Indonesian Journal of Medical Laboratory Science and Technology
Open Access
p-ISSN 2684-6748
e-ISSN 2656-9825

RESEARCH ARTICLE

Effect of dengue infection on liver profile and haematological parameters

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Article history:
Received: 2023-08-28
Revised: 2023-12-30
Accepted: 2024-01-16
Avalibale online: 2024-03-15

Keywords:
Aspartate-aminotransferase
Alanine-aminotransferase
Dengue
Platelets
White blood cells

https://doi.org/10.33086/ijmlst.v6i1.5039

Abstract

Dengue fever is endemic in Sri Lanka. Liver damage is common in dengue fever. Understanding the pattern change of the liver profile and haematological parameters is crucial for managing dengue patients and minimising liver damage. The purpose of this study was to determine the pattern change in liver profile and the haematological parameters of dengue patients. Sixty apparently healthy volunteers and 169 acute dengue patients aged 20 or older had their blood samples examined. Liver enzymes, albumin, protein, bilirubin, white blood cell count, platelet count, haematocrit, and haemoglobin were measured. There was an increase in aspartate aminotransferase (105.6 IU/L), alanine aminotransferase (82.6 IU/L), and gamma-glutamyl transferase (68.9 IU/L), which were 3.4, 3.9, and 3.2-fold higher, respectively, than those of the control group, suggesting liver injury. Eighty-four percent of patients had raised levels of aspartate aminotransferase, and 74% of patients had elevated levels of alanine aminotransferase, indicating the prominence of aspartate aminotransferase over alanine aminotransferase. The presence of a positive correlation between the levels of aspartate aminotransferase and alanine aminotransferase indicates that the elevation of enzymes is primarily due to a single cause, liver injury. White blood cells and platelet counts were significantly lower. Platelet count demonstrated a negative correlation with both haematocrit and haemoglobin in dengue patients. In conclusion, aspartate aminotransferase was identified as the most significant marker of dengue-associated liver injury, followed by alanine aminotransferase. Low platelet and white blood cell counts were the major unfavourable changes in dengue patients' haematological characteristics.

1. INTRODUCTION

Dengue fever (DF) is caused by the dengue virus (DENV), an RNA virus belonging to the genus Flavivirus. Infection with this virus can result in asymptomatic infection or a range of manifestations, including nonspecific fever, dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) (1). Diagnosis based on clinical signs and symptoms is unreliable due to nonspecific nature (2). Confirmation of the infection can be achieved by determining the presence of dengue viral antigen, genomic sequence, or specific antibody IgM or IgG in patients' serum or plasma.

The liver is one of the organs affected by dengue infection. Histological examination of liver biopsy samples from dengue-infected individuals revealed cell swelling, steatosis, and apoptosis in all areas of the hepatic

Citation: Hunais MM, Shiffana S, Udayangani WGN. Effect of dengue infection on liver profile and haematological parameters. Indones J Med Lab Sci Technol. 2024;6(1):9–17. https://doi.org/10.33086/ijmlst.v6i1.5039

acinus, with the highest incidence observed in mid-zonal locations, as reported by Ribeiro et al. (3). Additionally, Kupfer cell hyperplasia and hypertrophy were noted. Hepatocellular injury, identified in 60%-90% of DHF patients by Leowattana et al. (4), is attributed to both host immune responses to the virus and the direct cytopathic effect of the virus, leading to hepatocyte apoptosis. This hepatocellular injury contributes to alterations in the biochemical parameters of the liver profile, including changes in liver enzymes such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

A hospital-based study by Chandola et al. (5) revealed elevated levels of AST, ALT, GGT, ALP, and total bilirubin (BIL) in 78.3%, 55.6%, 36.1%, 8.24%, and 4.12% of dengue patients, respectively. Furthermore, it revealed a significant increase in AST (mean ± SE: 356.6 ± 51.2 IU/L) compared to the rise in ALT (mean ± SE: 166.2 ± 31.2 IU/L). ALT is primarily present in the cytosol of hepatocytes and detectable in serum at low concentrations. The loss of membrane integrity of hepatocytes or necrosis of hepatocytes results in a high concentration of ALT in the blood (6). Tiwari et al. (7) reported elevated ALT in 73% (237/324) and AST in 71% (231/324) of dengue-confirmed patients.

