

Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) as a Novel Score in Early Detection of Complicated Dengue Fever

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Introduction: The occurrence of dengue fever presents a considerable burden for public health care in developing countries. This study aims to validate APRI as predictor score for severity of dengue fever so that catastrophic events could be prevented, and early triage can save lives.

Methods: The retrospective cross-sectional study was done on dengue positive patients from August to November 2023. APRI score was calculated for every patient at the time of admission. The primary end-point was **non-complicated disease** (Simple dengue fever) vs **complicated disease** (dengue hemorrhagic fever and dengue shock syndrome). ROC curve was used to identify the role of APRI in prediction of dengue complication. Youden index was used to find the cut-off value of APRI along with sensitivity, specificity, positive and negative likelihood ratios. To further evaluate the role of APRI score, patients were divided into two groups, patients with APRI score greater and lesser than cut-off value. The qualitative variables among two groups were compared by chi-square testing. The predictors of complicated dengue were first determined by univariate regression analysis and then confirmed by multivariate regression analysis.

Results: The mean APRI score of 135 patients was 20.06 ± 6.31 . AUC for APRI score was 0.93 ($p < 0.0001$) indicating that APRI score calculated at the time of admission is an excellent marker in determining the complicated dengue. The cut-off value for APRI score was 9.04 (sensitivity 84.91%, specificity 89.02%, $p < 0.0001$). The patients with APRI < 9.04 mostly developed simple dengue fever (54.1%) vs DHF (4.4%) and DSS (1.5%), while patients with APRI > 9.04 had more DHF (20.7%) and DSS (12.6%) vs simple dengue fever (6.7%). None of the patient died with APRI < 9.04 while the mortality rate was 3.7% in patients with APRI > 9.04 .

Conclusion: The APRI score, calculated at the time of admission, is an excellent marker in determining the severe dengue.

Keywords: dengue, severe dengue, dengue hemorrhagic fever, aspartate aminotransferase, ROC curve, area under curve

Introduction

The global threat of dengue is escalating, with over 3.7 million cases reported. Almost 2000 dengue-related deaths have been reported in 70 countries around the world.¹ The dengue situation in Pakistan declared profoundly disturbing in 2021 due to the increasing number of cases, with the count reaching 48,906 cases and 183 deaths following flood crisis that started in mid-June and subsequently decreasing in year 2022 with 25,932 cases and 62 deaths, as reported by the WHO.^{2,3} The occurrence of dengue fever presents a considerable burden for public health care in developing countries. An annual surge in dengue cases in Pakistan follows a flood crisis that badly affects the national health system capacity and increases the risk of serious health impacts from dengue and concurrent disease outbreaks.⁴ The rising toll of dengue outbreaks every year seems multifactorial,

which includes climate change, virus evolution, rapid urbanization, population growth, poor socioeconomic conditions that are conducive to mosquito breeding, non-existent surveillance, as well as worldwide trade and travel.⁵

Dengue, also famous as break bone fever, is a mosquito-borne viral disease, and it causes flu-like illness, and at times, develops into a potentially lethal complication called severe dengue. Although most cases of dengue are mild, but the risk of severe dengue increases if re-infection by more than one serotype occurs. Severe dengue causes plasma leakage, ending in circulatory shock or respiratory distress, severe bleeding, organ damage, cardiac complications including myocarditis and death.^{6,7} Often, dengue cases are misdiagnosed because many manifestations of dengue are ambiguous, particularly in cases of severe dengue.⁸ Nonetheless, once diagnosed mortality rate can be reduced to 1% or less with adequate supportive care.^{9,10}

In our study, we aimed to observe the role of a novel indicator, the APRI (Aspartate aminotransferase-to-Platelet ratio index) score, in predicting disease progression since literature analyzing its prognostic value in anticipating dengue severity is scarce. By applying this indicator, healthcare professionals can potentially assess the disease severity, thereby assisting in the correct diagnosis and determining the accurate course of treatment for the patients.¹¹ This high AST to low platelet count index is a useful minimally invasive tool and a risk predictor of progression to severe dengue infection.¹² The higher the score, the higher the incidence of fatal complications. By calculating this score at admission and during the course of the disease one can readily assess which patients can potentially develop plasma leakage and can go into dengue shock syndrome.^{13,14}

This index has been used previously as a promising marker for identifying patients at risk of developing severe malaria.¹⁵ It has been witnessed as a screening tool for hepatic fibrosis in patients with NAFLD (Non-Alcoholic Fatty Liver Disease) as well as an excellent indicator for assessing increased cardiovascular risk, especially in female patients with NAFLD.^{16,17} However, its clinical application to anticipate dengue hemorrhagic fever and dengue shock syndrome has not been validated at large, except for a trivial number of studies.^{13,14}

We conducted a retrospective study of dengue cases in our tertiary care hospital to validate the APRI score as a diagnostic tool to predict the severity of dengue fever so that patient can be timely grouped into high vs low risk of complicated dengue. By strictly monitoring such high-risk patients, catastrophic events could be prevented, and rapid intervention could save lives.

