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Original Article

Evaluation of Serum Transaminase Levels Changes in Patients with Dengue Hemorrhagic Fever

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Abstract: Dengue hemorrhagic fever (DHF) is one of the most important diseases mosquitoes transmit due to its rapid spread and economic burden. DHF affects many organs in the body such as the liver, heart, and kidney. The liver damage results in the elevation of serum transaminases. This study aimed to assess the changes in serum aminotransferase levels (aspartate aminotransferase - AST and alanine aminotransferase - ALT) in DHF patients with or without warning signs and related factors. A cross-sectional study was conducted in the E hospital in 2019. Based on the guidelines of the World Health Organization (WHO) 2016, clinical information, medical history, and several laboratory results (complete blood count, ALT, AST, and dengue serology) were collected. 302 patients diagnosed with DHF were included in this study. 59.9% of patients had warning signs, and 40.1% of patients were without warning signs. 57.6% of patients had elevated AST and 36.8% of patients had elevated ALT. Both AST and ALT increased from the febrile phase (days 1 to 3) and were higher in the critical phase (days 4 to 7) of Dengue. Mean AST and ALT levels in two groups with and without warning signs were 79.75 ± 59.85 U/L and 111.53 ± 181.10 U/L, 51.61 ± 46.49 U/L and 74.64 ± 108.08 U/L, respectively. There was no correlation between the severity of Dengue with gender, age groups, BMI, history of biliary liver disease, and history of Dengue. Transaminase levels were higher in patients with decreased platelet counts, especially in the critical phase (days 4-7) ($p < 0.05$). Hepatic dysfunction was prevalent in Dengue patients. Serum aminotransferase levels increased from the early stages of the disease. There was a correlation between transaminases and the severity of Dengue fever.

Keywords: Dengue hemorrhagic fever, transaminase, liver function.

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1. Introduction

Dengue hemorrhagic fever (DHF) is a disease caused by the Dengue virus, a member of the Flavivirus group, transmitted by mosquitoes, most commonly *Aedes aegypti*. Even though Dengue fever has existed for a long time, good disease management is still a significant problem in most countries. Worldwide, about 3.6 billion people live in dengue-epidemic areas. Each year, there are 50 million to 200 million people infected with Dengue, of which 500,000 cases have severe dengue symptoms and 200,000 deaths related to dengue [1]. Over the past 50 years, the incidence of Dengue has increased 30-fold, so this disease has become one of the most important mosquito-borne diseases [1]. Vietnam is one of the countries with the highest dengue incidence in Southeast Asia. According to a report by WHO in 2019, Vietnam had 320,702 Dengue cases, with 54 deaths - an increase of 2.5 times compared to 2018 [2]. As of 12 June 2022, 62,966 dengue cases and 29 deaths cumulatively were reported in Viet Nam. These figures increased by 97% compared to the same period in 2021 (31,962 cases, including five deaths) [3]. The DHF has been happening still significantly complicated [3].

DHF has various clinical manifestations, from asymptomatic to cases of shock, multi-organ failure, and death if not diagnosed precisely and treated promptly. The pathogenesis of dengue fever is complicated, involving many factors, including virus and host response, affecting different cells, monocytes, polymorphonuclear leukocytes, platelets, Kupffer cells, and capillary endothelial cells [4]. That causes several disorders, especially plasma leakage and blood clotting disorders, as well as affecting the function of many organs in the body, such as the liver, kidney, heart, and central nervous system [5-8]. Many studies have shown that the liver is infected with the Dengue virus, causing an increase in liver enzymes or acute liver injury. Dengue viruses have been found in hepatocytes, Kupffer cells, endothelial cells, and immune complexes, which lead to necrosis and apoptosis of hepatocytes. Several pathways are involved in this process, including viral cells, hypoxic mitochondrial dysfunction, immune response, and oxidants [4, 8]. Liver damage may be related to coagulation disorders and disease severity [4]. Acute liver injury can be characterized by clinical manifestations such as right upper abdominal pain, hepatomegaly, and jaundice. These symptoms rarely occur in patients with dengue hemorrhagic fever and Dengue with warning signs. The liver enzymes AST and ALT are involved in the metabolism of amino acids. These indicators are released into the blood because of the parenchymatous lesion that results from the inflammatory process brought on by dengue virus infection [9]. Changes in liver function may appear earlier on laboratory tests through AST, ALT, prothrombin, and other indicators. Serum transaminase levels begin to increase in the early stages of the disease (1 to 3 days) and peak in the second week of illness. The AST level rises more rapidly, peaks at a higher level, and then returns to normal earlier than the ALT level [10]. Numerous investigations demonstrated a connection between changes in the blood markers AST and ALT, the degree of bleeding, and the severity of the disease [11, 12]. In Vietnam, there have not been many studies about the relationship between ALT levels and clinical characteristics of Dengue fever. Therefore, we carried out this study to assess the variation of AST and ALT related to clinical manifestations of dengue hemorrhagic fever.