The other biochemical parameters altered in dengue fever are total protein (PROT) and serum albumin (ALB). Swamy et al. (8) reported lower levels of serum ALB (<35 g/L) in 17.5% of dengue patients. According to Kularatnam et al. (9), the reduction in serum ALB occurs when the patient enters the plasma-leaking phase. Ayyadevara (10) revealed the PROT was significantly low (mean ± SD: 53±2.6 g/L) in DSS patients.

Dengue infection-induced liver injury is not equally reflected in all the parameters of the liver profile. Some values significantly differ from normal reference values, while others do not. Identification of parameters that differ significantly could be recommended for every dengue patient to assess the liver injury rather than requesting all liver profile tests to avoid unnecessary testing. This approach is not only cost-effective but also allows specific parameters to serve as efficient evaluation tools for dengue-associated liver injury.

Studies conducted in various parts of the world have examined the effects of dengue infection on the liver profile. However, the pattern of change in liver profile in dengue-infected patients compared to healthy individuals seemed not to be studied enough in the Sri Lankan context. Knowledge in this regard is crucial for estimating the degree of liver injury as well as for monitoring and managing dengue patients effectively. Some studies suggest that AST is the most prominent marker of dengue-associated liver injury, while others state that ALT holds this distinction.

When considering the haematological parameters of dengue patients' platelet (PLT) count and haematocrit (HCT), they are crucial for patient management. These two parameters play a significant role in indicating the severity of the infection and guide the implementation of necessary measures to ensure sufficient PLTs and maintain fluid balance in dengue patients. Research by Pathak et al. (11) reveals that HCT increases with the severity of dengue infection, while PLT count decreases.

Thrombocytopenia is a prevalent characteristic among dengue patients. Research by Jayadas et al. (12) found that 32% (25/78) of dengue patients had a PLT count less than 150 x 10^9/L and 52.5% (41/78) had a count of less than 100 x 10^9/L. In addition, the study observed a decreased white blood cell (WBC) count (< 5 x 10^9/L) in 85.8% (67/78) of dengue patients.

This study aimed to identify the pattern of changes in liver profile and haematological parameters of dengue-confirmed patients in comparison to a control group of healthy individuals. The objectives of the study were to determine which liver profile tests yield significantly different results in dengue patients compared to healthy individuals, identify the most notable liver profile parameters that are more sensitive to measuring dengue-associated liver injury, and explore any correlations within and between the haematological and liver profile parameters of dengue patients.

2. MATERIALS AND METHODS

2.1 Settings, Study Design, and Period

The study was conducted at Teaching Hospital Peradeniya in Sri Lanka. It involved an analytical cross-sectional design and spanned a period of ten months, from November 2019 to August 2020.

2.2 Sample Size and Sampling

The sample size was 229, with 169 serologically confirmed acute dengue cases and 60 apparently healthy volunteers. The convenience sampling technique was used in the sampling process.

2.3 Ethical Considerations

The Ethics Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka, granted ethical approval for the protocol of this study under the reference number 2019/EC/31. Each participant provided written, informed consent. The data collected from subjects and the test results were protected and kept confidential by the investigators.

2.4 Inclusion and Exclusion Criteria

The study included male and female patients aged 20 or more with serologically proven acute dengue fever admitted to the professorial medical unit of Teaching Hospital Peradeniya, and apparently healthy volunteers served as controls. It excluded patients who were pregnant, had a known liver illness, or had taken any alternative treatment or a known hepatotoxic drug within the preceding six months.

2.5 Detection of Dengue

The presence of acute dengue fever was verified by detecting dengue NS1 antigen, or IgM dengue-specific antibody, in patients' serum with the standard Q Dengue Duo immunological chromatographic test kit.

