



Original Article

The aspartate aminotransferase/platelet count ratio index as a marker of dengue virus infection: Course of illness[☆]Anwar E. Ahmed^{a,b,e,*}, Bassam Dahman^c, Asmaa Altamimi^d, Donna K. McClish^c, Hamdan AL-Jahdali^e^a Uniformed Services University of the Health Sciences, F. Edward Hébert School of Medicine, Department of Preventive Medicine & Biostatistics, Bethesda, MD, USA^b Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA^c Virginia Commonwealth University, Richmond, VA, USA^d Tropical Diseases Center, National Health Laboratory, Saudi Center for Disease Prevention and Control (Saudi CDC), Riyadh, Saudi Arabia^e King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Ministry of the National Guard – Health Affairs, Riyadh, Saudi Arabia

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ABSTRACT

Background: The usefulness of laboratory tests in the decision-making process with regard to early identification of dengue virus infection has not been widely reported, particularly the aspartate aminotransferase (AST)/platelet count ratio index during a patient's days of illness. The aim of this study was to examine the pattern of the ratio index over the course of illness and identify whether it is a marker of dengue virus infection in dengue patients, as well as to assess the role of other laboratory tests.

Methods: A chart review of 205 dengue patients was analyzed using available records of 845 laboratory results within different time intervals or exam dates during the course of illness. We used repeated measures mixed binary logistic regression analyses to model the dengue virus infection, defined as giving at least one positive antibody test (yes/no).

Results: The high risk of dengue virus infection in dengue patients was found in the male gender (adjusted OR = 4.316, 95% CI: 1.285–14.498, $P = 0.018$), in patients with a high AST/platelet count ratio index (adjusted OR = 1.438, 95% CI: 1.057–1.957, $P = 0.021$), in patients with a low MCV level (adjusted OR = 0.815, 95% CI: 0.679–0.978, $P = 0.028$), and in patients with a low ALT level (adjusted OR = 0.996, 95% CI: 0.993–0.999, $P = 0.010$).

Conclusion: Laboratory markers, in particular the AST/platelet count ratio index, can be useful for clinicians to strengthen the decision-making process in primary care settings. Furthermore, our model revealed that low MCV and low ALT are predictors of the dengue virus infection, while being a male increases the risk of dengue virus infection. More studies are needed to evaluate the impact of the AST/platelet count ratio index on the severity of dengue fever infection during the onset of symptoms and course of treatment.

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Introduction

Dengue fever poses a national public-health concern and threat, particularly in Western Saudi Arabia [1]. The first case of dengue fever virus (Type 2) detected at Dr. Soliman Fakeeh hospital in Jeddah, Saudi Arabia—was in 1994 [2]. The Western region remains at high risk of dengue epidemic threats due to mass gatherings in its two holy cities, as a large number of Muslims from all over the globe perform Hajj and Umrah in Saudi Arabia [1,3].

Like other mosquito-borne diseases, the dengue virus has the potential to be transported from one country to another. A Japanese study reported one case of dengue fever, virus Type 2, when the patient returned from Jeddah, Saudi Arabia, where they believe the

person was infected [4]. Another study reported dengue Type 1 virus in an Indian woman who visited Saudi Arabia [5]. Dengue fever is frequently reported in the Western region of Saudi Arabia [3] and in neighboring countries, namely Yemen [6] and Sudan [7], where they have experienced dengue fever outbreaks.

Dengue fever and other mosquito-borne diseases share a wide range of similar clinical manifestations that make it difficult to differentiate between them, particularly after illness onset [8]. A number of markers, however, are considered potential predictors of severe dengue fever [9–12]. The severity of dengue fever increases with a high white blood cell count (WBC) [9,11] and decreases with low platelets [10,11]. A study identified aspartate transaminase (AST)/platelets count ratio index as positive predictor of severe dengue infection [9]. There is limited data available supporting the usefulness of AST/platelets count ratio index in the decision-making process during the course of illness. A Saudi Arabian study reported that a low platelet count is a significant predictor of developing severe dengue infection (dengue hemorrhagic fever) in adult patients (but not pediatric) [12].