2. Subjects and Methods

2.1. Research Subjects

Patients who were diagnosed with Dengue fever and treated in the Department of Tropical Diseases, E Hospital, from July 2019 to December 2019.

2.2. Selection Criteria

The patients were diagnosed with hemorrhagic dengue fever according to the

guidelines of WHO 2016 [13]. Patients were admitted with dengue serology positive (IgM and/or NS1Ag).

2.3. Exclusion Criteria

Patients had negative serological results, patients had comorbidities- chronic liver disease, hepatotoxic drug use, or progressively viral hepatitis.

2.4. Research Methods

302 patients were included. All the patients were asked about medical history, and clinical examinations by the researchers, and collected blood parameters: complete blood count, ALT, AST, and dengue serology. The tests were performed at the Department of Biochemistry, Hematology, and Microbiology at E Hospital. The test results were extracted from medical records. These tests were carried out at three points: T1: 1-3 days; T2: 4-7 days; T3: after seven days with fever. The normal ranges for AST and ALT were under 50 U/L for both sexes. The patients were divided into two groups DHF with warning signs and DHF without warning signs, according to WHO 2016 [13].

2.5. Statistical Analysis

All data were analyzed using IBM SPSS Statistics 22.0. Results were presented as frequency and percentage for qualitative data or means and standard deviations for quantitative data. The Chi-square test was used to compare categorical variables. The Mann-Whitney U test or t-test was applied to compare the means between the two groups. The confidence interval was 95%, and a p-value of less than 0.05 was taken as significantly statistical. An odds ratio (OR) calculated the relationship between variables.

2.6. Ethics Statement

The Committee approved the study of the Science and Ethics of E hospital.

3. Results

3.1. General Characteristics

This study was conducted on 302 patients diagnosed with hemorrhagic dengue fever and treated at the Department of Tropical Diseases, E Hospital. Of those, 181 DHF patients (59.9%) had warning signs and 121 DHF patients (40.1%) did not have warning signs. None of these patients developed severe Dengue in the study (Table 1).

The age of patients ranges from 8 to 94 years old (44.56 ± 19.41). There was no statistical difference between the group of DHF with and without warning signs. In our study, there were 137 males and 165 females. The percentage of male patients was higher than that of females in the group Dengue without warning signs and conversely for the group Dengue with warning signs (p<0.001) (Table 1). Most patients had normal BMI and similar results between the two groups.

The total number of fever days was 4.01 ± 0.56, ranging from 3 to 9 days. The average number of treatment days was 5.76 ± 2.10, ranging from 2 to 14 days. There was no statistical difference in the number of fever days and the number of treatment days between two the groups of Dengue with and without warning signs (Table 1).

3.2. The Changes in Serum Transaminases Level

The study patients' mean AST and ALT values were 98.79 ± 145.89 U/L and 65.41 ± 89.31 U/L, respectively. AST and ALT increased from the early stages of the disease and were higher during the critical phase (T2: days 4-7) than the febrile phase (T1: days 1–3). During the febrile phase, ALT value in the group with warning signs increased remarkably than in the group without warning signs (p<0.05) (Table 2).