Materials and Methods

Study Aims and Settings

This retrospective cross-sectional study was completed in the dengue ward of Fauji Foundation Hospital from August to November 2023. Since the major outbreak of dengue endemic in 2013, a 40-bed ward has been deputed for the management of dengue patients by the hospital. The ward was designed and equipped with all the facilities needed for the patient's management. These include bedside availability of X-rays, ultrasounds, and a 24-hour running facility for laboratory investigations. In addition, there is the availability of crystalloids and colloid fluids for managing dengue hemorrhagic fever and dengue shock syndrome. To meet the demands of blood and blood products for patients, there is a well-established blood bank within the hospital's territory.

This study focuses on evaluating the importance of the APRI score in predicting the complicated dengue fever.

Operational Definitions

Dengue Fever (DF)

Patients suffering from acute febrile illness for more than 2 days but less than 10 days with two or more manifestations:¹⁸

1. Retro-ocular pain
2. Severe headache
3. Severe myalgias
4. Arthralgia, or joint pain
5. Platelets <150,000

The diagnosis was confirmed with either a positive NS1 antigen (fever < 5 days) or anti-dengue antibody IgM by ELISA (enzyme-linked immunoassay) (fever > 5 days). Anti-dengue antibodies IgG by ELISA in the presence of positive anti-dengue antibodies IgM or NS1 antigen suggested secondary dengue infection.

Dengue Hemorrhagic Fever (DHF)

Following FOUR features must be present for DHF:¹⁹

1. Presenting with acute febrile illness (from 2 to 10 days)
2. Platelet $\leq 100,000/\mu\text{L}$
3. Evidence of hemorrhagic phenomenon by at least ONE of the following features:
 - Hematemesis or melena
 - Purpura, petechiae or ecchymosis
 - Mucosal, gastrointestinal tract, injection sites or other sites bleeding.
 - Tourniquet test is positive
4. Evidence of plasma leakage by at the minimum ONE of the following features:
 - From baseline hematocrit, an increase in hematocrit $\geq 20\%$ (Hemoconcentration)
 - Evidence of low albumin or ascites or pleural effusion. (Signs of plasma leakage)

Dengue Shock Syndrome (DSS)

Evidence of circulatory failure: cold and clammy body, irritability, hypotension, weak and feeble pulse, pulse pressure ≤ 20 mmHg plus the features of DHF.¹⁹

Aspartate Aminotransferase to Platelet Ratio Index (APRI) Score

APRI score (Aspartate Transaminases-to-Platelet Ratio Index) is calculated by dividing patients AST (IU/L) value to Upper limit of AST value (IU/L). The value obtained is then divided by Platelets $\times 10^3$ cells/L and finally multiplied by 100.

Patients Characteristics

Patients diagnosed with dengue infection and admitted to the dengue ward from August to November 2023, aged ≥ 18 years, were included, while the following two groups of patients were excluded from the study.

Conditions Affecting the Platelet Count

Our study results can be altered by conditions that worsen or cause thrombocytopenia. Thus, such patients were not included in this study.

1. Drugs that cause thrombocytopenia (certain antibiotics, heparin, anti-platelets, etc.)
2. HELLP syndrome and gestational thrombocytopenia during pregnancy
3. Disseminated intravascular coagulation.
4. Bone marrow infiltration by lymphoma, leukemia, metastatic malignancy, or aplastic anemia
5. Autoimmune disorder
6. Hypersplenism due to any cause.
7. Patients who were actively infected with hepatitis C, hepatitis B virus, or HIV infection identified by PCR testing.

Conditions Affecting the Aspartate Aminotransferase (AST)

Similarly, results can be altered by conditions that affect AST. Thus, such patients were excluded.

Drugs that cause elevated AST (certain antibiotics, anti-epileptics, anti-tuberculosis drugs, statins, etc.)

1. Cirrhosis of the liver
2. Consumption of alcohol.
3. Nonalcoholic steatotic hepatitis (NASH)

4. Autoimmune hepatitis
5. Patients who were actively infected with hepatitis C or hepatitis B virus identified by PCR testing.

Methodology

Study was conducted in compliance with Declaration of Helsinki. The ethical registration number was issued by the research committee of Fauji Foundation Hospital, after analyzing the study methodology before the study was conducted. Every patient who is entitled to this tertiary care teaching hospital is given written informed consent at the time of registration, indicating the policy that laboratory, clinical, and biochemical parameters of patients can be utilized for research purposes and that full confidentiality of the patient's personal profile will be maintained. Every patient entitled to this hospital has a specific medical record number (MR number), and medical records can be retrieved by this number.

