Original Article

# APRI as a predictor of severe dengue fever

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## Abstract

**Introduction:** The AST/platelet ratio index (APRI) is a well-researched indicator of liver fibrosis. Some studies have shown that APRI can be used as a predictor of severe dengue, but the data is limited. As dengue epidemics are common in our country with limited healthcare resources, we believe APRI can help emergency physicians/primary physicians in predicting the severity of dengue and plan for the appropriate use of limited healthcare resources. **Objective:** 1) To determine the utility of APRI as a predictor of severe dengue. 2) To determine the association of APRI with length of hospital stay and platelet requirement. **Materials and Methods:** A retrospective cross-sectional study was done on patients presented to the Emergency Medicine department at Travancore Medicity Medical College with a positive Dengue NS1 antigen or IgM antibody. **Results:** We found from the univariate analysis results that ALT > 74.5 IU/L has a sensitivity of 59.6 and a specificity of 76.3 (AUC: 0.696; 95% CI: 0.606–0.786), AST > 160.5 IU/L has a sensitivity of 42.3 and a specificity of 93.7 (AUC: 0.747; 95% CI: 0.665–0.829), and APRI > 3.2 has a sensitivity of 69.2 and a specificity of 84.2 (AUC: 0.806; 95% CI: 0.72–0.884) to predict severe dengue. Patients with an APRI of >3.2 required a mean hospital stay of 5.47 days ($P = 0.005$); 27 (81.8%) requiring platelet transfusion had an APRI of > 3.2 ($P = 0.00$). **Conclusion:** APRI is a straightforward index that can be easily derived from AST and platelet values. APRI values of >3.2 can predict severe dengue with a sensitivity of 69.2 and a specificity of 84.2. APRI values of >3.2 are also associated with the length of hospital stay and requirement of platelet transfusion.

**Keywords:** Age, ALT, APRI, AST, chronic kidney disease, dengue, diabetes, gender, hematocrit, hypertension, platelet, severe dengue

## Introduction

As the world has been grappling with COVID-19 since December 2019, many tropical diseases such as dengue have been neglected. India recorded 1,93,245 dengue cases in 2021, and 1,10,473 cases of dengue were recorded till October 2022, as per the Ministry of Health and Family Welfare, Govt of India.[1] Numerous variables, including increased international trade and travel, urbanization, population growth, and climate variability and change, have contributed to a steady increase in the burden of dengue during the past 50 years.[2] Messina *et al.* through their statistical mapping techniques have projected a global burden of 2.25 billion cases by 2080.[3]

In most patients, dengue fever manifests as classical or non-severe dengue, but some patients enter a critical phase – severe dengue, characterized by plasma leakage severe enough to cause shock or respiratory distress, severe bleeding, or organ dysfunction.[4] Severe dengue has a lethality of 2.5%. The lethality of severe dengue can be decreased to less than 1% by early detection and proper supportive care.[4]

Early changes in platelet and AST levels are strongly associated with a high risk of developing severe dengue, according to several systematic reviews and meta-analyses.[5-7] AST/platelet ratio (APRI) can be a better predictor of severe dengue as per several studies done across the world. APRI has received

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extensive research as a diagnostic tool for hepatocellular carcinoma development or liver fibrosis.[8-10] Some studies have shown that APRI can be used as a predictor of severe dengue. Zhang *et al.* have identified APRI as a valuable predictor of patients with severe dengue.[11] Similarly, another study done by Ahmed et al found that patients with raised APRI have a high risk of developing dengue infection.[12] However, data regarding the usefulness of APRI as a predictor of severe dengue is extremely limited and not well studied.

APRI can be calculated readily from the common laboratory values of AST and platelet. As dengue epidemics have become common and the global burden is expected to rise due to various factors, we believe a simple index like APRI can help emergency physicians/primary care physicians in the early recognition of severe dengue and plan for appropriate use of limited healthcare resources in developing countries.

## Materials and Methods

### Study design

Cross-sectional study.