Table 1. General characteristics of the study population

		Total	DHF without warning signs	DHF with warning signs	p
Number of patients (n, %)		302 (100)	181 (59.9)	121 (40.1)	
Age ($\overline{x} \pm$ SD)		44.56 ± 19.41	45.437 ± 18.69	43.89 ± 19.93	0.533[1]
Gender	Male (n, %)	137 (45.4)	75 (62.0)	62 (34.3)	**<0.001[2]**
	Female (n, %)	165 (54.6)	46 (38.0)	119(65.7)	
Subgroups of BMI	≤18.5	35 (11.6)	10 (8.3)	25 (13.8)	0.317[2]
	18.5-25	236 (78.1)	99 (81.8)	138 (75.7)	
	≥25	31 (10.3)	12 (9.9)	19 (10.5)	
History of DHF	Primary (n, %)	277 (91.7)	108 (89.3)	169 (93.4)	0.204[2]
	Secondary (n, %)	25 (8.3)	13 (10.7)	12(6.6)	
Have chronic liver disease (n, %)		12 (100)	6 (50)	6 (50)	0.551[3]
Number of fever days ($\overline{x} \pm$ SD)		4.01 ± 0.56	4.07 ± 0.45	4.12 ± 0.62	0.653[1]
Number of treatment days ($\overline{x} \pm$ SD)		5.76 ± 2.10	5.80 ± 1.91	5.73 ± 2.23	0.629[1]

Note: Data are expressed as numbers (%) or mean ± standard deviation. [1]Mann-Whitney test; [2]Chi-square test; [3]Fisher's Exact Test

Table 2. The levels of AST and ALT in Dengue patients

| Index	Total ($\overline{x} \pm$ SD)		DHF without warning signs ($\overline{x} \pm$ SD)		DHF with warning signs ($\overline{x} \pm$ SD)		p
	($\overline{x} \pm$ SD)	Median	($\overline{x} \pm$ SD)	Median	($\overline{x} \pm$ SD)	Median	
AST (U/L)	98.79 ± 145.89	59.4	79.75 ± 59.85	60.8	111.53 ± 181.10	57.0	0.769
AST T1 (U/L)	92.26 ± 206.53	40.4	58.62 ± 63.53	36.8	109.65 ± 249.22	43.06	0.262
AST T2 (U/L)	96.72 ± 107.45	59.25	69.99 ± 32.97	65.8	127.13 ± 148.77	48	0.921
ALT (U/L)	65.41 ± 89.31	39.02	51.61 ± 46.49	39.30	74.64 ± 108.08	39.20	0.634
ALT T1 (U/L)	50.43 ± 69.31	30.4	42.25 ± 35.41	32.65	55.38 ± 83.18	29.7	0.909
ALT T2 (U/L)	71.15 ± 91.72	45.1	48.85 ± 35.29	42.8	91.95 ± 119.58	54.4	**0.018**
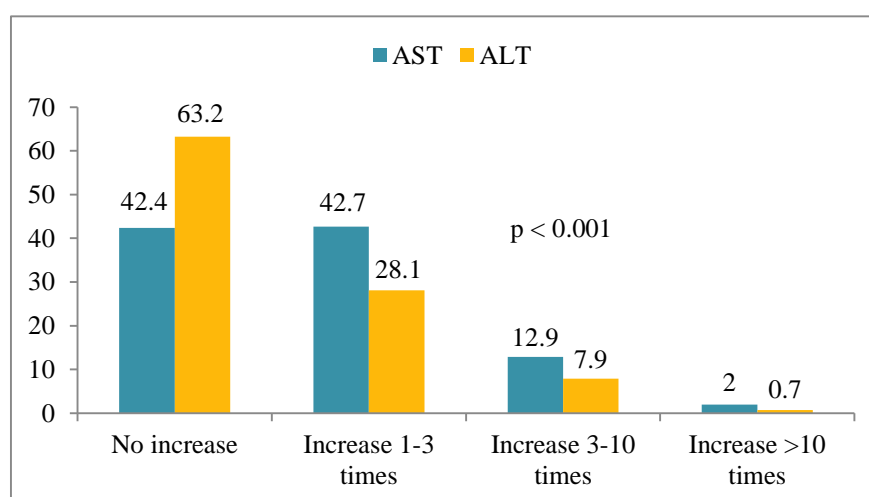
Figure 1. Comparison of increased rates of AST and ALT in Dengue patients.