2.6 Specimen Collection and Procedure

Five millilitres of blood were collected from dengue-confirmed patients and apparently healthy individuals (the control group), 2 mL of which was distributed into an EDTA tube for haematological investigations; the remaining 3 mL was transferred to a plain tube for biochemical tests including AST (aspartate aminotransferase), ALP (alkaline phosphatase), GGT (gamma-glutamyl transferase), total BIL (Bilirubin), total PROT (Protein), and ALB (Abumin). Serum separated from clotted blood in the plain tube was utilized to undertake biochemical examinations on an AU 480 Beckman Chemistry analyser manufactured in the USA. The Mindray 6800 six-part analyser made in China was used to perform haematological investigations such as WBC, haemoglobin (Hb), HCT, and PLT counts. Quality control (QC) samples were run alongside the tests to validate them technically, and the test results were accepted when the QC results were well within two standard deviations (SD).

2.7 Statistical Analysis

Statistical analysis was carried out using the "Minitab 16" software. The confidence interval (CI) was set at 95%, and statistical significance was defined as $P < 0.05$. The Anderson-Darling Normality Test was applied to determine whether the distribution of the test results was normal or not. The test results (median) of dengue patients and the control group were compared using the Mann-Whitney Test. Pearson's correlation test was performed to assess the relationship and significance between variables.

3. RESULTS AND DISCUSSION

The age range of the patients was 20 to 69, with a mean age of 41.77 ± 13.54 years. Among the 169 confirmed cases of dengue, there were 102 men and 67 women.

3.1. Biochemical Parameters

In this study, liver markers, including liver enzymes, were measured in acute dengue patients. The patient results differed from those of the control group. Many patients exhibited high values, while a few did not. AST, ALT, GGT, and total BIL were significantly higher ($p < 0.05$) in dengue patients (Table 1), while ALP did not show a significant difference ($p > 0.05$).

Table 1. The summary results of the biochemical analysis of blood samples

Analytes	Median	
	Dengue Patient	Control
AST (IU/L)	105.6	31.0
ALT (IU/L)	82.6	21.3
GGT (IU/L)	68.9	21.5
ALP (IU/L)	76.0	75.4
Total BIL (µmol/L)	10.8	8.0
Total PROT (g/L)	68.0	75.0
ALB (g/L)	40.0	41.5

When comparing AST (median: 105.6 IU/L) to the control group (median: 31 IU/L), it was more than three times higher (3.4); compared to the method's upper reference limit (50 IU/L), it was more than two times higher (2.1). The relative risk (RR) of elevated AST (AST > 31 IU/l) in dengue patients was 1.97. Similarly, the patients' ALT levels (median: 82.6 IU/L) were almost four times higher (3.9) than the control group (median: 21.3 IU/L) and 1.7 times higher than the reference upper limit (50 IU/L). The RR of elevated ALT (ALT > 21.3 IU/L) in dengue patients was 1.90.

According to a study on 2165 dengue seropositive patients by Chandola et al. (5), AST was 5.9 times higher than the upper reference limit and ALT was 3.7 times higher than the upper reference limit. In the current study, AST outperformed ALT in terms of enzyme levels (median AST: 105.6 IU/L, median ALT: 82.6 IU/L) in dengue patients. It cannot be ruled out as a possible source of AST from other organs such as the heart, skeletal muscles, kidneys, and brain (13). Similarly, there may be a contribution to elevated ALT from other organs such as skeletal muscles, kidneys, myocardium, brain, pancreas, spleen, and lung, but ALT is predominantly present in hepatocytes (6). The study by Chandola et al. (5) also supports the notion that the AST is more prominent than the ALT, as the AST and ALT levels were (mean ± SE) 356.6±51.2 IU/L and 166.2±31.2 IU/L, respectively, in dengue patients.

