Assessment of Dengue Severity via Correlation of Aspartate Aminotransferase/ Platelet Ratio Index with Other Biochemical Markers in Patients with Dengue Admitted To a Teaching Hospital in Lahore

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Abstract

Objective: To assess correlation of Aspartate Aminotransferase (AST) to platelet ratio index with other biochemical markers such as white cell count, platelet count, hemoglobin, hematocrit and liver function tests in patients of dengue fever for disease severity.

Methods: Data was collected from 223 dengue fever patients admitted to a hospital setting in an outbreak of 2022. Binary logistic regressions analysis was employed. AST to Platelet Ratio Index (APRI) was calculated and all parameters were studied to assess their association with the disease severity. Severity of dengue was based on development of complications like bleeding, shock, end organ damage and duration of stay in the hospital.

Results: The analysis done by software SPSS version 26.0 showed that 3.6% of the patients were severely ill while 96.4% were non severe with mean duration of stay in the hospital of 4.95 days. Univariate analysis showed ALT and age have positive correlation with disease severity with CI 95% and APRI significant positive correlation was at CI 90%. Multivariate analysis showed age and APRI to have association with disease severity with OR 1.06 and OR 1.16 respectively ($p < 0.05$). Area under the Receiver Operating Characteristic (ROC) curve for APRI was 0.59.

Conclusion: In addition to other biochemical parameters APRI can be used as an independent marker of predicting severity of disease in dengue patients thus it can add value in timely management of the dengue patients.

Keywords: Aspartate aminotransferase, Platelets, APRI, Biomarker, Dengue fever

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Introduction

Dengue is a febrile systemic illness which is transmittable via mosquito of Aedes genotype (Aedes Aegypti and Aedes Albopitcus)[1,2]. Infection with a serotype gives life-long immunity to that particular serotype but because of presence of different serotypes chances of secondary infection is present which has the potential of causing severe and fatal outcomes because of antibody dependent enhancement (ADE) and complement cascade[3]. In accordance with WHO recommendations, dengue vacci- nation can only be administered to seropositive individuals, not to seronegative patients; because of risk of infection development due to live attenuated nature of CVD-TDV vaccination[4].

Dengue is particularly prevalent in tropical and sub-tropical countries but now it has emerged as pandemic being endemic in tropical and sub-tropical regions[5]. Dengue cases have become higher in travelers from southeast Asian region have higher infectivity and rate of hospitalization[6,7]. Dengue is ende-

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mic in Pakistan; after two massive outbreaks in 1995 and 2005, outbreaks of dengue tend to afflict different cities on annual basis[1,8]. Dengue constitutes myalgia, arthralgia, retro-orbital pain, fever, headache and maculopapular rash commonly and rarely with myositis, arthritis, hepatitis and encephalitis as well[5,9]. Dengue severity is directly correlated with leukocytosis, thrombocytopenia and raised hematocrit levels[10] suggestive of vasculopathy and endothelial dysfunction, therefore hematocrit can be used as prognostic marker[8,11].

In severe dengue infections, deranged liver functions; raised aspartate aminotransferase, alanine aminotransferase[11], alkaline phosphatase and bilirubin with coagulation profile is seen due to hepatocyte damage in cases of dengue hemorrhagic fever making it a biomarker for severe infection. Although various biochemical markers have been identified having predictive potential of severity in dengue viral infection but AST to platelet ratio is considered as hallmark in the development of hepatocyte damage and injury[12].

AST to platelet ratio index (APRF) is determined by the equation (AST/upper level of normal range)/platelet count ×100[13]. APRI is defined as AST to platelet ratio, it is predictive marker of liver fibrosis and cirrhosis in patients of viral hepatitis, malaria and non-alcoholic fatty liver disease as well as in patients of metabolic syndromes including HELLP[14]. APRI could be a predictive marker for dengue severity and associated complication and can differentiate between primary and secondary infection[14]. But so far but data is limited and lacking in our part of world and needs investigation. Therefore, a study is warranted to assess serum AST, platelet levels and calculate APRI levels and correlate APRI with blood parameters in local patients of dengue fever.

Methodology

A cross-sectional study was conducted at Central Park Teaching Hospital from June 2022 to November 2022 in which data of all the patients who were admitted to a teaching hospital during dengue outbreak in 2022 was reviewed and was used after getting written informed consent from all the study participants. The minimum sample size was calculated as 217 using the dengue attack rate as 17% per[15] and 95% as the confidence coefficient by using WHO sample size calculator. Under the guidelines, of Helsinki declaration, ethical letter was obtained from Institutional Review Board of Central Park Medical College, Lahore. A total of 223 dengue patients were included in the study by non-probability convenient sampling technique which included both genders between the age 18 to 70 years with positive NS1 screening test for dengue.