In our study, the ratio of patients who increased AST was 57.6%. Most patients had an increase of 1-3 times in AST level accounting for 43.7%. The rate of ALT increase was less than that of AST (36.8%) and prevalently increased by 1-3 times (28.1%) (Figure 1).

AST rose from 1-3 times in the group without warning signs (51.2%), which was considerably higher than in the group with warning signs (37%), p=0.013. The rate of increase in AST from 3 to 10 times was higher in the group with warning signs (13.8%).

However, there was no statistical difference between the two groups (11.6%). The AST level rose more than 10 times in the group with warning signs while that did not occur in DHF without warning signs (Figure 2a).

There was no significant difference in ALT levels in the two groups (p>0.05). Whilst none of the Dengue patients without warning signs had ALT levels increased upper ten times, 1.1% of Dengue patients with warning signs induced ALT increases upper ten times (Figure 2b).
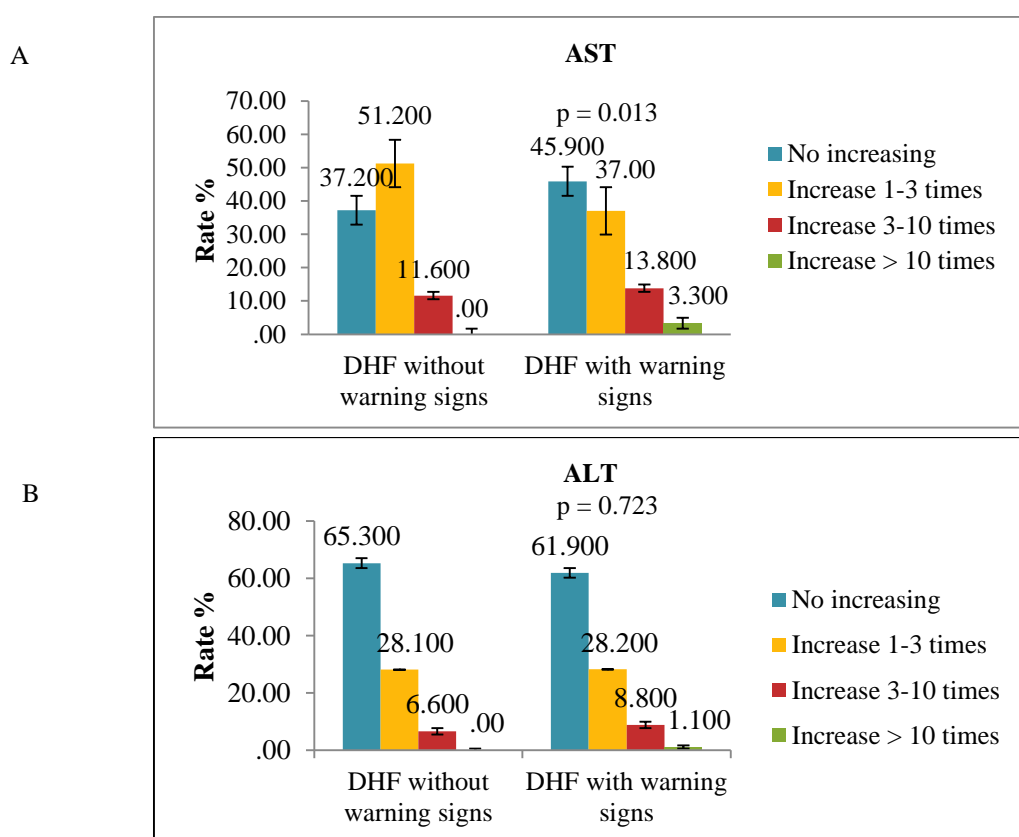

Figure 2. Comparison of the increase of AST (A) and ALT (B) in two study groups.