This is a study from which the findings may be useful, not only to Saudi Arabia but also to tropical and subtropical countries where dengue fever is more common. The study reviewed the medical charts of patients who were serologically screened by antibody tests and confirmed a diagnosis of dengue fever by reverse transcription polymerase chain reaction (RT-PCR). We hypothesized that laboratory tests, in particular AST/platelet count ratio index, can be useful markers in the prediction of dengue infection. The purpose of this research is to examine the pattern of the AST/platelet count ratio index over the course of illness and identify whether it is a marker of dengue virus infection in dengue patients, as well as to assess the role of other laboratory tests.

Materials and methods

This is a retrospective review of patients who were diagnosed with dengue fever between 2016 and 2018 at the Ministry of National Guard – Health Affairs (MNG-HA) hospitals and clinics across Saudi Arabia. An IRB ethics review was performed, and approval was obtained from the MNG-HA, approval #RC18/291/R.

The diagnosis was made according to RT-PCR and the clinical criteria International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). During the study period, we identified dengue hemorrhagic fever, code 065.4; dengue fever (classical dengue), code A90; and chikungunya virus disease, code A92.0. A total of 206 records were retrieved, of which one patient was found to be positive for chikungunya virus infection and was excluded, while 200 had classical dengue fever (97.09%) and 5 had dengue hemorrhagic fever. The final sample studied was comprised of 205 patients with classical dengue and dengue hemorrhagic fever.

The authors gathered data from electronic medical records, BestCare, on patient's characteristics: age, gender, dengue related-death, and Saudi Arabian region of diagnosis (West, Central, South, North, and East).

During admission, blood samples were collected and hemoglobin/mg per deciliter, hematocrit %, white blood cell count (WBC) $\times 10^9$ per liter, red blood cell (RBC)/million cells per microliter (mL), mean cell volume (MCV)/fl/red cell, platelet $\times 10^9$ per liter, neutrophils $\times 10^9$ per liter, alanine transaminase (ALT) units/liter, AST units/liter, and creatinine $\mu\text{mol/L}$ were measured on different days. There were 845 laboratory results with different time intervals or exam dates for the 205 patients studied. We limited the time intervals for analysis to within 7 days before and after the date of a positive antibody test [13]. This period refers to days of illness or the course of illness. We calculated the

Table 1
Summary of demographic and clinical outcomes (N = 205).

	Mean	Std Dev
Age	38.0	18.3
	Freq	Percent
Gender		
Female	98	47.8
Male	107	52.2
Region of primary diagnosis hospital		
Central	4	2.0
Western	201	98.0
Primary diagnosis disease		
Dengue fever [classical dengue]	200	97.6
Dengue hemorrhagic fever	5	2.4
Death		
Alive	203	99.0
Dead	2	1.0

AST/platelet ratio index [9] to assess its usefulness in predicting dengue virus infection in dengue patients. The viral infection was detected using immunoglobulin G (IgG), Immunoglobulin M (IgM), and NS1 antigen antibody enzyme-linked immunosorbent assay (ELISA) tests Innova Biosciences (Cambridge, UK), as they were performed routinely during the first week of illness onset [13–15].

The study outcome was dengue virus infection as measured by a positive antibody test (yes/no), it was defined as having had at least one positive antibody test, IgG, IgM, or NS1 antigen.

Data analysis

The analysis was carried out using SAS version 9.2 for Windows. Demographic and clinical data were summarized using mean and standard deviation and, when appropriate, we used count and percent (Table 1). The sensitivity of the IgG, IgM, and NS1 antigen antibody tests for identifying dengue virus infection in dengue cases was reported. The laboratory tests were summarized using mean and standard deviation (Table 1). The outcome modeled was dengue virus infection as measured by a positive antibody test (yes/no) which is defined as having had at least one positive antibody test, IgG, IgM, or NS1 antigen. The odds of dengue virus infection was evaluated using repeated measure mixed bivariate and multivariate binary logistic regression analyses. A P-value of less than 5% indicates significant findings. The ability of the AST/platelet ratio index to classify dengue virus infection was assessed using the AUC (areas under the receiver operating characteristic) curve and its 95% confidence intervals (CI).