After confirming the dengue infection, a history addressing the age and gender of patients, along with symptomology, duration of illness, and previous symptomatic dengue fever, was taken. A detailed physical examination as well as vital signs (BP, pulse pressure, pulse, and temperature) were noted.

For the calculation of the APRI score, AST was done by a chemistry analyzer (Max Chemistry Analyzer Dimensions RxL, Siemens Healthineers Laboratories; USA) after collecting about 2.5 mL of blood in EDTA tubes, and platelet count was done by an automated hematology analyzer (Automated Hematology Analyzer XT-2000i, Sysmex Corporation; Japan). The APRI score was calculated for each and every patient at the time of admission. Patients were classified into three groups according to disease severity:

Dengue fever (uncomplicated dengue infection)

Dengue hemorrhagic fever (complicated dengue infection)

Dengue Shock Syndrome (complicated dengue infection).

The primary outcome was uncomplicated vs complicated dengue infection. The outcome of dengue patients (survived or died) was also noted as an additional outcome of the study.

Statistical Analysis

MedCalc Statistical Software 19.6.4 (MedCalc Software, Ostend, Belgium) was used for the analysis of the data. Quantitative variables (age, duration of hospital stay and illness, vital signs, laboratory parameters) were expressed in terms of ranges, means, and standard deviation. Qualitative variables (gender, co-morbidities, symptomology, grades of dengue fever, ultrasonographic findings, outcome) were expressed in terms of percentages. The APRI score was calculated and expressed as the mean \pm Standard deviation.

To see the role of the APRI score in disease complications, the patients were broadly divided into two groups. The first group, in which patients are suffering from simple dengue fever and labeled as **uncomplicated dengue**, and the second group, in which patients either had DHF or DSS and were labeled as **complicated dengue**. The ROC curve was used to identify the role of APRI in dengue complications. The Youden index was used to find the cut-off value of APRI and sensitivity, specificity, and positive and negative likelihood ratios for this cut-off value were also expressed. To further evaluate the role of the APRI score, patients were divided into two groups according to the cut-off value. Patients with an APRI score $<$ cut-off value and patients with an APRI score $>$ cut-off value, and the qualitative variable comparison was done by Chi-Square testing. The predictors of complicated dengue were first determined by univariate regression analysis and then confirmed by multivariate regression analysis.

Results

Total 135 patients were admitted to the Dengue ward of tertiary care hospital from month of August to November 2023. The main aim of our study was to evaluate the importance of APRI score in predicting the complicated dengue fever.

General Characteristics

The mean age was 39.68 ± 18.92 (18–90) years. Among 135 patients, 63.7% (n = 86) were females and 36.3% (n = 49) were males.

Among 135 patients, only 24.4% (n = 33) patients had co-morbidities as majority of patients were young; <40 years 55.6% (n = 75) vs >40 years 44.4% (n = 60) (p < 0.05). Hypertension was the commonest co-morbidity 20.0% (n = 27), followed by diabetes mellitus 14.1% (n = 19) and ischemic heart disease 9.6% (n = 13).

The mean day of illness at the time of admission was 4.63 ± 1.68 (2–9) days. The most common presenting symptom was fever that was present in 98.5% (n = 133) patients. The second common symptom was body aches 81.5% (n = 110), followed by nausea 74.1% (n = 100), headache 73.3% (n = 99), right hypochondrium tenderness 69.6% (n = 94) and vomiting 67.4% (n = 91). Maculopapular rash (diffuse or localized) was present in 63.7% (n = 86) of patients. About 48.9% (n = 66) patients presented with bleeding from any site of body. Around 45.9% (n = 62) patients presented with diarrhea. Conjunctival hemorrhage was present in 40.7% (n = 55) patients.

At the time of admission, mean systolic blood pressure (BP) of dengue patients was 117.84 ± 15.18 (90–170) mmHg, and diastolic BP was 74.98 ± 11.80 (40–100) mmHg with pulse pressure of 42.98 ± 10.09 (10–90) mmHg. Mean pulse was 90.02 ± 14.21 (40–159) bpm and mean temperature was 100.94 ± 10.45 (98.5–104)° F.

Among 135 patients, 60.7% (n = 82) had only simple dengue fever, while 25.2% (n = 34) presented as dengue hemorrhagic fever. Trivial number of patients 14.1% (n = 19) developed dengue shock. The mortality percentage among the study cohort was 3.7% (n = 5) while 96.3% (n = 130) patients with dengue infection survived. The comparison of laboratory parameters, radiological findings and clinical outcome among three stages (Dengue fever, Dengue hemorrhagic fever and dengue shock syndrome) of dengue patients is shown in Table 1. The significant p values are highlighted bold.