When considering the number of patients with elevated liver markers (Table 2), 84% of dengue patients had a higher level of AST than its upper reference limit (50 IU/L), and 74% of dengue patients had a higher level of ALT than its upper reference limit (50 IU/L). This finding strongly indicates the prominence of AST over ALT. Similarly, Swamy et al. (8) found that 73.3% of dengue patients had elevated AST (>35 IU/L) compared to 50.8% with raised ALT (>45 IU/L). A study by Jayadas et al. (12) revealed elevated AST in 80.7% of dengue patients and elevated ALT in 41.0%. Saara et al. (14) found elevated AST in 85% and raised ALT in 67% of dengue-confirmed patients. All of these observations support our finding that AST takes precedence over ALT.

The relative risks of AST (1.97) and ALT (1.90) indicate that the risk of elevated levels of liver enzymes (AST > 31 IU/l, ALT > 21.3 IU/L) in dengue patients was almost double that of healthy individuals. Additionally, the relative risk of AST was slightly higher than that of ALT, suggesting that AST was more prevalent than ALT.

Table 2. Percentage of patients having elevated levels of liver parameters

Analyte	URL	Number of patients with a level higher than the URL. (Total = 169)	Percentage (%)
AST	50 IU/L	142	84
ALT	50 IU/L	125	74
GGT	55 IU/L	37	22
ALP	120 IU/L	10	6
Total BIL	21 µmol/L	34	20
Total PROT	83 g/L	52	31
ALB	52 g/L	27	16

URL: Upper Reference Limit

The analysis of the relationship between AST and ALT levels of dengue patients displayed a significant positive linear correlation (Figure 1), with Pearson's correlation coefficient of +0.630 and $p < 0.05$. However, no statistically significant linear correlation was found between the liver parameters ALP, BIL, GGT, PROT, and ALB and the levels of AST or ALT in dengue patients. Further analysis of the association between the PLT count of dengue patients and AST and ALT revealed (Figure 2) a negative linear correlation (-0.246, -0.211, $p < 0.05$); in contrast, no such correlation was observed in the control group.

The positive linear association between AST and ALT in dengue patients suggests that the rise is primarily due to a single cause, indicating dengue-associated liver damage. Kalluru et al. (15) also revealed a strong association between increased levels of AST and ALT and the severity of dengue fever. Additionally, the negative linear association between PLT count and AST and ALT present in our study demonstrates the impact of the dengue virus on both the liver and PLT count. Kalluru et al. (15) noted that individuals with dengue who have increased AST and ALT levels are more likely to have bleeding tendencies.

The ALP level of dengue patients (76.0 IU/L) in our study did not show any significant difference from the control group (75.4 IU/L), and it remained well within the reference range (30-120 IU/L). Moreover, only 6% of dengue patients (10 out of 169) exhibited elevated ALP beyond the upper reference limit. In contrast, Swamy et al. (8) observed that 19.2% (23 out of 120) of dengue patients had elevated ALP. ALP is not specific to the liver and is generally elevated in hepatobiliary disease. It may not increase until the biliary pole of hepatocytes in bile duct epithelia or any other source of ALP is affected by the dengue viral infection. The RR of elevated ALP (ALP > 75.4

IU/L) in dengue patients was 1.0, indicating that the risk of elevated ALP in dengue patients is equal to that of healthy individuals.

