher mortality, and were also associated with longer hospital stays.<sup>7,22,23</sup>

The high level of viremia after DENV infection is associated with the severity of disease affecting the liver, both direct viral toxicity and unregulated immunological damage in reaction to infection of the liver. Elevated liver transaminases can be asymptomatic until severe manifestations such as acute liver failure appear. A theory says for DENV to bind to hepatocytes occurs by facilitated binding, one binding promotes the binding of the next particle, either direct fusion or endocytosis is used to internalize the virus after binding. The entry pathway can be facilitated by the presence of receptors or even by the absence of receptors. Cellular apoptosis, a phenomenon demonstrated both in vivo and in vitro, is the end result of DENV infection of hepatocytes. After apoptosis, the cells remain as councilman bodies. Many pathways are involved in this apoptotic process including viral cytopathy, hypoxic mitochondrial dysfunction, immune response, and accelerated endoplasmic reticular stress.<sup>24,25</sup>

## CONCLUSION

There was no significant association between transaminase enzyme levels and the severity of dengue hemorrhagic fever, with higher rises in SGOT than SGPT. It is expected that further research will be conducted on transaminase enzyme levels during the treatment of dengue infection patients and after dengue infection is cured.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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