Table 3. Deritis index in Dengue patients

		Total	DHF without warning signs	DHF with warning signs	OR	CI	p
Deritis index	<1 (n, %)	40 (13.2)	17 (14.0)	23 (12.7)	1.123	0.572-2.203	0.736
	>1 (n, %)	262 (86.8)	104 (86.0)	158 (87.3)			

In our study, patients' Deritis index (AST/ALT) was common >1 accounting for 86.8%. The similarity was observed in two groups without and with warning signs which had Deritis index > 1 accounting for 86.0% and 87.3%, respectively (Table 3).

3.3. Some Factors Related to AST and ALT Levels in Dengue Patients

The results of analyzing the relationship between AST and ALT level changes and some clinical characteristics between the two groups of Dengue patients are shown in Table 4 and Table 5.

Table 4. Some characteristics of the AST index in Dengue patients

Index		DHF without warning signs		DHF with warning signs		p
		($\bar{x} \pm SD$)	Median	($\bar{x} \pm SD$)	Median	
Gender	Male	81.66 ± 62.91	60.3	131.85 ± 255.03	58	0.978
	Female	76.65 ± 55.04	61.8	100.94 ± 126.79	55.8	0.833
Age	<40	88.76 ± 66.63	62.8	122.86 ± 230.32	50.85	0.344
	40-60	78.06 ± 62.62	64.35	106.68 ± 105.71	62.1	0.603
	>60	65.98 ± 38.85	58.7	95.11 ± 120.31	64.95	0.673
BMI	<18.5	70.12 ± 63.05	47.6	96.04 ± 109.12	51.6	0.760
	18.5-25	82.14 ± 61.42	63.6	111.53 ± 181.10	55.3	0.466
	>25	68.09 ± 43.96	53.25	133.83 ± 190.57	71.9	0.484
History of Dengue	Primary	78.26 ± 56.01	61.5	110.98 ± 185.77	54.0	0.574
	Secondary	92.12 ± 87.51	55.9	119.19 ± 97.73	93.65	0.406
History of biliary liver disease	Yes	102.89 ± 87.22	54.3	94.56 ± 80.65	83.8	0.805
	No	78.33 ± 58.00	61.5	111.01 ± 183.71	55.8	0.835

Table 5. Some characteristics of the ALT index in Dengue patients

Index		DHF without warning signs		DHF with warning signs		p
		($\bar{x} \pm SD$)	Median	($\bar{x} \pm SD$)	Median	
Gender	Male	54.25 ± 41.87	41.4	100.94 ±126.79	44.3	0.538
	Female	47.29 ± 53.38	33.3	71.29 ±100.32	34.1	0.408
Age	<40	53.87 ± 45.15	40.4	81.87 ± 129.91	39.25	0.910
	40-60	56.22 ± 58.76	39.0	76.60 ± 82.51	39	0.511
	>60	41.77 ± 27.30	39.7	60.02 ± 79.92	39.7	0.781
BMI	<18.5	34.99 ± 29.73	21.4	64.63 ± 73.41	34.1	0.439
	18.5-25	53.29 ± 49.43	39.6	69.85 ± 98.84	36.9	0.894
	>25	51.50 ± 28.42	45.0	122.37 ± 181.95	49.8	0.435
History of Dengue	Primary	50.92 ± 46.00	39.0	74.57 ± 111.16	38.6	0.813
	Secondary	57.05 ± 52.05	41.1	75.55 ± 49.98	85.6	0.406
History of biliary liver disease	Yes	50.51 ± 46.02	55.2	74.41 ± 108.74	77.35	0.560
	No	69.40 ± 54.30	39.1	96.81 ± 108.57	38.8	0.902

When comparing two groups of AST and ALT indexes, there was no difference in gender, age, BMI, history of biliary liver disease, and the number of Dengue times (p>0.05).