APRI Score

The main aim of this study was to observe the role of calculated APRI at time of admission on the outcome (disease complication). The mean APRI score was 20.06 ± 6.31 (0.21–380.00). The APRI score calculated at the time of admission was

Table 1 Table Showing the Comparison of Laboratory Parameters, Radiological Findings and Clinical Outcome Among Three Stages (Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome) of Dengue Patients. Mean, Standard Deviation, Percentages and p value are Used for Expression of Variables

Variables	Uncomplicated Dengue infection	Complicated Dengue infection		
	Dengue fever (n=82)	DHF* (n=34)	DSS† (n=19)	P value
Age (years)	43.64 ± 21.42	38.62 ± 18.32	37.15 ± 16.44	0.36
Hemoglobin (g/dl)	13.34 ± 3.19	12.88 ± 1.87	12.73 ± 3.25	0.65
WCC‡ x 10 ³ cells/L	7.78 ± 5.28	2.77 ± 1.24	1.92 ± 0.66	0.03
HcT	35.88 ± 7.31	49.01 ± 1.24	51.06 ± 5.16	0.01
Platelets x 10 ³ cells/L	109.41 ± 78.95	42.00 ± 23.71	24.18 ± 15.62	0.001
Bilirubin (µmol/L)	8.95 ± 2.34	9.34 ± 5.23	10.59 ± 6.09	0.91
AST§ (IU/L)	94.32 ± 50.85	198.15 ± 58.00	295.00 ± 39.35	0.000
Albumin (g/L)	36.40 ± 8.92	33.00 ± 6.21	32.67 ± 8.83	0.53
Urea (mmol/L)	4.45 ± 1.58	6.26 ± 4.36	11.52 ± 2.75	0.02
Creatinine (µmol/L)	72.92 ± 29.64	81.63 ± 29.26	86.94 ± 47.13	0.30
Previous dengue infection	4.9% (4/82)	76.5% (26/34)	84.2% (16/19)	0.00
Ultra sonographic Findings				
Gall bladder wall thickness	0% (0/82)	97.1% (33/34)	100% (19/19)	0.00
Ascites	0% (0/82)	76.5% (26/34)	100% (19/19)	0.00
Pleural effusion	0% (0/82)	61.8% (21/34)	73.7% (14/19)	0.00
Clinical outcome				
Hospital stay (days)	2.12 ± 1.50	3.80 ± 1.26	5.40 ± 4.27	0.00
Survived	100% (82/82)	97.1% (33/34)	78.9% (15/19)	0.00
Died	0% (0/82)	2.9% (1/34)	21.1% (4/19)	

Notes: The significant p values are highlighted bold.

Abbreviations: *DHF, Dengue hemorrhagic fever; †DSS, Dengue Shock Syndrome; ‡WCC White cell count; §AST, Aspartate Aminotransferase.

statistically significant among the three stages of dengue infection: Dengue fever 4.52 ± 3.96 vs DHF 15.58 ± 9.39 vs DSS 97.55 ± 25.67 ($p < 0.0001$).

ROC Curve for APRI Score in Disease Complication

To find the role of APRI score in disease complication during hospital stay, ROC curve was used. The primary end point in this curve was taken as non-complicated disease vs complicated disease. Simple dengue fever was taken as non-complicated disease, while dengue hemorrhagic fever and dengue shock syndrome both were taken as complicated disease. APRI score calculated at the time of admission was found to be an excellent marker in predicting the disease complication. Patients with high APRI score are more likely to develop complicated disease as compared to patients with low APRI score. The area under the curve for APRI score in predicting the disease complication was 0.93 (95% CI = 0.87–0.97) ($p < 0.0001$). The cut-off value for APRI score was 9.04 calculated by Youden index. The ROC curve showing the AUC of APRI score in predicting the disease complication is shown in Figure 1. The sensitivity, specificity, positive and negative likelihood ratios for this cut-off value are shown in Table 2

Low Vs High APRI Score

The cohort was divided into two groups taking cut-off value (9.04) calculated by ROC curve. Around 60% ($n = 81$) patients with APRI < 9.04 and 40% ($n = 54$) patients with APRI > 9.04 . The comparison of occurrence of three stages of dengue infection and survival percentages among the two groups is shown in Table 3. The significant p values are

