

Original Article

Clinical Utility of NS1 Antigen level in Predicting Severity of Thrombocytopenia, Transaminitis and Appearance of Warning Signs in Dengue Patients

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Abstract

Objective: To find an association between plasma levels of NS1 antigen with thrombocytopenia, Transaminitis and appearance of warning signs that can help to better manage high-risk cases that would develop into DHF/DSS

Methods: This retrospective study analyzed 136 dengue patients admitted to the Department of Medicine at Fatima Memorial Hospital for dengue fever from August 1, 2022, and November 30, 2022. Qualitative and quantitative data was collected including warning signs of abdominal pain, persistent vomiting, mucosal bleeding, rising hematocrit from baseline, narrow pulse pressures, NS1 antigen levels, platelet levels, and ALT/AST levels. Pearson Correlation Coefficient was calculated to show correlation between quantitative laboratory variables with NS1 antigen.

Results: The median NS1 antigen was 13 (IQR 17.7), the median platelet count was 52 (IQR 67), A total of 134 (98.5%) patients were sent home safely after management which showed median NS1 antigen levels of 13(17.27) whereas 2 patients (1.5%) who died showed median Ns1 antigen level was 22.1. There was statistically significant inverse correlation ($p < 0.05$) between NS1 antigen and platelet count. Elevated NS1 antigen levels were significantly associated with abdominal pain and persistent vomiting, while higher levels correlated with increased morbidity and mortality.

Conclusion: On the whole; NS1 antigen's potential for risk assessment and early intervention in severe dengue cases, suggesting a shift from reactive to proactive care in dengue management. Although limited by sample size and single-center design, this study underscores the clinical value of NS1 antigen in improving patients' outcomes and warrants further validation in larger, multi-center studies.

Keywords: NS1 Antigen, Dengue Fever, Dengue Hemorrhagic Fever, Thrombocytopenia, Transaminitis, Clinical Utility, Dengue Hemorrhagic Fever.

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Introduction

Dengue Fever, commonly known as break-bone fever, is caused by the mosquito-transmitted dengue virus. Dengue infections encompass a spectrum of clinical presentations. While some individuals remain asymptomatic, others experience symptoms ranging from high-grade fever to severe complications.¹ Severe dengue forms, Dengue Hemorrhagic Fever and Dengue Shock Syndrome, entail symptoms like bleeding tendencies, plasma leakage, shock, and organ impairment. This can cause significant mortality if not managed early with fluids and other interventions.² It is for this reason

that dengue management requires intensive monitoring of clinical and laboratory parameters, typically conducted two or three times daily, which can place substantial strain on resource-stressed healthcare facilities. Given already that the burden of dengue is concentrated in many resource-limited nations, with 96 million cases of the 390 million annual cases located within Asia, a practical, easy, in-ward test capable of identifying patients at risk of severe disease is imperative.³

A critical component in the context of dengue infection is the NS-1 antigen, or Non-Structural Protein 1. NS-1 is produced by the dengue virus as a non-structural

protein and is released into the bloodstream of infected individuals.⁴ It serves as an exceptionally precise indicator of dengue infection, as there is no occurrence of cross-reactivity between the dengue NS1 protein and those from other closely related flaviviruses.⁵ The identification of NS1 has emerged as a promising diagnostic tool for early-stage dengue diagnosis during fever onset, attributed to its extended presence in the bloodstream due to a prolonged half-life.⁶

This retrospective study aims to find an association between plasma levels of NS1 antigen with thrombocytopenia, Transaminitis and appearance of warning signs that can help to better manage high-risk cases that would develop into DHF/DSS. Previous studies do exist which have investigated the usefulness of platelet counts, NS1 antigen levels and other clinical parameters to predict severe dengue complications.⁶ However, these associations have been established independent of each other and so this paper aims to use NS1 antigen as a predictor for these clinical parameters so it can be used as a tool to risk stratify patients. This study will also reaffirm previous studies findings of the relation of NS1 antigen levels with severity of disease.

Methods

A retrospective study was conducted in the Department of Internal Medicine at Fatima Memorial Hospital, Lahore. The study was conducted over a duration of four month. All patients diagnosed with dengue fever and admitted to the hospital between August 1, 2022, and November 30, 2022 were included in the study and hence, a total of 136 patients' medical records were retrieved and analyzed. Ethical approval was obtained from IRB before the commencement of the study to ensure the confidentiality and well-being of the patients involved.