### Study setting

Travancore Medical College, Kollam.

### Study population

Patients presented to the Emergency Medicine department of Travancore Medical College with dengue fever.

### Study duration

May 1, 2022 to February 28, 2023.

### Sample size

179.

### Sampling technique

Consecutive sampling. All the patients positive for the NS1 antigen or IgM dengue test were included in the study.

### Inclusion and exclusion criteria

- **Inclusion Criteria**: Patients positive for NS1 antigen or IgM dengue test were included in the study.
- **Exclusion Criteria:** Age <18 years, pregnant woman, patients with other co-infection, and history of fever >7 days.

### Methodology

Patients who presented to the Emergency Medicine department with a history of fever and positive dengue NS1 Ag test or dengue IgM report were included in the study. Basic demographic details, clinical findings, and investigation reports at the time of presentation to the ER were collected from the EMR. APRI Index was calculated for all patients by using AST and platelet levels during initial presentation at the ER. Patient data were classified into two groups – severe dengue and non-severe or classical dengue. Data from both groups were analyzed to determine the association between APRI and the severity of dengue. Data regarding the requirement for platelet transfusion at any time during the hospital stay and length of hospital stay was also collected and analyzed.

APRI was calculated using the following formula:

- APRI = [(AST/Upper Limit of AST)/Platelet Count $10^9$/L] × 100

Severe dengue was defined as dengue with any of the following symptoms: severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment (elevated transaminases ≥1000 IU/L and impaired consciousness or heart impairment).

The upper limit of AST was defined as 40 IU/L.

### Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS) version 20. The Chi-square test was used to find the statistical significance for the association of categorical variables. Student's *t*-test was used to compare continuous variables between the different groups in univariate analysis. The receiver operating curve (ROC) was graphed, and AUC was analyzed. $P < 0.05$ was considered statistically significant.

## Results

A total of 179 patients were included in the study. Our study population comprised 102 (57%) males and 77 (43%) females. A total of 52 patients had developed severe dengue. Out of 52 patients with severe dengue, 31 (59.6%) were males and 21 (40.4%) were females. Out of 52 patients with severe dengue, 42 patients had evidence of capillary leakage as pleural effusion or ascites, 16 patients developed bleeding manifestations, 10 patients developed shock, 2 patients developed encephalitis, and 1 developed hepatic failure. In our study, a total of 2 patients diagnosed with severe dengue had expired. Out of 52 patients with severe dengue, 7 (13.5%) patients had diabetes mellitus, 7 (13.5%) patients had hypertension, 3 (5.7%%) patients had coronary artery disease, and 1 (1.9%) patients had chronic kidney disease. Our study could not find any statistically significant association between comorbidities and severity of dengue [Table 1]. According to our research, there is no statistically significant association between dengue severity and either gender or age [Table 1].

In this study, the mean WBC value of 4777.3 × $10^9$/L among severe dengue and the mean value of 4170.07 × $10^9$/L among non-severe dengue were noted. Our study had a mean neutrophil count of 57.16% among severe dengue and a mean of 53.46% among non-severe dengue. The mean platelet count in our study population among the severe dengue group was 62.05 × $10^9$/L