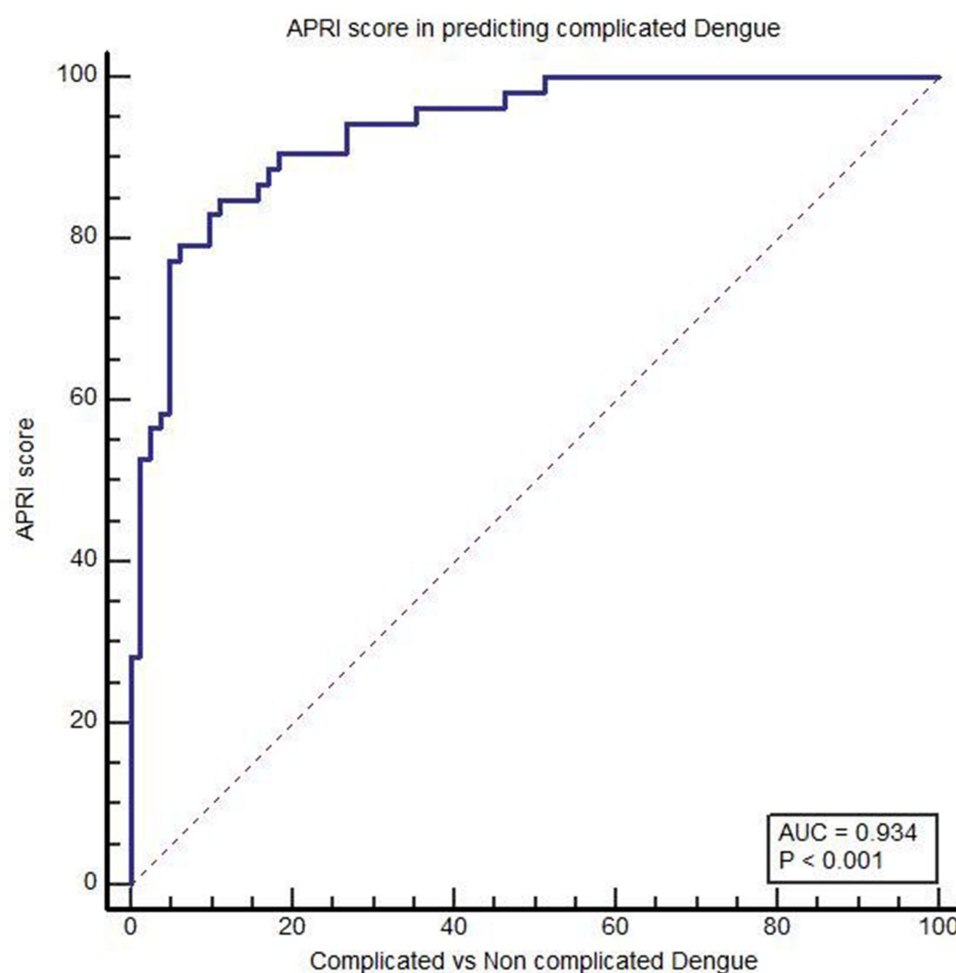


Figure 1 The ROC curve showing the area under the curve (AUC) of APRI score in predicting the disease complication. AUC=0.93 showing it is an excellent marker in predicting the dengue complications ($p < 0.001$).

Table 2 Table Showing the Area Under the Curve for APRI Score and the Sensitivity, Specificity, Positive and Negative Likelihood Ratios of Its Cut-off Value

	AUC*	Cut off value	Sen. §	95% CI	Sp. #	95% CI	+LR [†]	95% CI	-LR [‡]	95% CI	P value
APRI score	0.93	≥9.04	84.91%	72.4–93.3	89.02%	80.2–94.9	7.74	4.13–14.48	0.17	0.09–0.32	<0.0001

Abbreviations: *AUC, Area under the curve; [†]+LR, positive likelihood ratio; [‡]-LR, negative likelihood ratio; §Sen, Sensitivity; #Sp, Specificity.

Table 3 Table Showing the Comparison of Occurrence of Three Stages of Dengue Infection, Survival and Mortality Percentages Among the Two Groups Divided by Cut-off Value. Patients with APRI <9.04 and Patients with APRI >9.04

Variables	APRI* <9.04 (n=81)	APRI* >9.04 (n=54)	P value
Dengue fever	54.1% (73/135)	6.7% (9/135)	0.00
DHF [†]	4.4% (6/135)	20.7% (28/135)	0.00
DSS [‡]	1.5% (2/135)	12.6% (17/135)	0.00
Survived	60% (81/135)	36.3% (49/135)	0.00
Non survived	0	3.7% (5/135)	

Notes: The significant p values are highlighted bold.

Abbreviations: *APRI Aspartate Aminotransferase to Platelet ratio index; [†]DHFDengue Hemorrhagic Fever; [‡]DSS Dengue Shock Syndrome.

highlighted bold. This table shows that dengue shock syndrome occurred in only 1.5% of patients with APRI <9.04 vs 12.6% patients with APRI >9.04 ($p = 0.00$). Similarly, the mortality percentages in patients with APRI <9.04 are nil vs 3.7% patients with APRI >9.04 ($p = 0.00$). Meaning, all patients who died in the study cohort had APRI score >9.04.