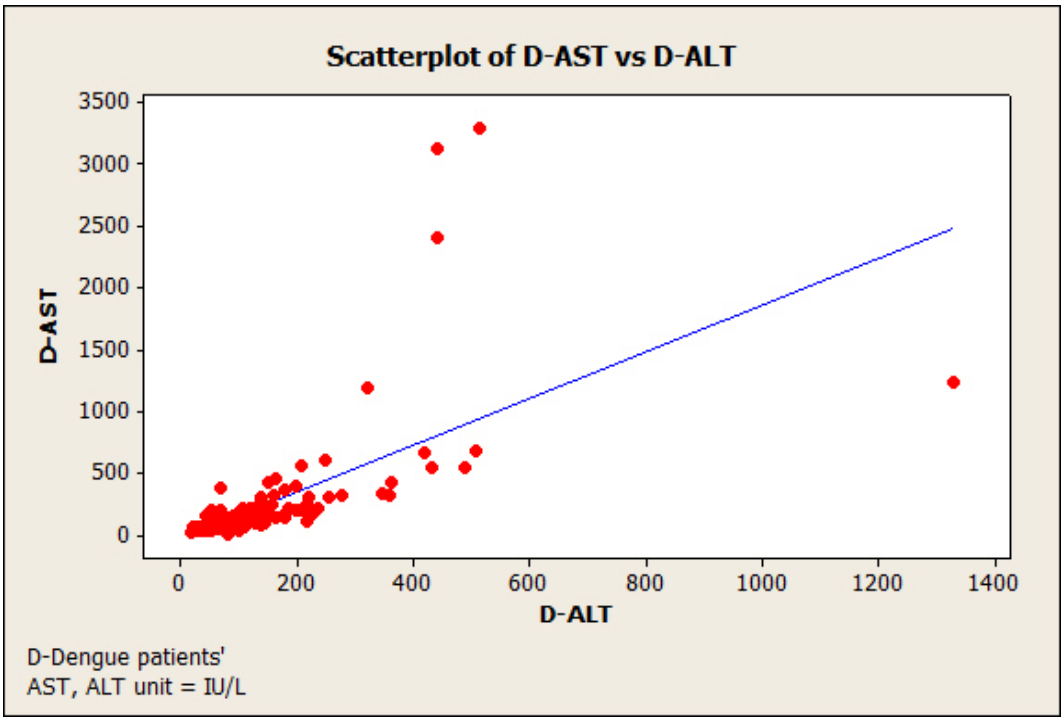

Figure 1. Correlation between AST and ALT levels in dengue patients

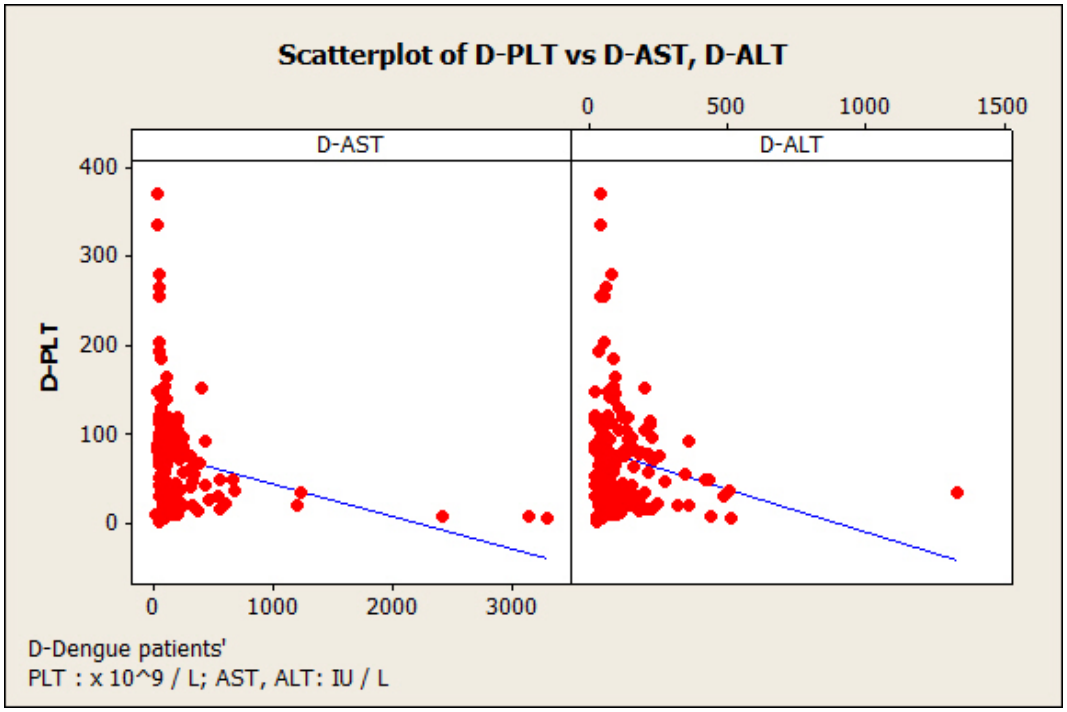

Figure 2. Correlation between PLT counts and AST and ALT in dengue patients

The GGT level of dengue patients (median: 68.9 IU/L) was found to be more than three times higher (3.2) than the control group (median: 21.5 IU/L) and 1.3 times higher than the upper reference limit (55 IU/L). The RR of elevated GGT (GGT > 21.5 IU/L) was 1.90. While GGT is widely used to assess liver function, it is not specific to the liver. This study revealed a statistically significant increase in GGT activity in dengue patients (median: 68.9 IU/L) compared to the control group (median: 21.5 IU/L). The relative risk of GGT (1.90) indicates that the risk of elevated GGT (GGT > 21.5 IU/L) in dengue patients was twice that of healthy individuals, equal to the relative risk

of increased ALT in dengue patients. Additionally, increased GGT was present in 22% (37 out of 169) of dengue patients, surpassing the upper reference limit of 55 IU/L. Research by Chandola et al. (5) found that 36.1% of dengue patients had elevated GGT (mean ± SE: 83.8±6.5 IU/L), higher than the top limit of normal. Bhriguvanshi et al. (16) observed that 26% of dengue patients had high GGT. The elevated GGT could be attributed to oxidative stress. According to Pillai et al. (17), there is an imbalance between oxidants and antioxidants in dengue infection, resulting in increased reactive oxygen species. Chandrasena et al. (18) reported that oxidative stress peaks around day 5 of dengue infection, characterised by low antioxidant enzymes and glutathione. A decrease in glutathione level, which is the substrate of GGT, results in increased cell GGT. However, the absence of elevated GGT in a significant proportion of dengue patients in this study makes GGT a poor primary candidate for measuring dengue-associated liver injury.