**Table 1: Comparison of sociodemographic and clinical profile of patients between the two groups**

| | Severe dengue (*n*=52) | Non-severe dengue (*n*=127) | *P* |
|---|---|---|---|
| Age group and Dengue | | | |
| <20 | 6 (11.5%) | 15 (11.8%) | 0.598 |
| 20–40 | 28 (53.8%) | 55 (43.3%) | |
| 40–60 | 13 (25.0%) | 43 (33.9%) | |
| >60 | 5 (9.6%) | 14 (11.0%) | |
| Gender | | | |
| Males | 31 (59.6%) | 71 (55.9%) | 0.649 |
| Females | 21 (40.4%) | 56 (44.1%) | |
| Diabetes Mellitus | | | 0.524 |
| Yes | 7 (13.5%) | 22 (17.3%) | |
| No | 45 (86.5%) | 105 (82.7%) | |
| Systemic Hypertension | | | 0.901 |
| Yes | 7 (13.5%) | 18 (14.1%) | |
| No | 45 (86.5%) | 109 (85.9%) | |
| Coronary Artery Disease | | | 0.250 |
| Yes | 3 (5.7%) | 3 (2.3%) | |
| No | 49 (94.2%) | 124 (97.7%) | |
| Chronic Kidney Disease | | | 0.669 |
| Yes | 1 (1.9%) | 3 (2.3%) | |
| No | 51 (98.1%) | 124 (97.7%) | |
| **Blood parameters and Dengue** | | | |
| | **Severe Dengue Mean±SD (*n*=52)** | **Non-severe Dengue Mean±SD (*n*=127)** | **P** |
| WBC | 4777.3±2425.67 | 4170.07±1824.05 | 0.069 |
| Platelet count | 62.05±50.75×$10^9$/L | 126.65±58.85×$10^9$/L | 0.001 |
| Hematocrit | 44.39±6.25 | 41.90±6.056 | 0.014 |
| ALT | 214.75±589.87 | 59.85±325.38 | 0.004 |
| AST | 480.46±2165.99 | 81.252±53.73 | 0.039 |

and 126.65 × $10^9$/L among non-severe dengue. Our study found a statistically significant association between platelet count and severity of dengue with a *P* value of 0.001. Mean hematocrit levels among severe dengue were 44.392% and 41.905% among non-severe dengue, respectively. Hematocrit and dengue severity were found to be statistically significantly correlated in our study, with a *P* value of 0.014 [Table 1].

The mean ALT was 214.75 IU/L among severe dengue and 59.85 IU/L among non-severe dengue. The mean AST among our study population was 480.46 IU/L among severe dengue and 81.25 IU/L among non-severe dengue. Our study found a statistically significant association between ALT and severity of dengue with a *P* value of 0.004 [Table 1]. From the univariate analysis results, we found that an ALT value of >74.5 IU/L has a sensitivity of 59.6 and a specificity of 76.3 to predict severe dengue; the AUC was 0.696, 95% CI was 0.606–0.786 [Figure 1], and *P* value was 0.01. We also found from the univariate analysis results that an AST value of > 160.5 IU/L has a sensitivity of 42.3 and a specificity of 93.7 to predict severe dengue; the AUC was 0.747, 95% CI was 0.665–0.829 [Figure 1], and *P* value was 0.001.

In this study, we found that the mean APRI among severe dengue was 25.43 and 1.83 among non-severe dengue. From the univariate analysis results, we found that an APRI value of > 3.23 has a sensitivity of 69.2 and a specificity of 84.2 to predict severe

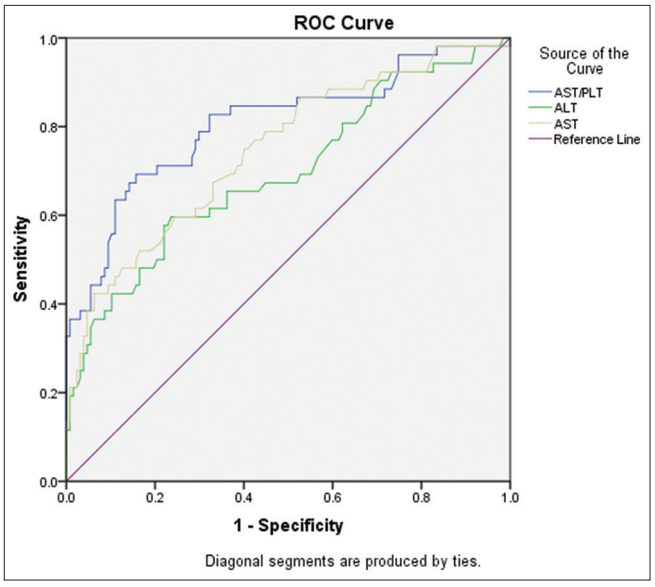


**Figure 1:** ROC Curve of AST/PLT Ratio Index (APRI), ALT and AST in predicting severe dengue fever

| Area Under the Curve | |
|---|---|
| **Test Result Variable (s)** | **Area** |
| AST/PLT | 0.806 |
| ALT | 0.696 |
| AST | 0.747 |

dengue; the AUC was 0.806, 95% CI was 0.72–0.884 [Figure 1], and *P* value was 0.01.