At the end, regression analysis was used to determine the factors influencing the severity of dengue infection. Variables were first tested with univariate regression analysis, then those found to be significant were further tested by multivariate analysis. The model was statistically fit for analysis according to Omnibus tests (chi-square test = 98.82, $p = 0.00$) covering 51% to 70% variation of variables (Cox and Snell pseudo R^2 and Nagelkerke pseudo R^2 , respectively) and classified 83.7% of cases. At time of admission, bleeding from any site of body, right hypochondrial tenderness, history of previous symptomatic dengue infection, low platelet count, raised AST levels, presence of ascites, APRI score and APRI categories according to cutoff value were found to be self-reliant predictors of complicated dengue in these patients. The various predictors that significantly influence the severity of dengue infection among the study cohort are shown in Table 4.

Discussion

In our study, the APRI score was calculated in 135 patients at the time of admission, and the mean score was 20.06. This score was statistically significant among the three groups of dengue infection, with the lowest APRI score (4.5) found in simple dengue fever, while dengue hemorrhagic fever patients had a score of 15.5, and the highest score (97.5) was seen in dengue shock syndrome, proving a high APRI score as an excellent marker for indicating complicated dengue ($p < 0.0001$). A similar APRI score of 19.18 was observed by Yeh C-Y et al²⁰ in patients with complicated dengue.

The study cohort was divided into two groups based on their APRI score. The cut-off value of the APRI score was 9.04. All the patients who had an APRI score of less than 9.04 survived. Despite the fact that a trivial number of patients in this group developed dengue hemorrhagic fever 4.4% (6/135) and dengue shock syndrome 1.5% (2/135), no mortality was observed in the low APRI score group. Patients with an APRI score greater than 9.04 suffered complications, in which 20.7% (28/135) had hemorrhagic manifestations, 12.6% (17/135) developed dengue shock syndrome, and 3.7% (5/135) died in this cohort ($9p < 0.05$). Meaning, all patients who died in the study cohort had an APRI score >9.04. In view

Table 4 Cox Regression Analysis Showing Statistically Significant Variables in Predicting the Severity of Dengue Infection Among the Study Cohort

Variables	OR* (95% CI [†])	P value
Bleeding from any site of body	0.07 (0.01–0.17)	0.00
Right hypochondrial tenderness	0.39 (0.19–0.97)	0.03
Previous symptomatic dengue infection	0.18 (0.03–0.85)	0.04
Platelets × 10 ³ cells/L	1.05 (1.03–1.07)	0.00
AST [‡] (IU/L)	0.96 (0.95–0.97)	0.00
Ascites	0.32 (0.08–0.74)	0.04
APRI category	0.37 (0.30–0.47)	0.00
APRI score	0.75 (0.68–0.83)	0.00

Abbreviations: *OR, Odd Ratio; [†]CI, Confidence Interval; [‡]AST, Aspartate Aminotransferase.

of these results, the APRI score appears to be a valuable predictor of complicated dengue and mortality, as supported in another study.²¹

Similarly, the area under the curve (AUC) for the APRI score was 0.93, which proves this clinical risk score to be an outstanding marker for anticipating complicated dengue infections with a sensitivity of around 85% and a specificity of approximately 90%. A close AUC of 0.7 for the APRI score has been observed by Zhang H. et al.¹¹ This ROC curve was statistically significant, making the APRI score a plausible indicator for predicting poor disease outcomes. A study on dengue patients showed that a dengue risk score comprising six variables, namely high AST and ALT, low platelet and albumin, deranged coagulation, and positive dengue IgM, had an AUROC of 0.90, distinguishing patients between severe and non-severe dengue infection.²²

The overall mortality of our study was 3.7%. This is akin to the mortality rate of 3.37% reported in another systemic review by Kaur G. et al.²³ However, a high mortality rate was observed in a study by Jain S. et al.²⁴

Our study results showed that, along with APRI scores, other parameters associated with severe dengue infection were younger age group, leucopenia, high hematocrit, history of previous dengue infections, raised transaminases, and radiological findings including pleural effusion on chest X-rays and ascites or gall bladder wall thickness on ultrasound. Another study showed similar parameters for dengue morbidity and mortality.²⁵ Comparable to our results, Chaudry S. et al.²⁶ established the practicality of ultrasound findings as prognostic markers of disease in their research.

A prolonged hospital stay was observed in patients with complicated dengue. No mortality was seen in patients with simple dengue fever, while one patient died of hemorrhagic complications and four patients died of bleeding complications and developed shock syndrome. All five of these patients had a high APRI score.