Consecutive Non-Probability Sampling Technique was employed for participant selection. For the inclusion criteria, all cases of Dengue fever with NS1 Antigen positive results within the first five days of illness between August 1, 2022 and November 30, 2022 were included in the study, whereas patients meeting any of the following criteria were excluded from the study: Those with chronic liver disease (CLD), patients with acute viral hepatitis diagnosed before diagnosis of dengue based on medical history, examination, and laboratory reports, individuals with autoimmune hepatitis (AIH), those diagnosed with non-alcoholic steatohepatitis (NASH), patients with idiopathic thrombocytopenic purpura (ITP), individuals with thrombotic thrombocytopenic purpura (TTP).

Dengue Fever (DF) is characterized by high-grade fever and body aches along with a positive NS1 antigen test in laboratory reports within the first five days of illness; thrombocytopenia refers to DF patients having platelet

counts below 100,000 cells/mm² or a reduction of 50% or more from baseline; transaminitis is defined by elevated alanine transaminase (ALT) and aspartate transaminase (AST) levels above their normal ranges of 0.7–55 U/L and 0.8–48 U/L respectively; Dengue Hemorrhagic Fever (DHF) includes fever, thrombocytopenia, hemorrhagic manifestations, and plasma leakage due to increased vascular permeability with a positive NS1 antigen test; Dengue Shock Syndrome (DSS) is a severe progression of DHF with significant plasma leakage leading to circulatory collapse, indicated by narrowing pulse pressure or hypotension; warning signs.⁷

Data was entered and analyzed using SPSS version 25. Descriptive analysis was conducted on all variables. Categorical variables, including warning signs of abdominal pain, persistent vomiting, mucosal bleeding, rising hematocrit from baseline, narrow pulse pressures and patients categorized DHF/DSS, were presented as frequencies and percentages, while quantitative variables, including NS1 antigen levels, platelet levels, and ALT/AST levels, were presented as medians and interquartile ranges (IQR).

Pearson correlation coefficient was calculated to assess the correlation between NS1 Antigen titers and laboratory parameters such as thrombocytopenia severity, Transaminitis, Dengue Hemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS), and length of hospital stay.

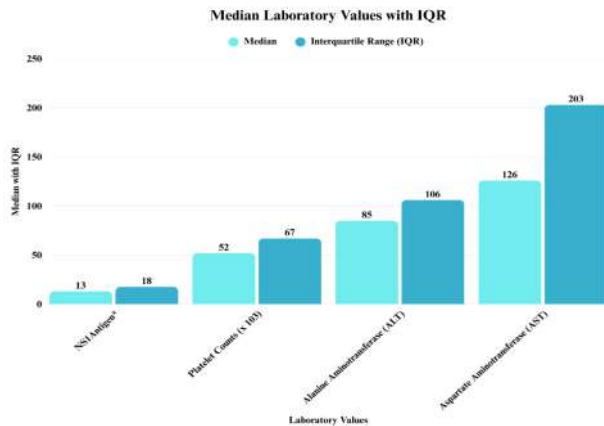
For analyzing the significance of warning signs in relation to different NS1 antigen titers/levels, the Mann-Whitney test was applied. This allowed us to determine the association between the appearance of warning signs and varying NS1 antigen levels.

Results

There were a total of 136 patients who fulfilled the inclusion criteria. The median NS1 antigen was 13 (IQR 17.7), the median platelet count was 52 (IQR 67), the median ALT level was 85 (IQR 106) and the median AST level was 126 (IQR 203) as noted in Figure 1. (Supplementary Table 1)

Regarding warning signs in patients, abdominal pain was seen in 43 (31.6%) patients, narrow pulse pressure was observed in 127 (93.4%) patients, persistent vomiting was seen in 63 (46.3%), mucosal bleed was reported in 113 (83%) patients, and rising hematocrit >20% baseline was seen in 84 (62.7%) patients. 123 (90.4%) patients were in DHF and 23 (16.9%) were in DSS. These are noted in Table 1.