Patients with concomitant infections such as hepatitis B, hepatitis C, HIV, or active tuberculosis were excluded from the study. History of malignant disease and immunosuppression therapy were also treated as exclusion criteria. Medical records of these patients were analyzed in reference to different biochemical parameters at presentation like total white blood cell (WBC) count, platelet count, hemoglobin (Hb), hematocrit (HCT), and liver function tests. In addition to other parameters APRI was calculated to see its value in predicting severity of dengue fever. Severity outcome was based on development of any complications like bleeding, shock, end organ damage and duration of stay in the hospital. APRI was calculated using the following formula.

APRI = [AST /upper limit of normal AST/Platelet] ×100

Data was analyzed using software SPSS ver. 26.0. Mean and standard deviation were used to summarize clinical and demographic data and when needed we also used count and percentage. Different parameters were assessed for severity of dengue infection using univariate and multivariate binary logistic regressions. The results were presented as odds ratio (OR) with 95% confidence interval (CI). A P-value of less than 0.05 and 0.1 was used to indicate significant findings. Pearson correlation was employed in between Hb, hematocrit, platelet, AST, ALT, ALP & GGT. The ability of the AST/platelet ratio index to predict dengue fever severity was studied using the AUC (areas under the receiver operating characteristic) curve with 90% and 95% confidence intervals (CI).

Results

All the responses were recorded (n=223) with a response rate of 100%. The mean age of study population was 36.14 ± 13.34 years with the age range of 18 to 70 years, out of which 71.7% (n=160) were males while 28.3% (n=63) were females. All the 223 patients were NS1 positive, but 8 patients (3.6%) were severely sick based on dengue hemorrhagic syndrome (DHS). Study parameters including hemoglobin (Hb), hematocrit, and platelet count, serum ALT and Serum AST were measured, and means were recorded as explained in figure 1.

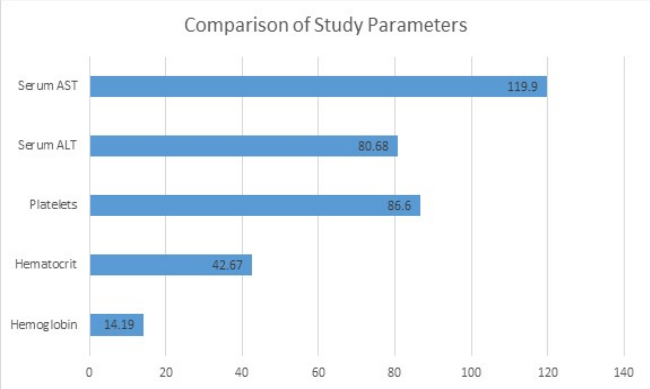

Fig 1. Comparison of different Study parameters in patients of Dengue fever

AST to Platelet ratio (APRI) was calculated for all the patients of dengue to assess the severity of diseases by assessing the insult of liver demage with the mean value of 4.94 ± 4.45. APRI was correlated with all the study parameters by employing spearman correlation as explained in table 1. APRI was negatively correlated with the serum platelet levels with r value of -.593 and p value of <0.0001 suggesting lower platelet levels are associated with higher APRI scores. Liver enzymes AST and ALT were positively correlated with the APRI scores with the p values of <0.001 while other liver enzymes including GGT and ALP were not significantly correlated with APRI as explained in table 1.

Table 1. Correlation of APRI with Study Variables by Employing Spearman Correlation at the confidence interval of 95%.

Parameters	R value	p-value
Hb	0.157	.019
Hct	0.169	.011
Platelets	0-.593	<.0001*
ALT	0.483	<.0001*
AST	0.716	<.0001*
ALP	-0.064	.344
GGT	0.258	.030

There was large variation in average platelets counts, TLC, ALT, AST, ALP, and APRI.

Uni-variable Binary logistic regression analysis was performed to observe the dependence of disease severity on biochemical parameters (Table 2). The significance value of the likelihood ratio test was less than 0.05 which indicated that binary logistic model is good to fit. Age was observed as a significant factor for the disease severity. For a year increase in age, the odds are 1.05 for the disease severity.