Patients with APRI < 3.2 required a mean hospital stay of 4.82 ± 1.46 days, whereas patients with APRI >3.2 required a hospital stay of 5.47 ± 1.39 days [Table 2]. Our study found a significant association between the APRI value and hospital stay with a *P* value of 0.005. A total of 33 patients required platelet transfusion, among which 27 (81.8%) patients had an APRI value of >3.2. We also found a significant association between the APRI value and the requirement for platelet transfusion, with a *P* value of 0.00 [Table 2].

## Discussion

Our study found that age and gender have no significant association with severe dengue [Table 1]. Contrarily, a recent meta-analysis by Sangkaew *et al.* revealed that older age and female gender were demographic risk factors for progression to severe disease, although Htun *et al.* were unable to detect any meaningful link.[5,13] To confirm these conclusions, more research is necessary.

According to multiple meta-analyses, comorbid conditions such as diabetes, hypertension, cardiovascular disease, and renal illness significantly increase the chances of developing severe dengue.[5,7,14] Contrary to this, however, our research was unable to identify any statistically significant link between comorbidities and severe dengue. Although no specific mechanism has been proposed, severe dengue is highly related with diabetes with a HbA1C of >7%.[15] This may be attributed to micro- and macrovascular impairment in advanced diabetes, which can cause plasma leakage and lead to severe dengue.[14-16] Studies have demonstrated that pro-inflammatory cytokines are considerably raised in chronic renal disease, which can cause vascular injury in dengue virus infection.[14,17] In addition, uremia associated with kidney illness causes endothelial dysfunction and contributes to hemostatic dysfunction, both of which can result in a severe dengue infection, as Salatti *et al.* have demonstrated in their study.[18] The association of cardiovascular disease and renal disease with the severity of dengue can be confounded by diabetes or hypertension as well.[5]

Hematological parameters in dengue fever shift from days 3 to 8 and begin with increasing leukopenia, followed by thrombocytopenia and hemoconcentration brought on by plasma leakage.[19] Because the bone marrow test revealed modest hypocellularity in the first seven days of fever rather than normal cellularity throughout the convalescent period, it is thought that the destruction or suppression of myeloid progenitor cells in dengue causes leukopenia.[20] In the most recent systemic investigation, there was no discernible association between WBC and dengue severity.[5] Similarly, our study (*P* = 0.069) was unable to detect any statistically significant association between WBC and the severity of dengue. In our study, the mean WBC in severe dengue was 4777.3, whereas in non-severe dengue, the mean WBC was 4170.07. WBC with non-severe dengue is comparatively lower; this can be due to bone marrow suppression during the acute phase (<1 week), which is evidenced by bone marrow studies showing mild hypocellularity and normal cellularity in the convalescent stage (>1 week).[20]

**Table 2: Association of APRI with length of hospital stay and need for platelet transfusion**

| | APRI <3.2 (*n*=122) | APRI >3.2 (*n*=57) | *P* |
|---|---|---|---|
| Hospital Stay | 4.82±1.46 days | 5.47±1.39 days | 0.005 |
| Platelet Transfusion | | | |
| Yes | 6 (18.2%) | 27 (81.8%) | 0.000 |
| No | 116 (79.5%) | 30 (20.5%) | |

Thrombocytopenia is frequently observed in dengue patients and has been used as a marker to monitor the course of dengue.[6,7] Dengue thrombocytopenia may result from viruses destroying bone marrow megakaryocytes or peripheral platelets, which lowers the synthesis of platelets.[20,21] In addition, studies have demonstrated that the dengue virus induces apoptosis and mitochondrial malfunction, both of which may be related to thrombocytopenia.[22] When assessed during the febrile phase, a recent systematic study has demonstrated that platelet count is substantially related with progression to severe disease.[5,7] Our study also found that platelet count has a good association with the severity of dengue (*P* = 0.001), which is statistically significant. Patients with severe dengue had a mean platelet count of 62.05 × 109/L.