The total BIL level of dengue patients (median: 10.8 µmol/L) was significantly higher than the control group (median: 8.0 µmol/L), but it remained well within the method reference range (BIL: 5-21 µmol/L). The RR of elevated BIL (BIL > 8.0 µmol/L) in dengue patients was 1.49. Additionally, 20% of dengue patients had bilirubin levels exceeding the upper reference range (> 21 µmol/L). Swamy et al. (8) observed that 9.2% of patients had elevated levels. Our study results imply that although bilirubin may be a sensitive measure for evaluating liver damage, it cannot be regarded as the main hepatic marker in dengue infection.

The present study found that dengue patients had statistically significantly lower levels of albumin (40 g/L) and protein (68 g/L) than the control group (ALB 41.5 g/L, PROT 75 g/L). However, these values were still well within the method reference range (ALB: 35–52 g/L, PROT: 66–83 g/L). The RR of decreased albumin level (albumin < 41.5 g/L) was 1.4, and the RR of decreased total protein level (protein < 75 g/L) in dengue patients was 1.6. Additionally, 16% and 31% of dengue patients showed decreased albumin and total protein, respectively. According to a study by Kularatnam et al. (9) on children with dengue infection aged 5 to 12 years, when a patient's condition deteriorates and they move into the plasma leak phase, their serum albumin levels begin to decrease (< 37.5 g/L). Teerasarntipan et al. (19) reported that patients with severe hepatitis caused by dengue had reduced albumin levels (36 ± 6 g/L). Ayyadevara (10) observed that protein decreased with increasing severity (DF: 67.9 ± 4.9 g/L, DHF: 58.4 ± 4 g/L, DSS: 53 ± 2.6 g/L) of dengue. Hypoproteinemia and hypoalbuminemia are typically observed in severe cases. In our study, no patient with fluid leakage, DHF, or in the critical stage was reported.