When grouping thrombocytopenia by 4 levels (>100G/L, 50-100G/L, 5-50-G/L, <5G/L), the results in Table 6 showed that the lower the platelet count group of patients, the higher the transaminase concentration. This was evident in the febrile phase (days 1-3) and the critical phase (4-7 days) for AST (p=0.05 and p=0.001) while for ALT, it was shown in the critical phase (p=0.003).

Table 6. The reduction of platelets related to AST and ALT levels

	Patients (n, %)	AST ($\overline{x} \pm$ SD) U/L	p^2	ALT ($\overline{x} \pm$ SD) U/L	p^2
Platelet T1					
> 100 G/L	145 (78.4)	79.31 ± 104.80	0.05	56.17 ± 67.46	0.321
50-100 G/L	31(16.8)	123.94 ± 306.18		64.22 ± 137.85	
5-50 G/L	9 (4.8)	147.68 ± 239.68		129.79 ± 225.62	
< 5G/l	0 (0.0)				
Platelet T2					
> 100 G/L	59 (25.0)	97.49 ± 230.34	0.001	68.56 ± 120.29	0.004
50-100 G/L	94 (39.8)	101.49 ± 123.05		65.81 ± 96.13	
5-50 G/L	81 (34.3)	129.15 ± 124.69		73.70 ± 74.06	
< 5G/l	2 (0.9)	207.70 ± 0.00		112.20 ± 0.00	

4. Discussion

4.1. General Characteristics and the Changes in Serum Transaminase Levels in the Patients

Dengue fever is still a significant challenge to public health in Southeast Asia, including Vietnam. Among 302 patients included in our study, 181 Dengue patients had warning signs, 121 Dengue patients did not have, and no one developed severe Dengue. According to a study in a hospital in Hanoi, Vietnam (2015), 122 of 143 patients (85.3%) had at least one dengue warning sign [14]. Another study in Vietnam showed that the percentage of Dengue patients with warning signs was lower than those without warning signs (110:117) [15]. The difference in results between the studies happened due to the distinction in area and time to do the research. The ratio of males to females in our study was 1:1.2. The proportions of female patients in total and the group of Dengue with warning signs were higher than that of males (p<0.001). Similar results were found in some studies around the world, such as: in India (2018), with 47% male and 53% female [8] and in Sudan (2012), male to female ratio was 3:4 [16]. However, according to a study in Hanoi, Vietnam (2015) [14] and another study in Vietnam (2022) [15], the proportions of Dengue-induced males were higher than females. There are various theories about the prevalence between men and women induced Dengue,

depending on each stage of age, geographic region, and demand for health services [17].

The age of patients in our study ranged from 8 to 94 years old. The mean age was 44.56 ± 19.41. A study in Thailand (2015) illustrated the mean age of Dengue patients was 49.9 ± 16.7 [19]. This figure in another study in Pakistan (2014) was 35.57 ± 3.81 [11].

Among 302 patients participating in our study, there were 25 patients (8.3%) with a history of secondary Dengue, and there was no significant difference between the two groups of Dengue with and without warning signs. Secondary Dengue can increase the risk of severe disease. However, we did not see a relationship between the number of dengue cases and the disease severity in this research. The number of fever days ranged from 3 to 9 days, 4.01 ± 0.56 days on average. The number of treatment days ranged from 2 to 14 days, and the mean was 5.76 ± 2.10. There were similarities between the time of fever and treatment between the two groups of patients in our study.