Table 2. Uni-variable Binary Logistic Regression Analysis for Disease Severity

Factors	B	Wald	Sig.	OR	Lower	Upper
Age	0.05	3.98	0.05*	1.05	1.00	1.10
Gender (Male)	-0.26	0.11	0.75	0.77	0.16	3.79
Hb	0.18	0.96	0.33	1.19	0.84	1.69
HCT	0.03	0.06	0.68	1.03	0.91	1.16
Platelet	0.00	0.00	0.96	1.00	0.99	1.01
TLC	0.10	1.82	0.18	1.10	0.96	1.27
Bilirubin	0.11	1.43	0.23	1.12	0.93	1.35
ALT	0.00	4.76	0.03*	1.00	1.00	1.01
AST	0.00	0.85	0.36	1.00	0.99	1.00
ALP	0.00	0.98	0.32	1.00	0.99	1.00
Ggt	0.00	1.09	0.30	1.00	0.99	1.00
Albumin	-0.89	1.69	0.19	0.41	0.11	1.57
DOS	0.08	0.22	0.63	1.08	0.77	1.52
APRI	0.11	3.22	0.07**	1.11	0.99	1.25

*P-value < 0.05, **P-value < 0.10

ALT was another significant factor for disease severity. The odds were more than 1.00 for increase in ALT. Similarly, APRI was significant factor for disease severity at 10% level of significance. For an increase in APRI, disease severity will increase by 1.11 odds. After the uni-variable binary logistic regression, multivariate binary logistic regression was applied with significance risk factors. From the mul-

tivariate binary logistic regression analysis, age and APRI were the significant factors (Table 3).

Table 3. Multivariate Binary Logistic Regression Analysis for Disease Severity

Factors	B	Wald	Sig.	OR	Lower	Upper
Age	0.06	4.02	0.05*	1.06	1.00	1.12
ALT	-0.01	1.06	0.30	0.99	0.96	1.01
APRI	0.15	4.86	0.03*	1.16	1.02	1.32

The severity of the disease was directly related to age i.e OR= 1.06. Similarly, APRI was directly related to disease severity. The odds were 1.16 times high for disease severity with an increase in APRI. Area under the Receiver Operating Characteristic (ROC) curve for APRI was 0.59 (Figure 2). The observed threshold for the disease severity was APRI equal to 4.75 with minimum sensitivity 0.63 and 1-specficity equals to 0.35. The confusion matrix after predicting the disease severity indicated that 33.6% of the cases were incorrectly predicted. The number of true positive (TP) was 144, 04 were true negative (TN). Similarly, the number of false positive (FP) and false negative (FN) were 04 and 71. Sensitivity, specificity, false positive ratio, likelihood ratio, precision and accuracy observed by prediction are given below:(Table 4)

Parameters	Formula	Value
Sensitivity	TP/ (TP+FN)	0.67
Specificity	TN/ (TN+FP)	0.50
Positive Likelihood Ratio	Sensitivity/FPR	1.34
Precision	TP/ (TP=FP)	0.97
Accuracy	(TP + TN)/ (TP + TN + FP + FN)	0.66

The sensitivity was observed as 67% and specificity was 50% from the classification table. The precision involved in classification was 97%, which was good. However, the accuracy was 66% using the observed threshold. The reason for such an accuracy and sensitivity could be the small sample size which was enough for generalization or the variation in the biochemical parameters.

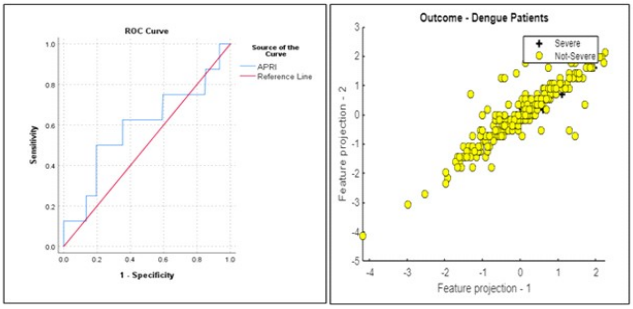

Fig 2. (Left) Receiver Operating Curve using APRI as a marker, (Right) Classification of Severe, Non-severe Dengue Patients

Discussion

This study is a retrospective analysis of the patients who were admitted with the diagnosis of dengue fever in a Teaching Hospital, in Pakistan during the outbreak in 2022. To the best of our knowledge this is the first study in Pakistan to assess the use of AST/platelet count ratio index as a marker of severity in dengue virus infection.

Data analysis of the study showed that most of the cases were not severe 96.4% while severe illness was found in 3.6% of the cases. These results were consistent with the study showing data from Western region at Khan et al with 93% and 7% of the cases as having classical dengue fever and severe dengue fever respectively[7] and was in keeping with a study from Saudi Arabia Population which showed 97.09 % uncomplicated dengue cases with 2.43% of the cases having severe dengue [11]. Mortality due to dengue virus infection was not observed in our data which was in accordance with a study from Taiwan[16] while it was around 5.3% in a previous study done in Saudi Arabia[17] and 1.5% in another study from Saudi Arabia[11]. This could be because the present study did not include dengue patients shifted to ICU.