Our research depicted independent variables that could influence the severity of dengue fever and were statistically significant. These included bleeding from any site of the body, right hypochondrial tenderness, previous symptomatic dengue infection, thrombocytopenia, high AST levels, ascites, APRI categories (high APRI and low APRI groups), and APRI score. Similar alert signs were depicted in other studies.^{7,27–29} A high AST and low platelet count within 72 hours of fever can predict the severity of dengue, as reviewed in a meta-analysis by Thach T. et al.³⁰ All these factors were associated with discrimination between uncomplicated dengue infection and severe dengue infection.

Currently, there are no definitive medications available for dengue virus infection or any effective vaccines to prevent further attacks of this disease, as debated in another study.^{31,32} Therefore, ensuring close monitoring of severity signs for dengue and supportive management, including temperature control and judicious use of intravenous fluids during the critical phase of dengue, can reduce complications and affect mortality, as conferred in another study.³³

Conclusion

In conclusion, current evidence-based research in pursuit of valuable markers for the diagnosis of disease severity could be imperative for early medical intervention and prevent the risk of hemorrhagic complications and circulatory failure. In this stance, our study reveals the impact of APRI scores (cut-off value > 9.04) on the severity of dengue fever, which can assist in patient triage into high vs low risk of complicated dengue. By strictly monitoring such high-risk patients, catastrophic events could be prevented, and rapid intervention could save lives. This simple score can be used as a guideline for routine practice in hospitals.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. European center for disease prevention and control. Available from: <https://www.ecdc.europa.eu/en/dengue-monthly>. (accessed from 7th, December, 2023.).
2. Khan U, Azeem S. The rising toll of dengue cases in Pakistan every year: an incipient crisis. *Ann Med Surg*. 2022;76:103549. doi:10.1016/j.amsu.2022.103549
3. Disease outbreak news. dengue-Pakistan. Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON414>. (accessed from 7th, December, 2023.).
4. Field Epidemiology & Disease Surveillance Division (FE & DSD) National Institute of Health (NIH) Islamabad, Pakistan National Focal Point for International Health Regulations (IHR) For Epidemic-prone infectious diseases in Pakistan Data Resources. Weekly Bulletin (2). 2023; Available from: <http://idsr-pak@nih.org.pk>. Accessed may 06 2024.
5. Khan J, Khan I, Ghaffar A, Khalid B. Epidemiological trends and risk factors associated with dengue disease in Pakistan (1980-2014): a systematic literature search and analysis. *BMC Public Health*. 2018;18(1):745. doi:10.1186/s12889-018-5676-2
6. Sandeep M, Padhi BK, Yella SST, et al. Myocarditis manifestations in dengue cases: a systematic review and meta-analysis. *J Infect Public Health*. 2023;16(11):1761–1768. doi:10.1016/j.jiph.2023.08.005
7. Waheed I, Khalid S, Jamil Z. Predictors of complicated dengue infections in endemic region of Pakistan. *Asian Pac J Trop Med*. 2022;15(11):1.
8. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. *Trop Med Int Health*. 2008;13(11):1328–1340. doi:10.1111/j.1365-3156.2008.02151.x
9. Lam PK, Tam DTH, Diet TV, et al. Clinical characteristics of Dengue shock syndrome in Vietnamese children: a 10-year prospective study in a single hospital. *Clin Infect Dis an off Publ Infect Dis Soc Am*. 2013;57(11):1577–1586. doi:10.1093/cid/cit594
10. Badreddine S, Al-Dhaheri F, Al-Dabbagh A, et al. Dengue fever. clinical features of 567 consecutive patients admitted to a tertiary care center in Saudi Arabia. *Saudi Med J*. 2017;38(10):1025–1033. doi:10.15537/smj.2017.10.20965
11. Zhang H, Xie Z, Xie X, Ou Y, Zeng W, Zhou Y. A novel predictor of severe dengue: the aspartate aminotransferase/platelet count ratio index (APRI). *J Med Virol*. 2018;90(5):803–809. doi:10.1002/jmv.25021
12. Sangkaew S, Ming D, Boonyasiri A, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. *Lancet Infect Dis*. 2021;21(7):1014–1026. doi:10.1016/S1473-3099(20)30601-0
13. Suwanto S, Hidayat MJ, Widjaya B. Dengue score as a diagnostic predictor for pleural effusion and/or ascites: external validation and clinical application. *BMC Infect Dis*. 2018;18(1):90. doi:10.1186/s12879-018-2996-x
14. Sigera PC, Amarasekara R, Rodrigo C, et al. Risk prediction for severe disease and better diagnostic accuracy in early dengue infection; the Colombo dengue study. *BMC Infect Dis*. 2019;19(1):680. doi:10.1186/s12879-019-4304-9
15. Guedes KS, Sanchez BAM, Gomes LT, Fontes CJF. Aspartate aminotransferase-to-platelet ratio index (APRI): a potential marker for diagnosis in patients at risk of severe malaria caused by *Plasmodium vivax*. *PLoS One*. 2019;14(11):e0224877. doi:10.1371/journal.pone.0224877
16. Amernia B, Moosavy SH, Banookh F, Zoghi G. FIB-4, APRI, and AST/ALT ratio compared to FibroScan for the assessment of hepatic fibrosis in patients with non-alcoholic fatty liver disease in Bandar Abbas, Iran. *BMC Gastroenterol*. 2021;21(1):453. doi:10.1186/s12876-021-02038-3
17. De Matteis C, Cariello M, Graziano G, et al. AST to Platelet Ratio Index (APRI) is an easy-to-use predictor score for cardiovascular risk in metabolic subjects. *Sci Rep*. 2021;11(1):14834. doi:10.1038/s41598-021-94277-3
18. Advisory-for-Dengue-Fever-May-2019; 2023. Available from: www.nih.org.pk. Accessed May 6, 2024.
19. Srikiatkachorn A, V GR, Green S, et al. Dengue hemorrhagic fever: the sensitivity and specificity of the world health organization definition for identification of severe cases of dengue in Thailand, 1994-2005. *Clin Infect Dis an off Publ Infect Dis Soc Am*. 2010;50(8):1135–1143. doi:10.1086/651268
20. Yeh C-Y, B-Z L, Liang W-J, et al. Trajectories of hepatic and coagulation dysfunctions related to a rapidly fatal outcome among hospitalized patients with dengue fever in Tainan, 2015. *PLoS Negl Trop Dis*. 2019;13(12):e0007817. doi:10.1371/journal.pntd.0007817
21. Ahmed AE, Dahman B, Altamimi A, McClish DK, Al-Jahdali H. The aspartate aminotransferase/platelet count ratio index as a marker of dengue virus infection: course of illness. *J Infect Public Health*. 2020;13(7):980–984. doi:10.1016/j.jiph.2020.03.009