Scattered plot reflected that with rising NS1 antigen levels, platelet counts drop drastically, thus demonstrating an inverse correlation between NS1 antigen and Platelet counts. This is demonstrated in Figure 2.



*NS1 = non-structural protein antigen

Figure 1: Laboratory Findings

Table 1: Clinical parameters & outcomes percentage patients.

Clinical Parameters	Frequency (%)	Median NS1 antigen level (IQR)	P-value
Abdominal pain	43 (31.6)	14 (16.17)	0.035
Narrow pulse pressure	127 (93.4)	17.2 (13.7)	0.093
Persistent vomiting	63 (46.3)	8.17 (17.3)	0.046
Mucosal bleed	113 (83)	15 (17.85)	0.172
Rising Haematocrit >20% from baseline	84 (62.7)	13 (14.42)	0.064
DHF*	123 (90.4)	-	-
DSS**	23 (16.9)	-	-
Discharge	134 (98.5)	13(17.27)	-
Death	2 (1.5)	22.1(-)	-

*DHF= Dengue Hemorrhagic fever,

**DSS= Dengue shock syndrome

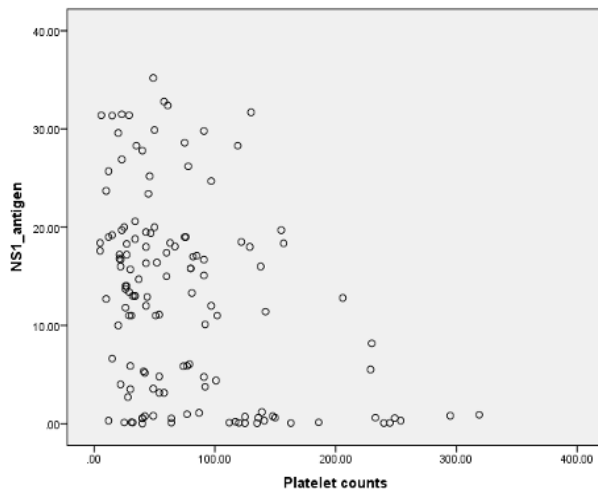


Figure 2: Scattered plot: showing Correlation of NS1 antigen with platelet counts

Table 2: Correlation of NS1 Antigen and lab parameters

	Correlation	P-value
Platelet count	-0.348	<0.05
ALT	0.074	0.424
AST	0.08	0.390
Hospital stay	-0.015	0.865

Pearson Correlation Coefficient was calculated to show correlation between quantitative laboratory variables with NS1 antigen, which revealed statistically significant inverse correlation ($p < 0.05$) between NS1 antigen and platelet count but no significant correlation between NS1 antigen and ALT/AST or hospital stay length. This is shown in Table 2.

In order to show the impact of the correlation of NS1 antigen levels with warning signs that normally predict dengue shock syndrome and prolonged hospital stay, Mann Whitney U test was calculated which demonstrated a statistically significant result when NS1 levels were correlated in patients with abdominal pain/ persistent vomiting as compared to those without. Other warning signs including mucosal bleeding, narrow pulse pressure, and rising hematocrit >20% from baseline did not show any statistical significance. This is shown in Figure 3. (Supplementary Table 2)

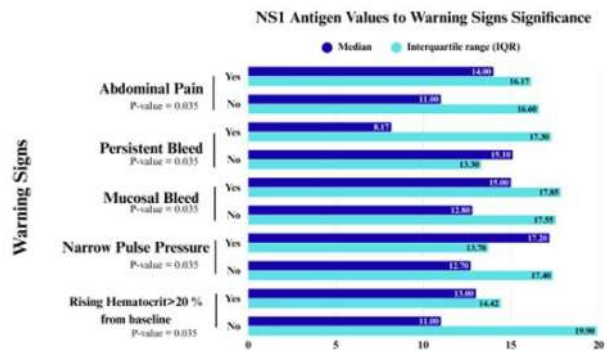


Figure 3: NS1 Antigen values to warning signs significance.

Lastly, median NS1 antigen levels were charted against those patients who were discharged versus those who experienced death in the hospital. Correlation of NS1 antigen with the outcome of the patients reveals that higher titers of NS1 antigen were associated with morbidity and mortality. A total of 134 (98.5%) patients were sent home safely after management which showed median NS1 antigen levels of 13(17.27) whereas 2 patients (1.5%) who died showed median NS1 antigen level was 22.1. This demonstrated that there was a trend linking higher NS1 antigen levels to mortality. This is shown in table 1.