3.2. Haematological Parameters

Haematological parameters are crucial for assessing the condition of dengue patients and providing appropriate patient care. The PLT count is one such important parameter. In our study, the PLT count of dengue patients was found to be 63.5 x 10^9/L (Table 3), significantly lower ($p < 0.05$) than that of the control group (median: 243.5 x 10^9/L). It was also lower than the lower reference limit (PLT: 150 x 10^9/L). A decreased PLT count is considered a typical characteristic of dengue infection. Our results align with a study by Jayadas et al. (12) at the Jaffna Teaching Hospital in Sri Lanka, which found that 52.5% (41/78) of dengue patients had a low PLT count (< 100 x 10^9/L). According to a study by Tiwari et al. (7), 99.0% (321/324) of dengue patients had low platelet counts (< 100 x 10^9/L). Moreover, Kadadavar et al. (20) reported that 97% of dengue patients had a low count (< 100 x 10^9/L). A decrease in PLT count was observed by Pathak et al. (11), with an increasing amount of virus load in children infected with dengue. Low platelet counts can result from bone marrow suppression, direct dengue virus infection of platelets, PLT adherence to leukocytes and vascular endothelium, and antiplatelet antibody activity (21).

Table 3. Summary of the results of the haematological analysis

Analytes	Median	
	Dengue	Control
WBC (per litre)	3.14 x 10^9	8.24 x 10^9
PLT (per litre)	63.5 x 10^9	243.5 x 10^9
HCT (%)	39.7	41.2
Hb (g/L)	133	135

When the WBC count of dengue patients (median: 3.14 x 10^9/L) was compared with the control group (median: 8.24 x 10^9/L), it was substantially lower ($p < 0.05$) and was also below the lower reference limit (WBC: 4 x 10^9/L). Juliansen et al. (22) found a low WBC count (median 4.01 x 10^9/L) in contrast to the control group (median 12.54 x 10^9/L). The study conducted by Jayadas et al. (12) reported a low WBC count; the mean count during the

febrile phase of dengue infection was 3.95 ± 1.66 x 10^9/L, and during the critical phase, it was 3.11 ± 1.51 x 10^9/L. One of the typical characteristics of dengue infection seems to be leukopenia; this could be because dengue infection causes hypocellularity in the bone marrow.

In the present study, the dengue patients' Hb level was found to be 133 g/L, which showed no significant difference ($p > 0.05$) from the level of Hb in the control group (135 g/L), and it was also well within the reference range (130-170 g/L).

The HCT of the dengue patients was 39.7%, which was below the level of HCT of the control group (median: 41.2%) and that of the method's reference range (45 ± 5%). In a study by Rafi et al. (23) on 319 patients with serologically confirmed dengue, HCT was 39.97 ± 6.23% (mean ± SD). According to Sahassananda et al. (24), HCT was 40.3 ± 5.2% (mean ± SD) in 163 dengue-confirmed patients. All of these findings support our findings and point to a somewhat decreased HCT in dengue patients. In contrast, Wisanuvej et al. (25) found the HCT was 41.6% in dengue patients, which is a bit higher than the control group HCT. Kularatnam et al. (9) observed a distinct and rapid rise of HCT in DHF at the onset of the critical phase. Increased HCT suggests haemoconcentration, often observed in cases of extensive fluid leakage. In our study, HCT was slightly lower compared to the control group. This difference may be attributed to the hospitalised patients receiving intravenous fluid replacement therapy and the absence of patients in a critical condition where plasma leakage may occur.

The relationship between dengue patients' PLT count and HCT and Hb was both negative and linear (Figure 3), where Pearson's correlation of PLT versus HCT was -0.214 ($p = 0.005$) and PLT versus Hb was -0.296 ($p = 0.000$). However, no relationship was observed between PLT count versus HCT and Hb in the control group. This linear association was significant ($p < 0.05$), despite not being stronger. It shows that in dengue patients, PLT counts negatively correlate with HCT and Hb. Indirectly, it demonstrates a tendency for dengue patients' haemoconcentration to rise in correlation with a decreased PLT count. Similar to our study, Pathak et al. (11) also found elevated HCT correlating with thrombocytopenia.