Results

A total of 205 cases of hemorrhagic fever and classical dengue fever were included in the analysis; 107 (52.2%) were males, and the majority were from the Western region 98% (Table 1). The average age was $38 \pm \text{SD } 18.3$ years (age ranges 4–91 years).

The antibody tests and laboratory parameters were recorded during presentation, within 7 days before and after the positivity of an antibody test. Due to repeated laboratory tests within different time intervals or exam dates during presentation, the rest of our analyses used 845 data points that resulted from the 205 dengue cases studied. The summary of antibody tests and laboratory parameters is included in Table 2. The sensitivity of IgG, IgM, and NS1 antigen antibody tests was 39.41%, 60.67%, and 59.64%, respectively. The sensitivity of at least one antibody positive test was 93.25%.

Repeated measure mixed bivariate binary logistic regression analyses were presented in Table 3. Platelet counts were associated with low odds of dengue virus infection (IgG, IgM, or NS1 antigen)

Table 2
Laboratory parameters and positivity of antibody tests (N = 845).

Lab	Mean	Std Dev
Creatinine	84.59	67.21
ALT	79.75	199.88
AST	86.52	209.38
Hematocrit	37.44	29.60
Hemoglobin	121.05	23.28
MCV	84.74	7.01
Neutrophils	3.52	2.91
Platelet	206.83	123.08
RBC	4.36	0.85
WBC	5.86	3.62
AST/platelet count ratio	1.93	4.33
Dengue screening test	Freq	Percent
IgG – positive	333	39.41
IgM – positive	509	60.67
NS1 antigen – positive	461	59.64
IgG/IgM/NS1 antigen – positive	788	93.25

Hemoglobin mg per deciliter, hematocrit %, white blood cell count (WBC) $\times 10^9$ per liter, red blood cell (RBC) million cells per microliter (mcl), mean cell volume (MCV) fl/red cell, platelet $\times 10^9$ per liter, neutrophils $\times 10^9$ per liter, alanine transaminase (ALT) units/liter, AST units/liter, and creatinine $\mu\text{mol/L}$. NS1 antigen test (nonstructural protein 1), immunoglobulin G (IgG), immunoglobulin M (IgM).

(unadjusted OR = 0.997, 95% CI: 0.995–0.999, $P = 0.003$). However, the AST/platelet ratio index alone was not significantly related to dengue virus infection.

Table 3
Factors associated with unadjusted odds of dengue virus infection (N = 845).

	B	SE	Z	Pr > Z	Unadjusted OR	95% Confidence limits for unadjusted OR	
						Lower	Upper
Male	0.738	0.464	1.590	0.111	2.092	0.843	5.190
Age	0.014	0.011	1.220	0.223	1.014	0.992	1.037
Creatinine	0.001	0.002	0.710	0.476	1.001	0.998	1.005
Hematocrits	-0.023	0.031	-0.750	0.452	0.977	0.919	1.038
Hemoglobin	-0.008	0.009	-0.910	0.364	0.992	0.974	1.010
MCV	-0.033	0.021	-1.630	0.104	0.967	0.929	1.007
Neutrophils	-0.042	0.044	-0.940	0.345	0.959	0.880	1.046
RBC	-0.042	0.230	-0.180	0.854	0.959	0.611	1.500
WBC	-0.024	0.039	-0.610	0.539	0.977	0.905	1.053
ALT	0.001	0.002	0.350	0.728	1.001	0.998	1.004
AST	0.002	0.003	0.610	0.542	1.002	0.996	1.007
Platelet	-0.003	0.001	-2.960	0.003 ^a	0.997	0.995	0.999
AST/platelet count ratio	0.213	0.223	0.950	0.341	1.237	0.799	1.916

^a Significant at $\alpha = 0.05$. Hemoglobin mg per deciliter, hematocrit %, white blood cell count (WBC) $\times 10^9$ per liter, red blood cell (RBC) million cells per microliter (mcl), mean cell volume (MCV) fl/red cell, platelet $\times 10^9$ per liter, neutrophils $\times 10^9$ per liter, alanine transaminase (ALT) units/liter, AST units/liter, and creatinine $\mu\text{mol/L}$.