Hematocrit increases of over 20% are regarded as indisputable proof of increased vascular permeability and plasma leakage.[23] Hematocrit levels may be affected by other factors such as fever, dehydration, and hemorrhage.[23] Hematocrit and dengue severity were not significantly correlated, according to a recent systematic analysis.[5,6] However, monitoring is still necessary to find plasma leakage during the crucial stage. Our study found a significant association between hematocrit values and severe dengue (*P* = 0.014).

Early in the course of the illness, liver transaminases start to vary with time, and the rise is noticeably higher in severe dengue.[24] According to studies, the AST elevation rate in dengue is higher than the ALT elevation rate.[24-26] According to Wang *et al.*'s findings, AST was high in 75% and 80% of cases with moderate and complex dengue, respectively, whereas the ALT level was elevated in 52% and 54% of cases, respectively.[27] Although the dengue virus strongly infects hepatocytes when hepatic tropism is present, elevated AST levels are a sign of systemic inflammation rather than hepatic harm.[28] Although AST or ALT readings rise in tandem with dengue severity, a study by Lee *et al.* demonstrated that they were unable to distinguish between severe and non-severe dengue.[24] The increased production of AST from injured myocytes during dengue infection may account for the greater elevation of AST compared to ALT in dengue illness.[29] Many systematic analyses have demonstrated a high association between AST and ALT and the severity of dengue.[5-7] Similar to other studies, we also found that elevated liver enzyme

AST and ALT also have a statistically significant association with severe dengue, with a *P* value of 0.039 and 0.004, respectively. Mean AST and ALT levels in severe dengue were 214 and 480.4, respectively. Concentrations greater than three times the upper limit of normal have been linked to the development of severe illness, according to Sangkaew *et al.*[5]

Some studies on the AST/platelet ratio index (APRI) have shown it to be useful in recognizing the severity of dengue in a primary care setting. A study done by Zhang H *et al.* has shown APRI as a novel predictor of severe dengue (AUC: 0.785; 95% CI: 0.724–0.893).[11] Similarly, another recent study by Ahmed *et al.* showed that high APRI is a marker of dengue infection.[12] Another study done by Matrin *et al.* showed that APRI can be used to differentiate secondary dengue (mean APRI: 1.84) from primary dengue (mean APRI: 0.6) with a sensitivity of 75% and a specificity of 76%.[30] Our study found that an APRI value of > 3.2 has a sensitivity of 69.2 and a specificity of 84.2 to predict severe dengue (AUC: 0.806, 95% CI: 0.72–0.884). Our study also found a significant association between APRI (>3.2) and length of hospital stay ($P = 0.005$) and requirement of platelet transfusion ($P = 0.00$) [Table 2].

## Conclusion

APRI is a straightforward index that can be easily derived from the platelet and AST readings. Our study has shown that an APRI value of 3.2 can predict severe dengue with a sensitivity of 69.2 and a specificity of 84.2. We also proved that APRI is a better marker of severe dengue than platelet, AST, or ALT value alone. An APRI value of >3.2 has a good relationship to predict the length of hospital stay and requirement of platelet transfusion. Primary care practitioners can identify patients with severe dengue earlier, start appropriate treatment earlier, and use resources more wisely with the aid of a straightforward index like APRI, especially in low-resource settings.

### Limitation

A modest sample size and short time frame were used in our investigation, which was conducted in one institution. Additional validation of our findings will require larger investigations. Because we are a tertiary-care facility, the majority of patients we treated had already had some outside treatment, which may have had an impact on the severity of dengue at the time of presentation.

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### Conflicts of interest

There are no conflicts of interest.

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