Present data showed that dengue fever was frequently seen in the male population with 71.7% of the patients being male while 28.3 % were females which was in line with the results from a study in Karachi which showed 61% males and 39% females and another one from Saudi Arabia also showed 67% adult male patients [1,17]. Mean duration of hospital stay in current analysis was 4.09 ± 2.09 days while the study from Karachi sho-

wed average duration to be 5.82±3.57 days[1].

Uni-variate analysis of variables in the present study, age was observed to be a significant factor for disease severity. With each year increase in age there was .05 times increased risk of severity of the disease with confidence interval of 5%. This was in keeping with a study at Taiwan which showed dengue to be more severe in older patients[10]. A meta-analysis also depicted a positive correlation of age with advanced disease although it was not found to be significant[18].

Another variable in current data was found to be ALT which had independent significant correlation with disease severity at; levels higher than 80.69. Increase in ALT was associated with increase in severity which was in keeping with study from Taiwan that also showed that raised ALT levels were associated with disease severity[10] while studies from Karachi and Indonesia did not show strong correlation of raised ALT levels with disease severity[1,12].

Correlation of AST with disease severity was not present in current analysis in line with a study from which also did not show any correlation of AST with dengue severity[7]. While different study has shown raised AST level to have a strong correlation with disease severity[19]. This is in keeping with an Indonesian study has also shown that ratio of AST more than or equal to 2.51 is correlated with higher risk of severe dengue[12].

The current study did not indicate an increase in total bilirubin levels linked with severity of the disease which in in contrast to previous data from another study in Pakistan which showed a positive correlation between the two factors[1].The current analysis did not reflect any significant correlation of serum alkaline phosphate levels with severity of dengue while a study from India has shown that raised serum Alp levels were statistically significant in severe cases in pediatric age group[20].

The correlation of different biochemical parameters with infection and severity of dengue fever has been studied in previous studies, but the amount of work on role of the AST/platelet count ratio index is scarce in the literature. A multivariate logistic regression analysis is valuable to look for parameters that can help identify patients at risk of severe disease. We used the three variables that were selected from the uni-variate analysis and multivariate regression analysis showed two of the variables i.e age and APRI to be the significant factors in disease severity in keeping with previous studies[7,10]. Increase in age was associated with .06 times increase in dengue severity while increase in APRI showed .16 times increase in dengue severity. We found the in our study showed AUC of the AST/ platelet count ratio index was = 0.59. In a retrospective analysis at Saudi Arabia which used APRI as marker of dengue infection AUC was found to be 0.703; 95% CI 0.599–0.807 with cut off value of 1.93[11]. Our data was in keeping with the aim of our study and showed that APRI was directly related to disease severity when APRI with cut off value of 4.96 as used. This is in keeping with study from China which showed that AST/platelet count ratio index can be used in predicting severe dengue virus infection which showed odds ratio 0f 1.05 with cut off value of 6.98[7]. APRI cut off values of 0.72 and0.89 has been found in studies in which APRI was used in assessment of NAFLD and chronic hepatitis C respectively[21,22].

Our study showed sensitivity of 67 % while specificity of 50% of APRI with cut off value of 4.95 as marker of dengue severity while a Brazilian study showed a 75% sensitivity and 76% specificity for AST/platelet count ratio index use with cut off value of 1.06 for differentiating primary and secondary dengue virus infection[13]. In our study, APRI was found to be an independent significant index in dengue virus infection. It is a valuable tool to use the AST/platelet count ratio index in making decisions regarding timely management of dengue cases at risk of severe outcome in a healthcare care setting. The course of AST/platelet count ratio index takes during treatment of dengue needs to be observed in follow-up research.

The current study is a retrospective analysis, so it lacked information on dengue serotype, primary vs secondary infection, symptoms at presen-

tation and clinical and biochemical response to treatment in the hospital. Very sick patients that needed ICU/HDU care at presentation or were shifted to ICU/HDU were also not included in this study. Adding these parameters in the data could give us more information and lead to better analysis to prove use of APRI in dengue fever. Findings of this study should be interpreted with caution, as presence of correlation between two variables does not prove causation. In addition, our study had limitations in that it was conducted with a relatively small number of patients.

Conclusion

In present study APRI was found to be a significant and independent parameter of disease severity in dengue patients so it has the potential of being used as a marker of predicting severity outcome in dengue virus infection. The combination of APRI with other parameters can be valuable in making decisions regarding management in dengue patients. Further research is needed to confirm these conclusions in a larger population.

Conflict of Interest: None

Disclaimer: None

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