Table 4
Factors associated with adjusted odds of dengue virus infection (N = 845).

Factors	B	SE	Z	Pr > Z	Adjusted OR	95% Confidence limits for adjusted OR	
						Lower	Upper
Intercept	22.352	7.971	2.800	0.005			
Male	1.462	0.618	2.370	0.018 ^a	4.316	1.285	14.498
Age	0.011	0.014	0.760	0.450	1.011	0.983	1.039
Creatinine	0.007	0.006	1.300	0.194	1.007	0.996	1.019
Hematocrits	0.451	0.302	1.490	0.135	1.570	0.869	2.836
Hemoglobin	-0.059	0.036	-1.650	0.100	0.942	0.878	1.011
MCV	-0.205	0.093	-2.200	0.028 ^a	0.815	0.679	0.978
Neutrophils	-0.291	0.199	-1.460	0.145	0.748	0.506	1.105
RBC	-2.938	2.168	-1.360	0.175	0.053	0.001	3.712
WBC	0.177	0.209	0.850	0.395	1.194	0.793	1.797
ALT	-0.004	0.002	-2.580	0.010 ^a	0.996	0.993	0.999
AST/platelet count ratio	0.364	0.157	2.310	0.021 ^a	1.438	1.057	1.957

^a Significant at $\alpha = 0.05$. Hemoglobin mg per deciliter, hematocrit %, white blood cell count (WBC) $\times 10^9$ per liter, red blood cell (RBC) million cells per microliter (mcl), mean cell volume (MCV) fl/red cell, platelet $\times 10^9$ per liter, neutrophils $\times 10^9$ per liter, alanine transaminase (ALT) units/liter, AST units/liter, and creatinine $\mu\text{mol/L}$.

A repeated measure mixed multivariate binary logistic regression analysis is presented in Table 4. Factors associated with a higher risk of dengue virus infection in dengue patients included male gender (adjusted OR = 4.316, 95% CI: 1.285–14.498, $P = 0.018$) and a high AST/platelet count ratio index (adjusted OR = 1.438, 95% CI: 1.057–1.957, $P = 0.021$). There was no correlation between age and dengue virus infection in dengue patients.

ALT levels (adjusted OR = 0.996, 95% CI: 0.993–0.999, $P = 0.010$) and MCV levels (adjusted OR = 0.815, 95% CI: 0.679–0.978, $P = 0.028$) were associated with a low risk of dengue virus infection in dengue patients. Fig. 1 shows the risk of dengue virus infection increases with an AST/platelet count ratio index and then decreases 2 days after a positive antibody test. Fig. 2 shows that low platelets tends to increase the risk of dengue virus infection. The AUC (areas under the receiver operating characteristic curve) for the AST/platelet count ratio index was 0.703 (95% CI: 0.599–0.807).

Discussion

This is a retrospective charts review of patients with RT-PCR-confirmed dengue fever disease who were admitted to the MNG-HA hospitals and clinics between 2016 and 2018. The study aimed to examine the pattern of the AST/platelet count ratio index over the course of illness and identify whether it is a marker of dengue virus infection in the Saudi dengue population.