Discussion

The results of this retrospective study demonstrate insightful findings that relate NS1 antigen levels, clinical parameters as well as patient outcomes in dengue patients. These findings play an important part in understanding how dengue severity can be predicted and thus, patients managed.

In the graphed data of patients, the observed scattered plot indicates a clear inverse correlation between NS1 antigen levels and platelet counts. As NS1 antigen levels rise, platelet counts drop significantly. This relationship aligns with the well-known association between dengue infection and thrombocytopenia and corroborates studies such as Kulkarni et al 2011 and Kantikhar et al 2016 which also show a strong association between the two^{8,9}. The significant inverse correlation emphasizes the potential of NS1 antigen levels as an early predictive marker of disease severity. Monitoring NS1 antigen levels could aid in identifying patients at risk of developing severe complications, such as bleeding tendencies, associated with decreased platelet counts. Early identification of such individuals is crucial because it enables healthcare providers to allocate resources, closely monitor patients, and initiate appropriate interventions before complications worsen. For instance, patients identified as having elevated NS1 antigen levels could receive enhanced monitoring, tailored fluid management, and other interventions to mitigate the risk of severe complications. Thus, using NS1 antigens levels can redirect resources allocated to all patients in resource-weak settings to cater to the needs of high-risk patients and thus improve outcomes.

Furthermore, The Mann-Whitney U test demonstrated a statistically significant correlation between NS1 antigen levels and warning signs of abdominal pain and persistent vomiting. Patients with elevated NS1 antigen levels were more likely to exhibit these warning signs. In previous studies conducted such as Tithi Pal et al 2014 and Passos et al 2008, abdominal pain and persistent vomiting were found to be recognized indicators of severe dengue infection, often predicting the development of DSS/DHF^{10,11}. This study that was conducted is unique in its findings because it indicates NS1 antigen as an additional sensitive marker that can identify patients at an increased risk of developing severe dengue complications of abdominal pain and vomiting.

This study also revealed a noteworthy correlation between NS1 antigen levels and patient outcomes. Patients who were discharged had significantly lower median NS1 antigen levels while patients who experienced mortality had higher median NS1 antigen levels (22.1). This observation indicates that higher NS1 antigen levels are associated with increased morbidity and mortality. Studies conducted before have demonstrated

that NS1 antigen levels are linked to more severe disease of dengue with greater lymphopenia detected in such cases, but this direct correlation to worse outcomes is uniquely supported by our data¹². This finding underscores the clinical significance of NS1 antigen in prognosticating patient outcomes and aiding in treatment decisions.

Ultimately, the findings from this study have the potential to modify the way dengue cases are managed, shifting the focus from reactive care to proactive prevention. It could reduce the burden on healthcare facilities by enabling targeted interventions and early risk stratification, leading to improved patient outcomes and reduced mortality rates. As always though, while this study provides good insight, there are limitations. The study's retrospective nature could introduce bias and reduce the internal validity of the study. The small sample size reduces the power of this study. Furthermore, the study's single-center design might limit the generalizability of the findings to broader populations. Future research could consider conducting multi-center studies with larger sample sizes to validate the findings and enhance their applicability.

Conclusion:

The results of this study offer substantial evidence for the potential clinical utility of NS1 antigen levels in dengue fever management. The inverse correlation between NS1 antigen levels and platelet counts, along with the associations with warning signs and patient outcomes, highlights the importance of NS1 antigen as an early predictive marker for disease severity and complications. Integrating NS1 antigen monitoring into clinical practice could enhance risk assessment, guide timely interventions, and ultimately improve patient outcomes in dengue-infected individuals.

Ethical Approval: The IRB/EC approved this study via letter no. FMH/11/01/2023-IRB-1167 dated January 23, 2023.

Conflict of Interest: None

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Authors' Contribution

KK: Conception.

DK, KhK: Design of the work.

AZKC, FS, JI: Data acquisition, analysis, or interpretation.

AZKC, FS, JI, DK: Draft the work.

KK, KhK: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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