Liver damage with the elevation of aminotransferases is a prevalent complication of dengue virus infection. In our study, AST and ALT indexes increased in all dengue patients, with mean values were 98.79 ± 145.89 U/L and 65.41 ± 89.31 U/L, respectively. The mean value of liver enzymes was lower than that of similar studies, possibly due to the difference in the group of patients [12, 19, 20]. The mean values

of liver enzymes in the group with warning signs were 115.53 ± 181.1 U/L in AST and 74.64 ± 108.08 U/L in ALT. Our results were similar to Lee (2012) (AST: 114 U/L, ALT: 73 U/L) [19] and lower than the results of Balakumar (2019) (AST: 134.84 U/L, ALT: 107.88 U/L) [20]. Though there was no difference in mean values of liver enzymes between the two groups, AST and ALT levels tended to be greater in the group with warning signs. Elevated AST occurred from the febrile phase of Dengue in the first three days, while elevated ALT mainly presented during the critical phase (days 4-7). In the critical phase of the disease, the increase in ALT in the group with warning signs was higher than in the group without warning signs (p < 0.05). The degree of ALT elevation associated with disease severity has also been shown in studies by Zubair (2017) [21] and Ayaz (2020) [23]. 58.6% of patients increased AST, and 37.8% of patients increased ALT. Our results were lower than other studies, with AST increased from 63-97% and ALT increased from 45-96% [12, 15, 19]. The liver enzyme elevation was primarily from 1-3 times: 42.7% with AST and 28.1% with ALT. The liver enzymes in our study increased from low to moderate, and this result was also shown in other studies [5, 12].

The level of AST in patients without warning signs increased from 1 to 3 times, which was higher than in patients with warning signs (p = 0.013). The elevated ALT was similar between the two groups, as shown in Rajoo's result (2008) [12]. Many studies demonstrated that the elevation of liver enzymes in Dengue is similar to the increase in viral hepatitis [19, 20]. Therefore, it is necessary to distinguish the cause of elevated liver enzymes due to DENV or hepatitis virus. Using the Deritis index, our study indicated that the AST level increased greater than ALT in most patients. This result was similar in both dengue patient groups [5, 8, 19, 20]. This might be because AST is also present in other organs, such as the heart, muscle, and bone while ALT is mainly in the liver. An AST/ALT ratio < 1 is commonly present in other virally acute liver injuries such as hepatitis A, B, and C [5].

4.2. Some Factors Related to AST and ALT Indexes in Dengue Patients

In our results, age, gender, BMI, history of Dengue, and history of chronic hepatobiliary diseases did not affect the elevation of AST and ALT in Dengue patients. Samanta (2015) illustrated a similar result: male and female gender equally affected liver enzyme elevation [19]. In Bandaru' study (2016), there was no difference in transaminase values between primary and secondary dengue infection [24]. However, in some other studies, liver damage was more prevalent in females than males and patients with primary infection [25]. In the study by Sekarn (2018), elevated ALT level was more frequently observed in obese compared to non-obese patients [26].

Thrombocytopenia is one of the essential criteria in assessing the severity of Dengue [28]. The hemorrhagic mechanism in DHF is involved in liver dysfunction and decreased platelet count [28]. Our study found that patients with lower platelet counts had higher transaminase levels, especially in the critical phase of the disease (p < 0.05). Similar to the results of Dr. Balakumar J (2019) [22] and Rajni R. (2018) [29], elevated AST and ALT levels were associated with decreased platelet count and thus related to levels of severity of Dengue.

5. Conclusion

AST levels in two groups of Dengue without and with warning signs were 79.75 ± 59.85 U/L and 111.53 ± 181.10 U/L, respectively. ALT levels in the two groups were 51.61 ± 46.49 U/L and 74.64 ± 108.08 U/L, respectively. There were no significant differences in mean AST and ALT values in the two groups (p > 0.05). Both AST and ALT increased from the early stage of Dengue infection. Notably, elevated ALT occurred from days 4-7 of the disease. The increases in AST from 1-3 times and > 10 times

were more common in group Dengue without warning signs, accounting for 51.2% and 3.3%, respectively. However, the two groups had no significant difference in ALT levels. The AST level was higher than ALT in most patients, resulting in a Deritis index > 1. There was no correlation between age, sex, BMI, history of Dengue, and chronic liver disease with elevated levels of liver enzymes in the two groups. Patients with lower platelet counts had greater transaminase levels, particularly during the disease's critical phase ($p < 0.05$), thus related to the severity of Dengue infection.

Acknowledgment

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