The majority of our dengue patients were detected in the Western region. This is consistent with other reports on dengue fever

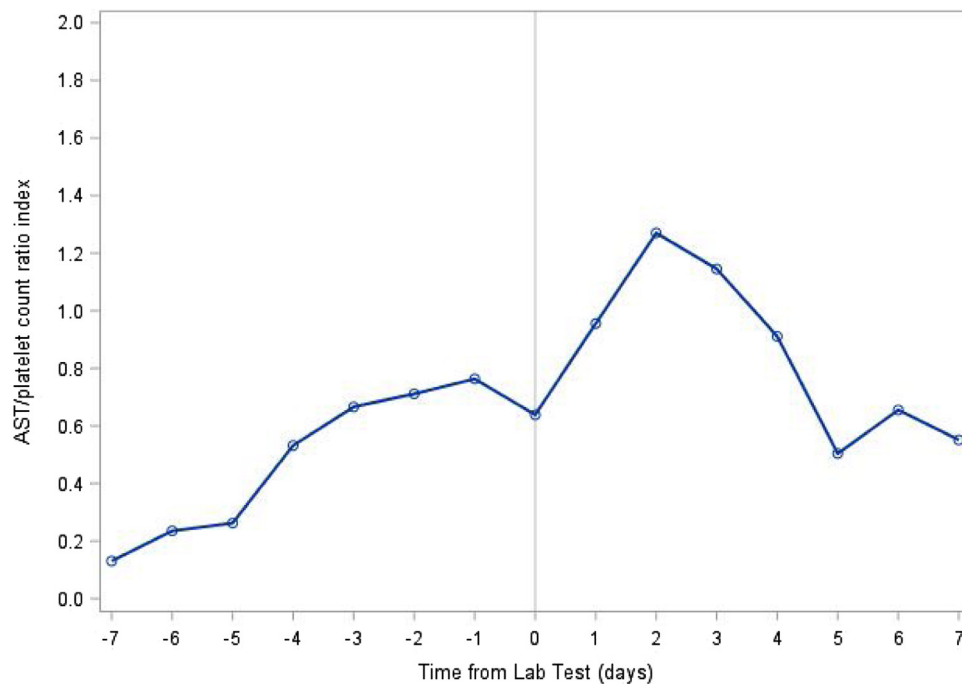


Fig. 1. The changes in AST/platelet count ratio index during 7 days before and after positive antibody test. Day 0 is the time when patients identified having dengue fever infection as per antibody test(s).

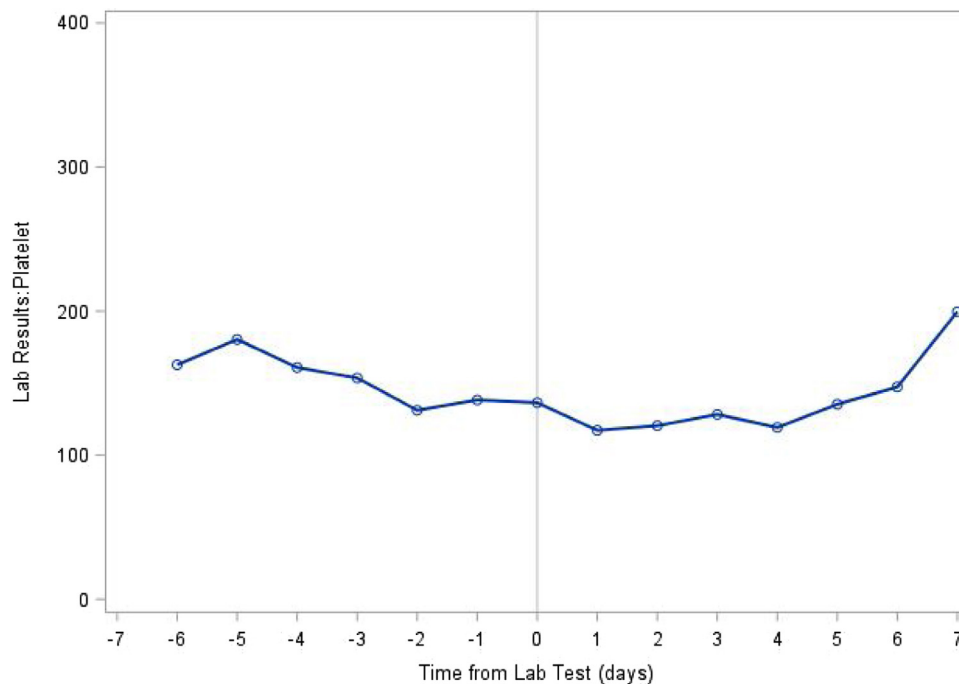


Fig. 2. The changes in platelet during 7 days before and after positive antibody test. Day 0 is the time when patients identified having dengue fever infection as per antibody test(s).