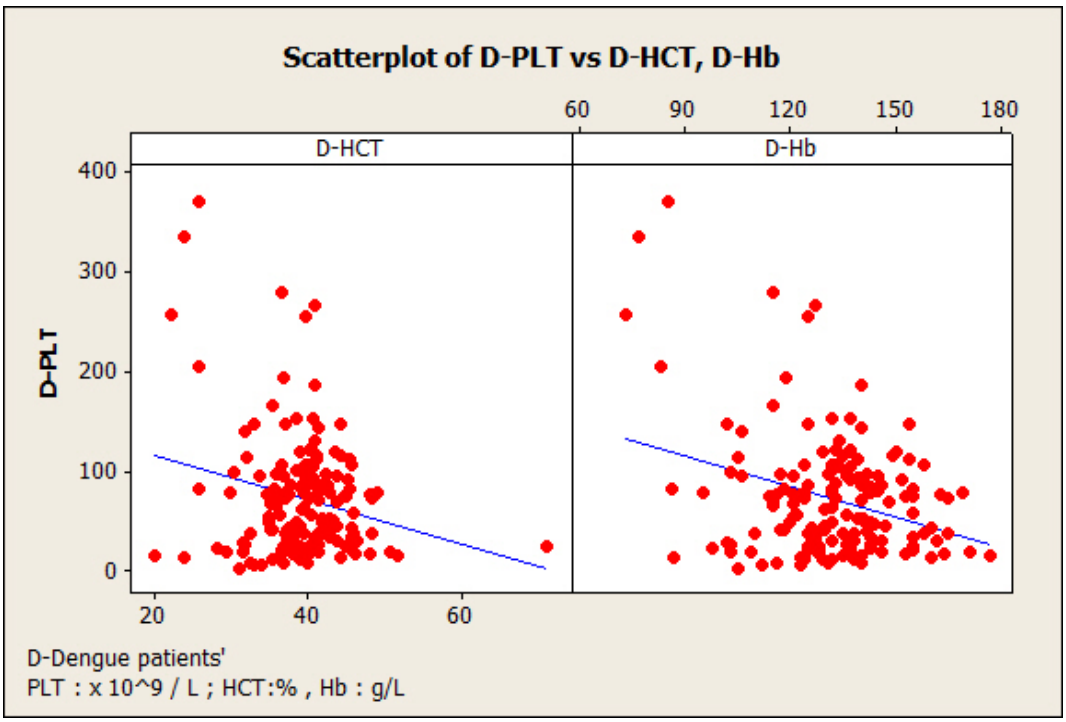

Figure 3. Correlation between dengue patients' PLT count and HCT and Hb

4. CONCLUSIONS

Among the elevated liver profile values observed in dengue-infected patients, AST emerged as the most prominent marker of dengue-associated liver damage, followed by ALT. Leukopenia and thrombocytopenia serve as crucial indicators of the detrimental impact of dengue on haematological parameters.

Author contributions: All three authors contributed equally to the work's planning and design. SS, WGNU: Collected and analysed the samples. MMH: Performed the statistical analysis, interpreted the results, and worked on the manuscript.

Funding: This research received no external funding.

Acknowladgements: We sincerely thank Dr. Arjuna Thilakarathne, Director of Teaching Hospital Peradeniya, and Professor Udaya Ralapanawa of the Faculty of Medicine, University of Peradeniya, Sri Lanka.

Ethics statement: The ethical clearance was provided by the Ethics Review Committee of the Faculty of Medicine, University of Peradeniya in Sri Lanka. 2019/EC/31 serves as the reference number.

Conflict of interest: There is no conflict of interest in the process of carrying out the research.

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