22. Srisuphanunt M, Puttaruk P, Kooltheat N, Katzenmeier G, Wilairatana P. Prognostic indicators for the early prediction of severe dengue infection: a retrospective study in a University Hospital in Thailand. *Trop Med Infect Dis.* 2022;7(8):1.
23. Kaur G, Kumar V, Puri S, Tyagi R, Singh A, Kaur H. Predictors of dengue-related mortality in young adults in a tertiary care centre in North India. *J Fam Med Prim Care.* 2020;9(2):694–697. doi:10.4103/jfmpe.jfmpe_605_19
24. Jain S, Mittal A, Sharma SK, et al. Predictors of dengue-related mortality and disease severity in a tertiary care center in North India. *Open Forum Infect Dis.* 2017;4(2):1.
25. Teerasarnitpan T, Chaiteerakij R, Komolmit P, Tangkijvanich P, Treeprasertsuk S. Acute liver failure and death predictors in patients with dengue-induced severe hepatitis. *World J Gastroenterol.* 2020;26(33):4983–4995. doi:10.3748/wjg.v26.i33.4983
26. Chaudhary S, Manrai K, Dhagat P, et al. Abdominal and chest ultrasonography: a predictor for disease progression in nonsevere dengue. *Med J.* 2023;79(4):386–391. doi:10.1016/j.mjafi.2021.03.012
27. Marois I, Forfait C, Inizan C, et al. Development of a bedside score to predict dengue severity. *BMC Infect Dis.* 2021;21(1):470. doi:10.1186/s12879-021-06146-z
28. Huy BV, Toàn NV. Prognostic indicators associated with progresses of severe dengue. *PLoS One.* 2022;17(1):e0262096. doi:10.1371/journal.pone.0262096
29. Mahmuduzzaman M, Chowdhury AS, Ghosh DK, Kabir IM, Rahman MA, Ali MS. Serum transaminase level changes in dengue fever and its correlation with disease severity. *Mymensingh Med J.* 2011;20(3):349–355.
30. Thach TQ, Eisa HG, Ben HA, et al. Predictive markers for the early prognosis of dengue severity: a systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2021;15(10):e0009808. doi:10.1371/journal.pntd.0009808
31. Park J, Kim J, Jang Y-S. Current status and perspectives on vaccine development against dengue virus infection. *J Microbiol.* 2022;60(3):247–254. doi:10.1007/s12275-022-1625-y
32. Malik S, Ahsan O, Mumtaz H, Tahir Khan M, Sah R, Waheed Y. Tracing down the updates on dengue virus-molecular biology, antivirals, and vaccine strategies. *Vaccines.* 2023;11(8):1328. doi:10.3390/vaccines11081328
33. Tayal A, Kabra SK, Lodha R. Management of dengue: an updated review. *Indian J Pediatr.* 2023;90(2):168–177. doi:10.1007/s12098-022-04394-8

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