in Saudi Arabia [1,3,16]. Their data shows that dengue fever is frequently reported in the Western region. Our study shows dengue fever could still exist in other regions, but with a small chance of infection, as we noted 2% were detected in the Central region. However, our study did not include database from the Southern region, where dengue fever also commonly exists [16,17], as no MNG-HA health centers exist in this region.

The majority of cases were not life-threatening, as classical dengue fever was found in 97.09%, while dengue hemorrhagic fever was observed in 2.43%, which were considered severe dengue infec-

tions [18]. This is in agreement with a study in the Western region by Khan et al. where the noted 93% had dengue fever and only 7% had dengue hemorrhagic fever [19]. Dengue-related death was observed in 1% of our sample; a similar rate of 0.53% has been reported in a previous study [12]. We found that the odds of dengue virus infection was higher among males. Similar findings have been reported in the literature that dengue infection is frequently common in males [12].

The relationship between markers and dengue virus infection has been reported in the literature, but with limited data on the role

of the AST/platelet count ratio index [20]. Our regression analysis revealed that the AST/platelet count ratio index was an important indicator of increasing the odds of dengue virus infection. This is consistent with Zhang H et al. where they present the AST/platelet count ratio index as a novel predictor of severe dengue infection [9]. In their study, the AUC of the AST/platelet count ratio index was AUC = 0.785; 95% CI 0.724 to 0.893, while our study was AUC = 0.703; 95% CI 0.599–0.807. In line with these findings, an Indonesian study reported that a low platelet count and a ratio of AST greater than or equal to 2.51 are associated with increased risk of severe dengue [21]. A Brazilian study reported a sensitivity of 75% and a specificity of 76% for AST/platelet count ratio index as a marker of dengue infection [22]. It is important to include the AST/platelet count ratio index to improve the screening process for dengue fever in a primary care setting. As per Fig. 2, the decreases in the AST/platelet count ratio index after 2 days post positive antibody test could be due to treatment course and other supportive care. The impact of treatment on the AST/platelet count ratio index must be studied in a follow-up observational study.

We found that higher markers levels such as MCV and ALT have been correlated with a decrease in the odds of dengue virus infection in dengue patients. These biomarkers can be used to identify individuals at risk of developing dengue fever at an earlier stage, increase the likelihood of proper management, and prevent severe infection.

Although the study was based on available MNG-HA hospitals and clinics across Saudi Arabia, most of the cases were detected from the Western region. However, the number of cases included in this study may not be considered as representative of the dengue fever population in Saudi Arabia, as we did not include cases from the Southern region. Due to the nature of retrospective study design, we did not have information available on dengue type of treatments and symptoms/signs at presentation such as fever, vomiting, and others. Evaluating the role of such information could give added value to the diagnostic process in the primary care setting. Our findings must be interpreted carefully, as correlation does not mean causation.

Conclusion

Laboratory markers, in particular the AST/platelet count ratio index, can be useful for clinicians to promote the decision-making process in primary care settings. Furthermore, our model revealed that low MCV and low ALT are predictors of dengue virus infection, while being of the male gender increases the risk of dengue virus infection. More studies are needed to evaluate the impact of the AST/platelet count ratio index on severity of dengue fever infection during the onset of symptoms and treatment course.

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Conflicts of interest

There are no conflicts of interest.

Ethics approval

This study was approved by the Ethics Committee at MNG-HA, Riyadh, Saudi Arabia (#RC18/291/R). This study has been com-

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